

1. J Clin Pathol. 2013 Feb 7.

Eosinophilic oesophagitis in children: responders and non-responders to swallowed Fluticasone.

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Eosinophilic Oesophagitis (EO) is characterised by large numbers of eosinophils in oesophageal mucosa in response to food or inhaled antigens. Treatment with elimination diet or corticosteroids lead to improvement in some children, but their efficacy is not optimal. AIM: of this study is to identify clinical, endoscopic and/or histological features associated with response to treatment with swallowed fluticasone propionate. PATIENTS AND METHODS: In the last 12 years 34 children (M/F 25/9) with EO were treated with fluticasone propionate spray 250 µg/puff by inhaler without spacer, three puffs three times a day for 6 weeks, and returned for a follow-up endoscopy. At histology 25 of them were found to be responders to therapy (73.5%) and 9 were non-responders. Anthropometric characteristics, symptoms at presentation, endoscopic and histological data at baseline between responders and non-responders were compared. RESULTS: Age, sex, height, duration and type of main symptom at presentation, type of allergy and number of allergens, peripheral eosinophil counts and serum IgE were similar in responders and non-responders. At baseline histology findings responders had a more severe inflammation: median peak eosinophils/high power field was higher (76 vs 44 in non responders $p=0.04$), eosinophilic microabscesses were present in a significantly higher number of responders ($p=0.04$) and peak mast cells/ high power field was significantly higher ($p=0.001$). CONCLUSIONS: Clinical characteristics of children with EO at baseline were similar in responders and non-responders, but a more severe inflammation in oesophageal mucosa was associated with a higher response rate to fluticasone treatment.

2. Br J Cancer. 2013 Feb 19;108(3):621-8. doi: 10.1038/bjc.2013.9. Epub 2013 Jan 29.

The expression of Axl receptor tyrosine kinase influences the tumour phenotype and clinical outcome of patients with malignant pleural mesothelioma.

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Background:Recent preclinical studies identified Axl, a tyrosine kinase receptor implicated in tumour progression and epithelial-to-mesenchymal transition, as a putative therapeutic target in malignant pleural mesothelioma (MPM), an invariably fatal malignancy with limited treatment options. Here, we studied the expression of Axl and its ligand Gas-6 (growth arrest signal-6) in primary specimens of MPM, correlating their expression levels with tumour phenotype and

clinical outcomes. Methods: Two independent cohorts of consecutive patients diagnosed with MPM were studied: a derivation cohort composed of 63 cases and a validation set of 35 cases. Clinical variables including patients' demographics, tumour stage, histotype, performance status (PS), Axl and Gas-6 staining were tested for predicting overall survival (OS) using univariate and multivariate analyses. Results: In the derivation cohort, Axl (P=0.001) but not Gas-6 overexpression (P=0.35) emerged as a univariate prognostic factor for OS, together with stage (P=0.05), PS (P<0.001) hypoalbuminaemia (P<0.001) and anaemia (P<0.001). Multivariate analyses confirmed Axl overexpression (P=0.01), PS (P=0.01), hypoalbuminaemia (P<0.001) and anaemia (P=0.04) as independent predictors of OS. The prognostic role of Axl overexpression was externally validated in an independent cohort (P=0.03). Conclusion: Overexpression of Axl is found in the majority of MPM specimens and influences patient's survival independently from other established prognostic factors. Such information may support patient selection for future trials.

3. *Minerva Chir.* 2012 Oct;67(5):464-6.

K-RAS mutation analysis in a case of pancreatic cystic tumour: an additional tool in making decision of surgical management.

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PMID: 23232489 [PubMed - in process]

4. *Pigment Cell Melanoma Res.* 2013 Jan;26(1):144-6. doi: 10.1111/pcmr.12037. Epub 2012 Nov 12.

Nicotinamide phosphoribosyltransferase (NAMPT) is over-expressed in melanoma Lesions.

Maldi E, Travelli C, Caldarelli A, Agazzone N, Cintura S, Galli U, Scatolini M, Ostano P, Miglino B, Chiorino G, Boldorini R, Genazzani AA.

PMID: 23051650 [PubMed - in process]

5. *Infect Agent Cancer.* 2012 Oct 2;7(1):25. doi: 10.1186/1750-9378-7-25.

NLRP1 polymorphisms in patients with asbestos-associated mesothelioma.

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BACKGROUND: An increasing incidence of malignant mesothelioma (MM) cases in patients with low levels of asbestos exposure suggests the interference of alternative cofactors. SV40 infection was detected, as co-morbidity factor, only in 22% of asbestos-MM patients from a North-Eastern Italy area. An additional mechanism of injury related to asbestos exposure in MM development has been recently associated to inflammatory responses, principally driven by interleukin (IL)-1 beta (β) activated within the inflammasome complex. NLRP3 inflammasome has been described as the intracellular sensor for asbestos able to induce inflammasome activation and IL-1 β secretion while NLRP1 is expressed in lung epithelial cells and alveolar macrophages and contributes to the immune response and to survival/apoptosis balance. This study proposes to evaluate the impact of known NLRP3 and NLRP1 polymorphisms in the individual susceptibility to asbestos-induced mesothelioma in subjects from a hyperendemic area for MM.

METHODS: 134 Italian patients with diagnosis of mesothelioma due (MMAE, n=69) or not (MMAF, n=65) to asbestos, 256 healthy Italian blood donors and 101 Italian healthy subjects exposed to asbestos (HCAE) were genotyped for NLRP1 (rs2670660 and rs12150220) and NLRP3 (rs35829419 and rs10754558) polymorphisms.

RESULTS: While NLRP3 SNPs were not associated to mesothelioma, the NLRP1 rs12150220 allele T was significantly more frequent in MMAE (0.55) than in HCAE (0.41) ($p=0.011$; OR=1.79) suggesting a predisponent effect of this allele on the development of mesothelioma. This effect was amplified when the NLRP1 rs2670660 allele was combined with the NLRP1 rs12150220 allele ($p=0.004$; OR=0.52).

CONCLUSION: Although NLRP3 SNPs was not involved in mesothelioma predisposition, these data proposed NLRP1 as a novel factor possibly involved in the development of mesothelioma.

6. Can J Cardiol. 2012 Aug 24. [Epub ahead of print]

Different Expression and Function of the Endocannabinoid System in Human Epicardial Adipose Tissue in Relation to Heart Disease.

Cappellano G, Uberti F, Caimmi PP, Pietronave S, Mary DA, Dianzani C, Micalizzi E, Melensi M, Boldorini R, Nicosia G, Crosio E, Chiocchetti A, Aina F, Prat M, Dianzani U, Vacca G, Ariatti C, Grossini E.

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BACKGROUND: The endocannabinoid system reportedly plays a role in the pathogenesis of cardiovascular diseases. This system is expressed also in adipose tissue, which could thus be involved in cardiac disorders through modulation of metabolically triggered inflammation. The current study aims to determine the relevance of the endocannabinoid system in epicardial adipose tissue in heart disease. **METHODS:** Expression of the endocannabinoid receptors CB1 and CB2, and of the endocannabinoid-degrading enzyme, fatty acid amidohydrolase, and activation of protein kinase A (PKA), phospholipase C (PLC), protein kinase C (PKC), endothelial nitric oxide synthase (eNOS) and inducible (i)NOS, and extracellular signal-regulated kinases 1 and 2 (ERK1/2) (a member of the reperfusion-injury

salvage kinase pathway), were analyzed by Western blot in patients after coronary artery bypass surgery (ischemics; N = 18) or valve surgery (nonischemics; N = 15) and in preadipocytes isolated from epicardial adipose tissue. RESULTS: In ischemics, the CB1-to-CB2 expression ratio shifted toward CB1 and was accompanied by higher PKA activation. In contrast, in nonischemics, CB2, fatty acid amidohydrolase, PLC and PKC, and ERK1/2 were upregulated. Moreover, NO production and iNOS-to-eNOS ratios were higher in preadipocytes from ischemics. CONCLUSIONS: These results show a different modulation and functioning of the endocannabinoid system in ischemics compared with nonischemics. Hence, while CB2, PLC and PKC, ERK1/2, and eNOS are more strongly expressed in patients without ischemic heart disease, high CB1 and PKA expression is associated with low survival intracellular pathway activation and high iNOS activation in ischemic heart disease patients. The changes in the endocannabinoid system in ischemics may contribute to cardiac dysfunction and therefore represents a potential therapeutic target.

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7. Am J Clin Pathol. 2012 Sep;138(3):377-81. doi: 10.1309/AJCPVAGIUC1AHC3Y.

Epidermal growth factor receptor gene analysis with a highly sensitive molecular assay in routine cytologic specimens of lung adenocarcinoma.

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Epidermal growth factor receptor (EGFR) gene mutational analysis is critical for guiding the treatment of lung adenocarcinoma. In everyday clinical practice, EGFR testing is frequently centralized in referral laboratories that may receive paucicellular cytologic specimens, often fixed in various ways. We conducted a search for EGFR mutations in 108 cytologic samples of lung adenocarcinoma from different hospitals using the TheraScreen EGFR29 kit. These samples included 80 (74.1%) fine-needle aspirations, 13 (12%) pleural/ascitic fluids, 13 (12%) bronchial washings, and 2 bronchial brushings. The samples were fixed in ethanol (n = 79), Dubosq-Brasil (n = 18) or formalin (n = 10); 1 was unfixed. Ninety-two (85.2%) were amplified, 16 (14.8%) were not. Mutations were detected in 22 (23.9%) of 92 amplified samples, 9 containing less than 200 cancer cells, and 4 with less than 50% cancer cells. DNA was amplified in 12 of 18 Dubosq-Brasil-fixed samples. These findings indicate that cytologic specimens are adequate for EGFR testing when a highly sensitive assay is used, even if they are paucicellular or not optimally fixed.

PMID: 22912354 [PubMed - indexed for MEDLINE]

8. Euro Surveill. 2012 Jul 12;17(28). pii: 20221.

Japanese encephalitis virus RNA detected in Culex pipiens mosquitoes in Italy.

Ravanini P, Huhtamo E, Ilaria V, Crobu MG, Nicosia AM, Servino L, Rivasi F, Allegrini S, Miglio U, Magri A, Minisini R, Vapalahti O, Boldorini R.

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Comment in

Euro Surveill. 2012;17(32). pii: 20242.

Euro Surveill. 2012;17(35). pii: 20257.

Mosquitoes collected in northern Italy were screened for flavivirus RNA. Positive amplicons were sequenced and found most similar to insect flavivirus (ISF), Usutu virus (USUV) and surprisingly also to Japanese encephalitis virus (JEV). The sequence (167 bp), obtained from one pool of *Culex pipiens*, was found identical to JEV strains from bats in China. Unfortunately additional sequence data or virus isolations were not obtained in this study. Confirmation of potential introduction of JEV to Italy and other European countries is urgently needed.

PMID: 22835438 [PubMed - indexed for MEDLINE]

9. Pathol Res Pract. 2012 Jun 15;208(6):356-9. doi: 10.1016/j.prp.2012.03.005. Epub 2012 Apr 19.

Extra-osseous Ewing sarcoma of the thyroid gland mimicking lymphoma recurrence: a case report.

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Extra-osseous Ewing sarcomas/peripheral primitive neuroectodermal tumors (EOES/pPNETs) are high-grade malignant tumors found in various organs, such as the lung, skin, intestine, kidney and female genital tract; however, to the best of our knowledge, only two cases have previously been identified in the thyroid gland. We describe a case of primary EOES/PNET of the thyroid gland in a 66-year-old man with a previous history of large B cell lymphoma. During a routine follow-up examination, the patient underwent an ultrasound cervical scan showing a solid nodule of the left thyroid lobe. The fine-needle aspiration biopsy of the nodule suggested a neuroendocrine tumor. Histological and immunohistochemical examination of the surgical specimen supported a diagnosis of EOES/PNET, which was further confirmed by the demonstration of EWSR1 gene translocation by means of fluorescent in situ hybridization and by the detection of glycogen particles and neurosecretory granules by means of electron

microscopy. Total body computed tomography and magnetic resonance imaging excluded the involvement of other sites, and therefore a diagnosis of primary EOES/PNET of the thyroid gland was made. This paper also discusses the main differential diagnoses, including lymphoma recurrence, other small round cell tumors (primary or metastatic), and a thyroid localization of an EWS/PNET from another organ.

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PMID: 22520405 [PubMed - indexed for MEDLINE]

10. Eur J Intern Med. 2012 Apr;23(3):e78-80. doi: 10.1016/j.ejim.2011.11.014. Epub 2011 Dec 15.

Pseudo-myelofibrosis: a new clinical entity.

Bartoli E, Sola D, Sainaghi PP, Rossi L, Boldorini R.

PMID: 22385894 [PubMed - indexed for MEDLINE]

11. Endocrine. 2012 Oct;42(2):382-90.

Clinical-pathological changes in differentiated thyroid cancer (DTC) over time (1997-2010): data from the University Hospital "Maggiore della Carità" in Novara.

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Comment in

Endocrine. 2012 Oct;42(2):229-30.

Differentiated thyroid cancer (DTC) is an important clinical entity in our population (Novara, Piedmont, Italy) which is characterized by important environmental influences, as iodine deficiency (ID) and subsequent supplementation, thyroiditis and occupational exposure. To evaluate the features of DTC in our population 20 years after the iodine-prophylaxis pondering the effects of the introduction of the new guidelines for diagnosis and management of DTC after 2005. 322 patients [244 females, age: mean (\pm SD) 53.8 \pm 15.8 years] treated for DTC in a tertiary care center between 1997 and 2010 were retrospectively evaluated. Medical history, demographics, and pathological features were considered. Patients were subdivided into two groups: A (n = 139, diagnosis 1997–2005) and B (n = 183, diagnosis 2006–2010). The population of group A showed a mild ID, while normal iodine status was recorded in group B. A significant increase in histological tumor-associated thyroiditis was found from group A to B (p = 0.021). Recurrent or persistent diseases were found to be correlated with lymph nodes metastases and/or a distant disease at diagnosis,

stimulated thyroglobulin levels at the first follow-up and an additional radioiodine therapy. Twenty percent of our patients were females employed in textile industries. The tumor-related inflammation and the occupational exposure should be considered as important factors in the pathogenesis of DTC. Further studies are required in order to confirm our findings.

PMID: 22315013 [PubMed - in process]

12. Eur J Gastroenterol Hepatol. 2011 Nov;23(12):1178-84. doi: 10.1097/MEG.0b013e328349923c.

A case-control histological study on the effects of phlebotomy in patients with chronic hepatitis C.

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OBJECTIVE: The aim of this study was to assess the actual effectiveness of long-term phlebotomy by comparing histological improvement (HI) in 69 Caucasian HCV-RNA-positive CHC patients undergoing phlebotomy or receiving an interferon-based therapy without virological response [nonresponders to interferon therapy (IBT-NR)].

METHODS: HI was defined by at least one point reduction of the staging score or, in the case of unchanged stage, by at least two points reduction of the grading score (Knodel's Activity Index) and was retrospectively evaluated by comparing two consecutive (56 ± 28 months apart) liver biopsies from 30 phlebotomized and 39 IBT-NR patients.

RESULTS: HI was observed in 15 of 30 (50%) patients treated with phlebotomy and in six of 39 (15%) IBT-NR subjects ($P=0.002$). Furthermore, AST, ALT, and GGT serum levels were significantly reduced only in phlebotomized patients ($P \leq 0.003$) at the time of the second biopsy. Univariate and multivariate analysis showed that histological grading score before therapy ($P=0.001$) and phlebotomy ($P=0.002$) were independently predictors of HI.

CONCLUSION: HI induced by long-term phlebotomy effectively exceeds that spontaneously occurring in patients IBT-NR confirming the efficacy of iron depletion in attenuating CHC progression when other therapies have failed.

PMID: 22002003 [PubMed - indexed for MEDLINE]

13. J Pharmacol Exp Ther. 2011 Sep;338(3):829-40. doi: 10.1124/jpet.111.184630. Epub 2011 Jun 17.

Reciprocal potentiation of the antitumoral activities of FK866, an inhibitor of nicotinamide phosphoribosyltransferase, and etoposide or cisplatin in neuroblastoma cells.

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NAD is an essential coenzyme involved in numerous metabolic pathways. Its principal role is in redox reactions, and as such it is not heavily "consumed" by cells. Yet a number of signaling pathways that bring about its consumption have recently emerged. This has brought about the hypothesis that the enzymes that lead to its biosynthesis may be targets for anticancer therapy. In particular, inhibition of the enzyme nicotinamide phosphoribosyl transferase has been shown to be an effective treatment in a number of preclinical studies, and two lead molecules [N-[4-(1-benzoyl-4-piperidinyl)butyl]-3-(3-pyridinyl)-2E-propenamide (FK866) and (E)-1-[6-(4-chlorophenoxy)hexyl]-2-cyano-3-(pyridin-4-yl)guanidine (CHS 828)] have now entered preclinical trials. Yet, the full potential of these drugs is still unclear. In the present study we have investigated the role of FK866 in neuroblastoma cell lines. We now confirm that FK866 alone in neuroblastoma cells induces autophagy, and its effects are potentiated by chloroquine and antagonized by 3-methyladenine or by down-regulating autophagy-related protein 7. Autophagy, in this model, seems to be crucial for FK866-induced cell death. On the other hand, a striking potentiation of the effects of cisplatin and etoposide is given by cotreatment of cells with ineffective concentrations of FK866 (1 nM). The effect of etoposide on DNA damage is potentiated by FK866 treatment, whereas the effect of FK866 on cytosolic NAD depletion is potentiated by etoposide. Even more strikingly, cotreatment with etoposide/cisplatin and FK866 unmasks an effect on mitochondrial NAD depletion.

PMID: 21685314 [PubMed - indexed for MEDLINE]

14. Clin Cancer Res. 2011 Jul 15;17(14):4901-14. doi: 10.1158/1078-0432.CCR-10-3137. Epub 2011 Jun 1.

Increased detection sensitivity for KRAS mutations enhances the prediction of anti-EGFR monoclonal antibody resistance in metastatic colorectal cancer.

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PURPOSE: KRAS mutations represent the main cause of resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs) in metastatic colorectal cancer (mCRC). We evaluated whether highly sensitive methods for KRAS investigation improve the accuracy of predictions of anti-EGFR MoAbs efficacy. **EXPERIMENTAL DESIGN:** We retrospectively evaluated objective tumor responses in mCRC patients treated with cetuximab or panitumumab. KRAS codons 12 and 13 were examined by direct sequencing, MALDI-TOF MS, mutant-enriched PCR, and engineered

mutant-enriched PCR, which have a sensitivity of 20%, 10%, 0.1%, and 0.1%, respectively. In addition, we analyzed KRAS codon 61, BRAF, and PIK3CA by direct sequencing and PTEN expression by immunohistochemistry.

RESULTS: In total, 111 patients were considered. Direct sequencing revealed mutations in codons 12 and 13 of KRAS in 43/111 patients (39%) and BRAF mutations in 9/111 (8%), with almost all of these occurring in nonresponder patients. Using highly sensitive methods, we identified up to 13 additional KRAS mutations compared with direct sequencing, all occurring in nonresponders. By analyzing PIK3CA and PTEN, we found that of these 13 patients, 7 did not show any additional alteration in the PI3K pathway.

CONCLUSIONS: The application of highly sensitive methods for the detection of KRAS mutations significantly improves the identification of mCRC patients resistant to anti-EGFR MoAbs.

PMID: 21632860 [PubMed - indexed for MEDLINE]

15. Clin Endocrinol (Oxf). 2011 Oct;75(4):528-34. doi: 10.1111/j.1365-2265.2011.04107.x.

Thyroid incidentaloma identified by ¹⁸F-fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT): clinical and pathological relevance.

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OBJECTIVE: The percentage of patients with thyroid cancer incidentally diagnosed during a (18) F-fluorodeoxyglucose Positron Emission Tomography with computed tomography (CT) (FDG-PET/CT) for nonthyroid diseases ranges between 26% and 50%.

DESIGN: Retrospective assessment of the clinical and pathological features of thyroid incidentalomas at FDG-PET/CT, aiming to identify potential predictors of malignancy.

PATIENTS: Fifty-two patients with incidental thyroid uptake at FDG-PET/CT were retrospectively included [38 W, age 64.1 ± 12.5 years (mean ± SD)]. An arbitrary cut-off level of 5.0 for the 'maximum standardized uptake value' (SUV max) was chosen to differentiate benign from malignant tumours. Complete thyroid function, neck ultrasonography (US) features, and cyto-histological results were reported for all cases.

RESULTS: In our institution, the prevalence of incidental thyroid (18) F-fluorodeoxyglucose ((18) F-FDG) uptake was nearly 1.76%. The prevalence of focal uptake correlated with greater risk of malignancy (P < 0.01). In particular, the euthyroidism (P < 0.003) and a SUV max >5.0 (P < 0.0001) were associated with the diagnosis of thyroid cancer. Diffusely increased FDG-PET/CT uptake in the thyroid was related to benign conditions.

CONCLUSIONS: The presence of focal uptake with high SUV max and euthyroidism correlate with high likelihood of malignancy. Performing a neck US would have to be recommended in all patients with euthyroidism and an incidental FDG-PET/CT focal thyroid uptake. We do not suggest to use FDG-PET/CT as a screening tool for

thyroid cancer in the general population, because of both its high cost and low incidence of thyroid incidentaloma at FDG-PET/CT.

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PMID: 21575027 [PubMed - indexed for MEDLINE]

16. Pathology. 2011 Jun;43(4):335-9. doi: 10.1097/PAT.0b013e32834642c0.

Fluorescence in situ hybridisation in the cytological diagnosis of pancreatobiliary tumours.

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AIMS: To assess the sensitivity, specificity, positive and negative predictive values of fluorescence in situ hybridisation (FISH) and conventional cytology in identifying bile duct stricture malignancies.

METHODS: Brushing samples were collected from 64 patients by means of endoscopic retrograde cholangiopancreatography, and assessed cytologically and by means of a multi-probe FISH set. The cytological diagnoses were: positive, negative and suspicious, whereas criteria for FISH positivity were: more than five polysomic cells or more than 10 trisomic cells for chromosomes 3 or 7.

RESULTS: Forty-eight of the 64 patients showed histological or clinical signs of malignancy. The sensitivity of cytology was high (77%) if suspicious cases were considered positive, but was significantly lower than that of FISH if suspicious cases were considered negative (58% versus 90%; $p < 0.05$). The specificity of cytology was 81% (positive and suspicious) or 100% (negative and suspicious), and the specificity of FISH was 94% ($p = 1$). FISH yielded one false negative result (isolated chromosome 7 trisomy). FISH allowed a definite diagnosis of 9/12 cytologically inconclusive cases.

CONCLUSIONS: Our findings suggest using FISH in the case of bile duct strictures cytologically negative or inconclusive; a FISH diagnosis of malignancy should only be made in the presence of polysomic pattern.

PMID: 21519286 [PubMed - indexed for MEDLINE]

17. J Gen Virol. 2011 May;92(Pt 5):1044-50. doi: 10.1099/vir.0.028571-0. Epub 2011 Feb 9.

Serological evidence of vertical transmission of JC and BK polyomaviruses in humans.

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Vertical transmission of JC virus and BK virus has been investigated by few authors, with conflicting results. We performed a combined serological and genomic study of 19 unselected pregnant women and their newborns. Blood and urine samples were collected during each gestational trimester from the pregnant women. Umbilical cord blood, peripheral blood, urine and nasopharyngeal secretion samples were taken from newborns at delivery and after 1 week and 1 month of life. Polyomavirus DNA was detected by nested PCR. Polyomavirus IgG-, IgM- and IgA-specific antibodies were measured in maternal and newborn serum samples using a virus-like-particle-based ELISA method. BKV and JCV DNA were detected in urine from 4 (21%) and 5 (26%) women, respectively. BKV and JCV seroprevalences in the pregnant women were 84% and 42%, respectively. Using a rise in the IgG level or the transient appearance of an IgA or IgM response as evidence of infection in the newborn, we detected BKV and JCV infections in four (21%) and three (16%) newborns, respectively. Three infants had serological evidence of infection with both BKV and JCV. In two of the four possible BKV-infected newborns, the mothers seroconverted during pregnancy, while another mother was viruric and IgA seropositive. The mother of one of the three possible JCV-infected newborns was viruric and IgA seropositive; another mother was viruric. These results suggest JC virus and BK virus can be transmitted from mother to newborn during pregnancy or soon after birth.

PMID: 21307224 [PubMed - indexed for MEDLINE]

18. Arch Pathol Lab Med. 2010 Dec;134(12):1818-22. doi: 10.1043/2009-0551-OAR1.1.

Reliability and reproducibility of the edmondson grading of hepatocellular carcinoma using paired core biopsy and surgical resection specimens.

Pirisi M, Leutner M, Pinato DJ, Avellini C, Carsana L, Toniutto P, Fabris C, Boldorini R.

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CONTEXT: It has been claimed that the Edmondson and Steiner grading system (EGS) values should be obtained preoperatively to select patients with hepatocellular carcinoma for liver transplantation. However, EGS reliability in biopsy specimens has been questioned.

OBJECTIVE: To verify the reliability of the EGS using core biopsy specimens and its reproducibility among pathologists.

DESIGN: Paired biopsy and surgical specimens obtained from 40 patients (subset 1) were retrieved by means of computer-aided search of the pathology records and blindly and independently reviewed. The EGS interrater agreement was measured using κ statistics. After having held a consensus meeting, pathologists graded an additional 21 paired hepatocellular carcinoma specimens (subset 2).

RESULTS: Analyzing subset 1, pathologists gave significantly lower EGS grades to the biopsy specimens ($P < .001$), for which the observed agreement was 32.5% ($\kappa = 0.021$), which increased to 82.5% ($\kappa = 0.186$) if only 2 categories were considered (low grade, EGS I-II; high grade, EGS III-IV). The observed agreement in the case of the surgical specimens was 52.5% ($\kappa = 0.199$), which increased to 62.5% ($\kappa = 0.275$) when the low- and high-grade scores were merged. The observed agreement between the assessments of paired biopsy and surgical specimens was 50.0% for pathologist 1 ($\kappa = 0.057$) and 35.0% for pathologist 2 ($\kappa = 0.078$). Merging the EGS grades did not improve the strength of the agreement. Analyzing subset 2 (after the consensus meeting), the observed agreement between pathologists improved more on biopsies (76.2%, $\kappa = 0.614$) than on surgical specimens (61.9%, $\kappa = 0.434$).

CONCLUSIONS: The EGS is easily underestimated in core biopsy specimens, and interrater disagreement between pathologists can be significant unless consensus meetings are held.

PMID: 21128781 [PubMed - indexed for MEDLINE]

19. J Med Virol. 2010 Dec;82(12):2127-32. doi: 10.1002/jmv.21923.

BK virus sequences in specimens from aborted fetuses.

Boldorini R, Allegrini S, Miglio U, Nestasio I, Paganotti A, Veggiani C, Monga G, Pietropaolo V.

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Given the conflicting results of the few published studies, the aim of this retrospective molecular-based study of 10 aborted fetuses that underwent complete autopsy and 10 placentas was carried out to determine whether BK polyomavirus (BKV) can be transmitted transplacentally. The interruption of pregnancy was due to a miscarriage (five cases) or a prenatal diagnosis of severe intrauterine malformations (five cases). Samples from the brain, heart, lung, thymus, liver, and kidney were taken from each fetus, and two samples were obtained from all of the placentas. The presence of BKV was investigated by means of PCR using primers specific for the transcription control region (TCR) and viral capsidic protein 1 (VP1) and DNA extracted from formalin-fixed, paraffin-embedded tissue. BKV genome was detected in 22 of 60 samples (36.6%) from seven fetuses (70%), regardless of the cause of abortion: VP1 was amplified in 12 samples (54%), TCR in seven (32%), and both in three (14%). VP1 was also detected in one placental sample. BKV sequences were most frequently detected in heart and lung (five cases), but sequence analyses of TCR and VP1 revealed a high degree of genomic variability among the samples taken from different organs and the placenta. These results indicate that BKV can cross the placenta during pregnancy and become latent in fetal organs other than the kidney and brain (previously considered the main targets of BKV latency). This may happen in early pregnancy and does not seem to

be associated with an increased risk of abortion.

PMID: 20981804 [PubMed - indexed for MEDLINE]

20. Acta Cytol. 2010 May-Jun;54(3):311-3.

Peritoneal psammocarcinoma diagnosed by a Papanicolau smear: a case report.

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BACKGROUND: Serous psammocarcinoma is a rare variant of epithelial neoplasia that can arise from the ovaries or peritoneum. It is characterized by massive psammoma body formation, invasiveness and low grade cytologic features.

CASE: A 70-year-old woman was admitted to our hospital; a bimanual examination with cervicovaginal smear was performed. The smears revealed neoplastic cells with psammoma bodies; afterward, endocervical curettage revealed microaggregates of epithelial neoplastic cells with psammoma bodies. Computed tomography of the abdomen showed a diffuse peritoneal carcinosis with left ovarian calcification. An exploratory laparotomy was carried out. Final pathologic findings showed peritoneal serous psammocarcinoma with ovarian implants.

CONCLUSION: Our report suggests that a Pap smear can play a role in the detection of peritoneal psammocarcinoma and underlines the significance of psammoma bodies as a cytologic marker of this rare tumor.

PMID: 20518416 [PubMed - indexed for MEDLINE]

21. World J Gastroenterol. 2010 Feb 7;16(5):596-602.

Phlebotomy improves histology in chronic hepatitis C males with mild iron overload.

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AIM: To investigate the usefulness of mild iron depletion and the factors predictive for histological improvement following phlebotomy in Caucasians with chronic hepatitis C (CHC).

METHODS: We investigated 28 CHC Caucasians with persistently elevated serum aminotransferase levels and non responders to, or unsuitable for, antiviral therapy who underwent mild iron depletion (ferritin \leq 70 ng/mL) by long-term phlebotomy. Histological improvement, as defined by at least one point reduction in the staging score or, in case of unchanged stage, as at least two points reduction in the grading score (Knodell), was evaluated in two subsequent liver

biopsies (before and at the end of phlebotomy, 48 +/- 16 mo apart).

RESULTS: Phlebotomy showed an excellent safety profile. Histological improvement occurred in 12/28 phlebotomized patients. Only males responded to phlebotomy. At univariate logistic analysis alcohol intake ($P = 0.034$), high histological grading ($P = 0.01$) and high hepatic iron concentration (HIC) ($P = 0.04$) before treatment were associated with histological improvement. Multivariate logistic analysis showed that in males high HIC was the only predictor of histological improvement following phlebotomy (OR = 1.41, 95% CI: 1.03-1.94, $P = 0.031$). Accordingly, 12 out of 17 (70%) patients with HIC ≥ 20 micromol/g showed histological improvements at the second biopsy.

CONCLUSION: Male CHC Caucasian non-responders to antiviral therapy with low-grade iron overload can benefit from mild iron depletion by long-term phlebotomy.

PMCID: PMC2816272

PMID: 20128028 [PubMed - indexed for MEDLINE]

22. Arch Gynecol Obstet. 2010 Aug;282(2):193-7. doi: 10.1007/s00404-009-1316-5. Epub 2009 Dec 12.

Role of HPV testing in the follow-up of women treated for cervical dysplasia.

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PURPOSE: The aim of study was to investigate factors predicting persistence or relapse of disease after cervical conisation for high-grade squamous intraepithelial lesions (CIN 2 or 3).

METHODS: The study involved 78 women with high-grade squamous intraepithelial lesions, conservatively treated with loop electroexcision procedure for cervical conisation and subsequent with CO(2) laser-vaporisation of the cervical bed. Histological specimens were totally included and examined by an experienced pathologist. To evaluate the efficacy of treatment, the patients were examined with colposcopy and Pap smear 4 months after surgery and with PCR to search for and genotyping of HPV, 10 months after treatment.

RESULTS: During the post-treatment follow-up, the cytologic examination showed persistent/relapsing disease in six patients (7.6%). In only 1 case, the deep margin of the cone was considered positive for CIN (16%). Ten months after treatment, viral typing revealed the persistence of high-risk HPV in all of these patients. Conversely, the viral follow-up of the other 72 patients without persisting/relapsing disease after treatment disclosed low-risk HPV genotypes in 6 cases, high-risk HPV in 2 cases (2.7%), whereas 7 cases had positive margins for CIN (9.7%). The risk of persistence and relapse of CIN in the group with positive margins was not statistically significant ($P = 0.87$), whereas it was in the group with HR-HPV positive ($P = 0.000048$).

CONCLUSION: HPV testing is the most sensitive mean of identifying persistence or relapse early and is therefore capable of optimising follow-up after the treatment of high-grade CIN.

PMID: 20012636 [PubMed - indexed for MEDLINE]

23. J Med Virol. 2010 Jan;82(1):138-45. doi: 10.1002/jmv.21558.

Viral infection in bone marrow transplants: is JC virus involved?

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Hemorrhagic cystitis is characterized by hematuria due to inflammation of the bladder. In bone marrow transplants, this disease is linked to the infection by human polyomavirus BK, whereas the role of the human polyomavirus JC is unclear. The transcriptional control regions of both viruses contain important cellular transcription factor binding sites that undergo rearrangement process generating suitable variants that could be more active for viral replication and for the onset of hemorrhagic cystitis. In this study urine obtained from seven patients with bone marrow transplant were examined. Polyomavirus genomes were quantified by PCR and viral loads were compared. The transcriptional regions of both viruses were amplified and sequenced to determine the presence of variants. Subtypes of polyomaviruses were determined by amplification and sequencing of the viral protein 1 region. The results showed that four of seven patients were positive for BK DNA, two of seven patients had BK and JC DNA and one of seven had JC DNA. Positive samples were amplified and sequenced successively for transcriptional regions. The viral archetype was always found in both viruses. Finally, typing showed that BK virus subtype I infected patients with BK, whereas JC virus genotype IA and genotype 1B were found in patients infected with JC. The data suggest that new and different approaches are required to improve the morbidity and mortality caused by polyoma-associated hemorrhagic cystitis, since it known that BK virus is involved in the onset of hemorrhagic cystitis, whereas the role of JC virus should be investigated further.

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PMID: 19950244 [PubMed - indexed for MEDLINE]

24. J Cell Physiol. 2010 Jan;222(1):195-9. doi: 10.1002/jcp.21937.

Mutations in the external loops of BK virus VP1 and urine viral load in renal transplant recipients.

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Polyomavirus-associated nephropathy (PVAN) is a major complication that occurs

after renal transplantation and is induced by reactivation of the human polyomavirus BK (BKV). The structure of the viral capsid protein 1 (VP1) is characterized by the presence of external loops, BC, DE, EF, GH, and HI, which are involved in receptor binding. The pathogenesis of PVAN is not well understood, but viral risk factors are thought to play a crucial role in the onset of this pathology. In an attempt to better understand PVAN pathogenesis, the BKV-VP1 coding region was amplified, cloned, and sequenced from the urine of kidney transplant recipients who did, and did not, develop the pathology. Urine viral loads were determined by using real time quantitative PCR (Q-PCR). Amino acid substitutions were detected in 6/8 patients, and 6/7 controls. The BC and EF loop regions were most frequently affected by mutations, while no mutations were found within the GH and HI loops of both patients and controls. Some mutations, that were exclusively detected in the urine of PVAN patients, overlapped with previously reported mutations, although a correlation between changes in amino acids and the development of PVAN was not found. Urine viral loads were higher than that of the proposed cut-off loads for identification of patients that are at a high risk of developing PVAN (10(7) copies/ml), both in the PVAN and control groups, thus confirming that urine viral load is not a useful predictive marker for the development of PVAN.

PMCID: PMC2783606

PMID: 19780025 [PubMed - indexed for MEDLINE]

25. Pathol Res Pract. 2010 Jul 15;206(7):476-9. doi: 10.1016/j.prp.2009.07.006. Epub 2009 Aug 4.

Primary vulvar Ewing's sarcoma/primitive neuroectodermal tumor in a post-menopausal woman: a case report.

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Ewing's sarcomas/peripheral primitive neuroectodermal tumors (ES/pPNETs) are high-grade malignant neoplasms rarely found outside the skeletal system. Only 12 cases of vulvar ES/pPNET have so far been reported, all involving children or women of child-bearing age. We describe the case of a 52-year-old woman who was admitted to our hospital for the local excision of a 4cm vulvar mass, originally thought to be a Bartholin's gland cyst. It was subsequently found to consist of small round cells positive for anti-CD99 antibody, thus suggesting a diagnosis of ES/pPNET. The demonstration of EWSR1 gene translocations by means of fluorescent in situ hybridization excluded small-cell carcinoma, squamous cell carcinoma of the small type, Merkel cell carcinoma, and lymphoblastic lymphoma. After surgery, the patient received six cycles of polychemotherapy and radiotherapy; she is still alive and well after 1 year of follow-up. Our findings underline the crucial role of molecular biology techniques in the differential diagnosis of small round cell tumors in these unusual locations.

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PMID: 19656640 [PubMed - indexed for MEDLINE]

26. J Med Virol. 2009 Aug;81(8):1385-93. doi: 10.1002/jmv.21520.

Genomic mutations of viral protein 1 and BK virus nephropathy in kidney transplant recipients.

Boldorini R, Allegrini S, Miglio U, Paganotti A, Veggiani C, Mischitelli M, Monga G, Pietropaolo V.

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Genomic variability in the viral protein 1 region of BK polyomavirus (BKV) may change the ability of the virus to replicate. The significance of such changes was studied in clinical samples taken from kidney transplant patients with and without BKV nephropathy. A 94 base-pair fragment of viral protein 1 was amplified from 68 urine, 28 blood, and 12 renal biopsy samples from eight patients with BKV nephropathy, and from 100 urine samples, 17 blood and three renal biopsy samples from 41 of 218 controls. The DNA was sequenced and the amino acid changes were predicted by the Expert Protein Analysis System program (ExPASy, Swiss Institute of Bioinformatics, Geneva, Switzerland). Single base-pair mutations were detected more frequently in the samples from the BKV nephropathy patients than in the controls, and this was the only statistically significant finding of the study ($P < 0.05$), thus suggesting a greater genetic instability in BKV nephropathy associated strains. The amino acid changes were distributed at random in both BKV nephropathy patients and controls. However, one aspartic acid-to-asparagine substitution at residue 75 was detected in all samples of the one patient with BKV-associated nephropathy, who developed disease progression confirmed by histology, and not in any of the other patient or control samples. Whether this specific amino acid change plays a role in disease deserves further study.

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PMID: 19551827 [PubMed - indexed for MEDLINE]

27. Arch Pathol Lab Med. 2009 May;133(5):766-74. doi: 10.1043/1543-2165-133.5.766.

Detection, distribution, and pathologic significance of BK virus strains isolated from patients with kidney transplants, with and without polyomavirus-associated nephropathy.

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CONTEXT: BK virus strains or regulatory region sequence variations may play a

role in the pathogenesis of polyomavirus-associated nephropathy (PVAN), although no definite relationship has yet been demonstrated.

OBJECTIVE: To investigate the pathologic significance of BK virus strains and regulatory region sequence variations.

DESIGN: Eight (3.5%) of 226 patients with renal transplants developed PVAN; the remaining 218 cases were used as controls. From the patients who developed PVAN, 70 urine samples, 63 blood samples, and 17 renal biopsy samples were taken, and 682 urine samples, 677 blood samples, and 101 renal biopsy samples were taken from the control cases. Amplification and sequence analyses of regulatory region were obtained, and the sequences were analyzed using the Basic Local Alignment Search Tool program.

RESULTS: The WWT strain was more frequently detected in PVAN cases than in the control cases (urine: 88.5% vs 22.1%; blood: 85.2% vs 40%; renal biopsies: 77.8% vs 0%), and the AS and WW strains were only isolated from controls. Strain 128-1 was frequently associated with JC virus coinfection in both groups (PVAN: 78.3%; controls: 98%). Major WWT rearrangements were detected in 29.6% of the urine samples, 30.4% of the blood samples, and one renal biopsy from the PVAN cases, but in only one urine sample from the controls. Insertion of 8 base pairs (P block) was found in all 128-1 strains; WW and AS were archetypal in 78.9% and 57.7% of the samples, respectively.

CONCLUSIONS: Although the study included only 8 PVAN cases, regulatory region sequence variations seem to be frequent and independent of the development of the disease, and the WWT strain seems more frequently related to the development of nephropathy than other strains.

PMID: 19415951 [PubMed - indexed for MEDLINE]

28. *Helicobacter*. 2008 Dec;13(6):557-63. doi: 10.1111/j.1523-5378.2008.00642.x.

Clarithromycin resistance of *Helicobacter pylori* strains isolated from children' gastric antrum and fundus as assessed by fluorescent in-situ hybridization and culture on four-sector agar plates.

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AIM: To assess validity of culture on four-sector agar plates and fluorescent in-situ hybridization (FISH) test, and clarithromycin resistance rate in *Helicobacter pylori* strains isolated from children in the last 10 years.

METHODS: In the last 5 years, gastric biopsy specimens from antrum and fundus were taken from 89 consecutive children (median age 9 years) with *H. pylori* gastritis and from 21 controls. Culture was performed on 176 gastric biopsies (89 from antrum, 87 from fundus) on four-sector agar plates, and FISH test with DNA ProbeMix. After its validity was evaluated, FISH test was applied on additional 119 biopsies from 68 children (68 from the antrum, 51 from the fundus) stored in the Pathology archive in the previous 5 years.

RESULTS: Culture was positive in 157 of 176 biopsies (sensitivity: 89.2%, 95% confidence interval (CI) 85-94). In 33 of 89 children (37%) resistant strains

were found in one or both gastric sites. FISH test was positive in 148 of 176 biopsies from infected children (sensitivity 84.1%, 95% CI 79-89) and in none of 42 biopsies from controls (specificity 100%). When applied on archive biopsies, FISH test was positive in 96 of 119 (80.7%, 95% CI 74-88). Total children harboring resistant strains in the last 10 years, as assessed by FISH test, were 66 of 157 (42%). Mixed infection with both sensitive and resistant strains were found in 40 children (25%) and in 12 of them resistant strains were in the fundus only.

CONCLUSIONS: Culture on four-sector agar plates and FISH test had a high sensitivity and specificity and showed co-presence of sensitive and resistant strains. In one-third of children with mixed infection, the resistant strains were in the fundus only. Clarithromycin resistance should be assessed in biopsies both from the antrum and the fundus, utilizing antral biopsies only can underestimate its prevalence.

PMID: 19166422 [PubMed - indexed for MEDLINE]

29. J Neurosurg Spine. 2009 Jan;10(1):51-3. doi: 10.3171/2008.10.SPI08277.

Primary choroid plexus papilloma of the sacral nerve roots.

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The authors describe a unique case of a choroid plexus papilloma of the sacral nerve roots. This 60-year-old woman was admitted to the hospital because of a 1-year history of sacral pain, rectal and urinary bladder retention, and paradoxical episodic incontinence. Physical examination revealed sensory abnormalities in the S-2 dermatomes and poor rectal and bladder sphincter contractions. Contrast-enhanced spinal MR imaging showed a well-circumscribed, ovoid, homogeneously enhancing mass at the S1-2 level suggesting a diagnosis of ependymoma or schwannoma, and surgery allowed the identification and complete removal of a soft gray mass intimately adhering to the sacral nerve roots.

Histological examination revealed a tumor consisting of papillary structures lined by a single layer of columnar cells, with an immunophenotype that satisfied the diagnostic criteria of choroid plexus papilloma. After diagnosis, contrast-enhanced brain MR imaging excluded the presence of a primary choroid plexus papilloma in the cerebral ventricles, thus ruling out a drop metastasis along the CSF pathways. A review of the literature did not reveal any similar cases of choroid plexus papilloma, and so the authors also discuss the inclusion of primary or metastatic papillary tumors in this unusual location as part of the differential diagnosis.

PMID: 19119933 [PubMed - indexed for MEDLINE]

30. J Med Virol. 2008 Dec;80(12):2147-52. doi: 10.1002/jmv.21313.

Presence and expression of JCV early gene large T Antigen in the brains of immunocompromised and immunocompetent individuals.

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JC virus (JCV) is a polyomavirus that asymptotically infects up to 80% of the worldwide human population and establishes latency in the kidney. In the case of host immunodeficiency, it can cause progressive multifocal leukoencephalopathy (PML), which is a fatal demyelinating disease of the central nervous system. In an attempt to understand better PML pathogenesis and JCV infection, the presence of the JCV genome and expression of the early viral protein in the brain of deceased individuals, with and without HIV infection, was investigated. Sixty autopsy samples of brain tissues were collected from 15 HIV-positive PML patients, 15 HIV-positive patients with other neurological diseases, 15 HIV-positive patients without neurological disorders, and 15 HIV-negative individuals who died from diseases unrelated to the central nervous system. By means of specific Real Time Polymerase Chain Reaction, the JCV genome was detected in 14 of 15 PML brains, three of 15 HIV-positive brains (with and without neurological diseases), and 1 of 15 HIV-negative brains. JCV genotyping was also performed. Expression of the early JCV protein T Antigen was verified by a specific immunohistochemistry assay, and it was found in the brain tissues from 12 PML cases and one case with other neurological disease. The data obtained demonstrate that infection of the brain with JCV can also be observed in the brains of HIV-negative individuals, without neurological disorders. However, viral protein expression was limited to PML brains and to one brain from a patient with other neurological disease, suggesting that JCV can also be present in the brains of patients without PML.

PMCID: PMC2597165

PMID: 19040292 [PubMed - indexed for MEDLINE]

31. Virol J. 2008 Mar 3;5:38. doi: 10.1186/1743-422X-5-38.

Complications post renal transplantation: literature focus on BK virus nephropathy and diagnostic tools actually available.

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Clinical diagnosis of kidney transplants related illnesses is not a simple task. Several studies were conducted to define diseases and complications after renal transplantation, but there are no comprehensive guidelines about diagnostic tools for their prevention and detection. The Authors of this review looked for the

medical literature and pertinent publications in particular to understand the role of Human Polyomavirus BK (BKV) in renal failure and to recognize analytical techniques for BK virus associated nephropathy (BKVAN) detection.

PMCID: PMC2268664

PMID: 18315864 [PubMed - indexed for MEDLINE]

32. Pathology. 2008 Jan;40(1):72-7.

Latent human polyomavirus infection in pregnancy: investigation of possible transplacental transmission.

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AIMS: The purpose of the study was to investigate the transplacental transmission of the human polyomaviruses JCV and BKV.

METHODS: Urine and blood samples from 300 pregnant women underwent cytological analysis to search for 'decoy cells', nested PCR to identify presence and genotype of isolated polyomaviruses, and sequence analysis of the transcription control region. Nested PCR was also used to study the umbilical cord blood of all their newborns.

RESULTS: Decoy cells were identified in only one urine sample (1/300; 0.33%); polyomavirus DNA was detected in 80 urine samples (26.6%) corresponding to BKV alone in 28 samples (9.3%), JCV alone in 49 samples (16.3%) and both JCV-BKV in three samples (1%). Blood samples were positive in 17 cases (5.6%), corresponding to BKV alone in 10 (3.3%), and JCV alone in 7 (2.3%). Rearrangements of the transcription control region were found in only one urinary JCV strain, consisting of the insertion of 13 bp at D block, whereas point mutations were identified in 11 BKV and 11 JCV strains detected from urine. Sequence analysis of the BKV strains detected in blood samples revealed a 20 bp insertion of P block (P42-61) in human chromosomes 20 (five cases) and 14 (three cases); two JCV strains had single bp point mutations. The search for polyomavirus DNA in umbilical cord blood samples was always negative.

CONCLUSIONS: Polyomavirus DNA was frequently detected in pregnancy, whereas genomic rearrangements were rare, and no evidence of transplacental transmission of polyomavirus was obtained.

PMID: 18038319 [PubMed - indexed for MEDLINE]

33. J Pediatr Gastroenterol Nutr. 2007 Nov;45(5):611-4.

Clinical pattern of celiac disease is still changing.

Garampazzi A, Rapa A, Mura S, Capelli A, Valori A, Boldorini R, Oderda G.

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The clinical presentation of celiac disease in children changed in the last decades of the 20th century. To ascertain whether changes are still in progress, we analyzed symptoms at presentation and age at diagnosis in 307 children receiving diagnoses of celiac disease for the past 20 years. The prevalence of typical forms of celiac disease decreased in the past decade, particularly in the past 5 years (from 76% in 1987-1990 to 44%, $P < 0.0001$). Age at diagnosis (5.9 y, $P = 0.01$) and silent forms (10.6%, $P = 0.003$) have significantly increased in the past 5 years. Histological examination showed decreased subtotal and increased partial villous atrophy prevalence ($P = 0.02$).

PMID: 18030243 [PubMed - indexed for MEDLINE]

34. J Pediatr Gastroenterol Nutr. 2007 Sep;45(3):301-5.

Increased interleukin-10 in Helicobacter pylori infection could be involved in the mechanism protecting from allergy.

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BACKGROUND: A protective effect of *Helicobacter pylori* infection against allergic diseases has been reported. The increasing incidence of childhood allergy in developed countries may be a result of reduced stimulation of the immune system by early chronic infections, with the protective effect of gastrointestinal microbes being mediated by regulatory T lymphocytes and production of interleukin (IL)-10. To elucidate a possible mechanism involved in protecting against the development of atopy, we measured expression of IL-10 in gastric mucosa of children with *H pylori* gastritis.

PATIENTS AND METHODS: Gastric biopsies were performed during endoscopy in 48 children (median age, 9 years), 32 of whom had *H pylori* gastritis and 16 of whom served as controls. Interferon-gamma (IFN-gamma), interleukin-1beta (IL-1beta), and IL-10 were measured in tissue homogenate by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR). The amounts of IFN-gamma, IL-1beta, and IL-10 transcripts were quantified via competitive RT-PCR with use of dilution series of specific competitors.

RESULTS: Expression of IFN-gamma and IL-10 were significantly higher in *H pylori*-infected children. No direct correlation with age was found, but a further increase in IL-10 expression was found in *H pylori*-infected children older than 4 years, whereas in control subjects, IL-10 expression tended to be lower in older children. IL-1beta expression was similar in infected children and control subjects. In *H pylori*-infected children, the prevalence of allergy was significantly higher in children with lower cytokine expression in gastric mucosa.

CONCLUSIONS: In children, *H pylori*-induced inflammatory response is associated with development of cell-mediated immunity of T-helper 1 type, as demonstrated by increased IFN-gamma expression. The significantly increased expression of gastric

IL-10 in H pylori-infected children and its further increase in older children suggest that this chronic infection may influence IL-10 production even beyond the age of 4 years. H pylori may be one of the infections with the potential to modulate immune responses.

PMID: 17873741 [PubMed - indexed for MEDLINE]

35. Eur J Obstet Gynecol Reprod Biol. 2008 Oct;140(2):276-7. Epub 2007 Jun 8.

Fallopian tube torsion and hematosalpinx in a menopausal woman.

Fortina E, Riboni F, Leo L, Catinella A, Surico D, Boldorini R.

PMID: 17560708 [PubMed - indexed for MEDLINE]

36. Pathology. 2006 Dec;38(6):579-81.

Pure Sertoli cell tumour of the ovary with Meig's syndrome.

Boldorini R, Bozzola C, Ribaldone R, Tosoni A, Monga G.

PMID: 17393991 [PubMed - indexed for MEDLINE]

37. J Med Genet. 2007 Apr;44(4):257-63. Epub 2007 Jan 26.

Chromosome 11 segmental paternal isodisomy in amniocytes from two fetuses with omphalocele: new highlights on phenotype-genotype correlations in Beckwith-Wiedemann syndrome.

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BACKGROUND: The phenotypic variability in Beckwith-Wiedemann syndrome (BWS) reflects the genetic heterogeneity of the mechanism which by default leads to the deregulation of genes located at 11p15.5. Genotype-phenotype correlation studies have demonstrated an association between omphalocele and CDKN1C/p57 mutations or hypermethylation. Paternal uniparental disomy 11 (pUPD11) has been described only in the mosaic condition with both uniparental and biparental cell lines, and no association with omphalocele has been pointed out.

METHODS: Two cases are presented here, in which a paternal segmental UPD11 was detected by molecular investigation of amniotic fluid cell cultures after the presence of apparently isolated omphalocele was revealed in the fetuses by ultrasound scan. Further studies were performed on additional autoptic fetoplacental tissues to characterise the distribution of the uniparental cell line and to unmask any biparental lineage in order to document in more detail the

as yet unreported association between omphalocele and pUPD11.

RESULTS: Results on the UPD distribution profile showed that the abdominal organs have a predominant uniparental constitution. This condition could mimic the effect of CDKN1C/p57 inactivation, causing the omphalocele.

CONCLUSION: New genotype-phenotype correlations emerge from the investigated cases, suggesting that molecular analysis be extended to all cases with fetal omphalocele in order to establish the incidence of pUPD11 in complete BWS and in monosymptomatic/mild forms.

PMCID: PMC2598040

PMID: 17259293 [PubMed - indexed for MEDLINE]

38. J Magn Reson Imaging. 2007 Jan;25(1):200-7.

Shoulder MR arthrography: in vitro determination of optimal gadolinium dilution as a function of field strength.

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PURPOSE: To find the optimal contrast agent dilution to maximize signal intensity (SI), signal-to-noise ratio (SNR), and contrast-to-noise ratio (CNR) in shoulder MR arthrography using MR systems operating at different magnetic field strengths.

MATERIALS AND METHODS: Autoptic human glenohumeral ligaments were inserted in eight egg-shaped 20-mL phantoms filled with saline and gadolinium diethylenetriaminepentaacetic acid bismethylamide (Gd-DTPA-BMA) in different dilutions of 0.5, 1, 2, 2.5, 5, 12.5, 50 mmol/liter, to simulate the shoulder articular capsule. These phantoms were inserted inside two plastic 240-mL phantoms filled with water. MRI was performed on 0.2-, 0.5-, 1.0-, 1.5-, and 3.0-T MR systems using a three-dimensional gradient echo (GRE)-T1-weighted pulse sequence. SI, SNR, and CNR were determined.

RESULTS: Peak SI and SNR were found at 5 mmol/liter, with the exception of the 0.2-T scanner, where the maximum was at 2 mmol/liter. Peak CNR was observed at 1 mmol/liter for the 3-T scanner, at 2 mmol/liter for the 0.2- and 0.5-T scanners, and at 5 mmol/liter for the remaining scanners.

CONCLUSION: The optimal SI and SNR are provided by 5 mmol/liter contrast agent dilution. Peak CNR was found in a range between 1 and 5 mmol/liter dilutions, depending on the strength of the magnetic field.

PMID: 17152058 [PubMed - indexed for MEDLINE]

39. Arch Pathol Lab Med. 2006 Dec;130(12):1792-8.

Histopathology of gastric and duodenal Strongyloides stercoralis locations in fifteen immunocompromised subjects.

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CONTEXT: Strongyloidiasis is a worldwide parasitic infection affecting approximately 75 million people. In Italy, it was more prevalent in the past among rural populations of irrigated areas.

OBJECTIVE: To determine the histopathologic alterations of the gastric and duodenal mucosa associated with the presence of *Strongyloides stercoralis* parasites.

DESIGN: Fifteen cases of strongyloidiasis were observed in immunocompromised patients during a recent 6-year period in Italy. *S. stercoralis* was found histologically in gastric biopsies (10 cases), in a gastrectomy (1 case), and in duodenal biopsies (9 cases). In 5 cases the parasite was present both in gastric and duodenal biopsies. Four patients were affected by lymphoma, 2 by multiple myeloma, 2 by gastric carcinoma, 1 by chronic myeloid leukemia, 1 by sideroblastic anemia, 1 by colorectal adenocarcinoma, 1 by chronic idiopathic myelofibrosis, 1 by chronic gastritis, 1 by gastric ulcers, and 1 by rheumatoid arthritis in corticosteroid therapy. No patient was affected by human immunodeficiency virus infection. Strongyloidiasis was not clinically diagnosed.

RESULTS: Histologic examination revealed several sections of *S. stercoralis* larvae, many eggs, and some adult forms. All the parasites were located in the gastric and/or the duodenal crypts. Eosinophils infiltrating into the lamina propria were found in all cases; their intensity was correlated with the intensity of the infection.

CONCLUSIONS: Histologic diagnosis of strongyloidiasis must be taken into consideration when examining both gastric and duodenal biopsies in immunocompromised patients, to avoid the development of an overwhelming infection of the parasite, which is dangerous for the life of the patient.

PMID: 17149952 [PubMed - indexed for MEDLINE]

40. J Pediatr. 2006 Dec;149(6):817-21.

High accuracy of noninvasive tests to diagnose *Helicobacter pylori* infection in very young children.

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OBJECTIVE: To validate the (13)C-urea-breath-test (UBT) and stool antigen test (HpSA) in children aged 5 years or younger, against invasive histologic study and rapid-urease-testing or culture.

STUDY DESIGN: On all consecutive children aged 5 years or younger undergoing endoscopy in 1 single center during the last 7.5 years, UBT and HpSA were performed.

RESULTS: Of a total of 184 children (median age 2.2 years, range 0.2-5.5), 30 were *Helicobacter pylori*-positive (16.3%). Sensitivity and specificity of UBT

were 93.3% (95%CI 77.9%-99.2%) and 95.5% (90.9-98.2), with a cutoff of 5 per thousand, but specificity increased to 98.1% (94.4%-99.6%) with a cutoff of 8 per thousand. Sensitivity and specificity of HpSA were 93.3% (77.9%-99.2%) and 98.7% (95.4%-99.8%).

CONCLUSION: Accuracy of noninvasive tests in our single-center study were satisfactory: specificity of UBT improved with a cutoff at 8%, and sensitivity of HpSA was high when determined locally without transportation after long or inadequate storage that could impair results.

PMID: 17137899 [PubMed - indexed for MEDLINE]

41. Gut. 2007 May;56(5):693-8. Epub 2006 Nov 29.

Heterozygous beta-globin gene mutations as a risk factor for iron accumulation and liver fibrosis in chronic hepatitis C.

Sartori M, Andorno S, Pagliarulo M, Rigamonti C, Bozzola C, Pergolini P, Rolla R, Suno A, Boldorini R, Bellomo G, Albano E.

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Comment in

Gut. 2007 May;56(5):613-4.

BACKGROUND: Iron accumulation is a well-known risk factor for the progression of chronic hepatitis C (CHC) to fibrosis. However, the profibrogenic role of the genes controlling iron homeostasis is still controversial.

AIM: To evaluate the relative role of haemochromatosis (HFE), ferroportin and beta-globin gene mutations in promoting iron accumulation and fibrosis in patients with CHC.

METHODS: Genetic analysis was performed together with the assessment of hepatic iron content and histology in 100 consecutive HIV-antibody and hepatitis B surface antigen-negative patients with biopsy-proven CHC.

RESULTS: Among the patients investigated, 12 were heterozygous for various beta-globin gene mutations (39[C-->T], IVS1.1[G-->A], 22 7 bp deletion and IVS1.6[T-->C]) and 29 carried HFE (C282Y, H63D and S65C) gene mutations. One further patient was heterozygous for both HFE (H63D) and beta-globin (39[C-->T]) variants, whereas 58 had the wild-type alleles of both the genes. Hepatic iron concentration (HIC) and hepatic stainable iron were significantly higher ($p < 0.05$) in patients with CHC carrying beta-globin mutations than in those with HFE mutations or the wild-type alleles. Multivariate analysis confirmed that the presence of beta-globin mutations was independently associated with both HIC ($p = 0.008$) and hepatic-stainable iron (odds ratio (OR) 6.11; 95% CI 1.56 to 23.92; $p = 0.009$). Moderate/severe fibrosis or cirrhosis (Ishak's score > 2) was observed in 48 of 100 patients. Logistic regression demonstrated that age (OR 1.05; 95% CI 1.02 to 1.09; $p < 0.005$) and beta-globin mutations (OR 4.99; 95% CI 1.22 to 20.3; $p = 0.025$) were independent predictors of the severity of fibrosis.

CONCLUSIONS: Heterozygosity for beta-globin mutations is a novel risk factor for both hepatic iron accumulation and the progression to fibrosis in patients with CHC.

PMCID: PMC1942129

PMID: 17135308 [PubMed - indexed for MEDLINE]

42. J Thorac Cardiovasc Surg. 2006 Sep;132(3):690-1.

Capillary hemangioma of the aortic valve: false preoperative diagnosis of endocarditis.

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PMID: 16935132 [PubMed - indexed for MEDLINE]

43. Cancer Res. 2006 Aug 15;66(16):8147-54.

Frequent alterations in the expression of serine/threonine kinases in human cancers.

Capra M, Nuciforo PG, Confalonieri S, Quarto M, Bianchi M, Nebuloni M, Boldorini R, Pallotti F, Viale G, Gishizky ML, Draetta GF, Di Fiore PP.

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Protein kinases constitute a large family of regulatory enzymes involved in the homeostasis of virtually every cellular process. Subversion of protein kinases has been frequently implicated in malignant transformation. Within the family, serine/threonine kinases (STK) have received comparatively lesser attention, vis-a-vis tyrosine kinases, in terms of their involvement in human cancers. Here, we report a large-scale screening of 125 STK, selected to represent all major subgroups within the subfamily, on nine different types of tumors (approximately 200 patients), by using in situ hybridization on tissue microarrays. Twenty-one STK displayed altered levels of transcripts in tumors, frequently with a clear tumor type-specific dimension. We identified three patterns of alterations in tumors: (a) overexpression in the absence of expression in the normal tissues (10 kinases), (b) overexpression in the presence of expression by normal tissues (8 kinases), and (c) underexpression (3 kinases). Selected members of the three classes were subjected to in-depth analysis on larger case collections and showed significant correlations between their altered expression and biological and/or clinical variables. Our findings suggest that alteration in the expression of STK is a relatively frequent occurrence in human tumors. Among the overexpressed kinases, 10 were undetectable in normal controls and are therefore ideal candidates for further validation as potential targets of molecular cancer therapy.

PMID: 16912193 [PubMed - indexed for MEDLINE]

44. APMIS. 2006 Jul-Aug;114(7-8):567-74.

Detection of *Dirofilaria (Nochtiella) repens* DNA by polymerase chain reaction in embedded paraffin tissues from two human pulmonary locations.

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We here report two new cases of human pulmonary dirofilariasis in men aged 62 and 64 from Northern and Central Italy, respectively. Both were asymptomatic and the infections were discovered incidentally when chest radiographs taken for another reason revealed the presence of a coin lesion. The initial clinical diagnosis was oriented towards a lung tumour, and an excisional lung biopsy after thoracotomy was necessary for the final diagnosis. Pathologically, the lesion consisted of a roundish subpleural infarct with a central thrombotic artery containing sections of an immature nematode: *Dirofilaria repens* was diagnosed histologically in one case, the necrotic condition of the worm allowing only genus identification, *Dirofilaria*, in the other case. In both samples, PCR analysis amplified a 246 bp product, specific for the IpS insert 11 of *D. repens*. The authors stress the role of PCR in the diagnosis of this parasite from paraffin samples, also in cases in which identification of the species was not possible by conventional morphology due to poor conservation of the worm. These cases represent the first PCR-based diagnosis of *D. repens* in a human pulmonary dirofilariasis on samples embedded in paraffin.

PMID: 16907864 [PubMed - indexed for MEDLINE]

45. Arch Pathol Lab Med. 2006 Aug;130(8):1231-2.

Fatal splenic rupture in a pregnant woman with hemoglobin C/beta-thalassemia and myeloid metaplasia.

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Splenic rupture with intraperitoneal hemorrhage is a fatal condition that is rarely encountered during the third trimester of pregnancy; its pathogenetic mechanisms and causes are largely unknown. We report a case of splenic rupture in a pregnant woman that caused the death of the mother and child. The patient was a carrier of double heterozygosis for hemoglobin C/beta-thalassemia. Spleen and liver enlargement due to extramedullary hematopoiesis was found at autopsy. Our data suggest that rare and hidden hematologic disorders should be considered as possible causes of splenic enlargement and rupture during pregnancy.

PMID: 16879031 [PubMed - indexed for MEDLINE]

46. Clin Lymphoma Myeloma. 2006 Mar;6(5):414-6.

A malignant fibroleiomyoma of the testis.

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The patient described has a 2-cm, hard, painless nodule close to an atrophic testis that had been present for > 10 years, suggesting inactive disease, recently associated with fever of undetermined origin with constitutional symptoms. Extensive examinations of pleural, spinal, and bronchoalveolar fluids; bacterial and mycobacterial cultures; bone biopsies; and computed tomography scans were inconclusive. Orchiectomy demonstrated an angiotropic large B-cell lymphoma (CD19+CD20+CD79a+) in the context of a benign fibroleiomyoma. The symptoms abated after the first of 4 rituximab injections. Reports suggest that benign tumors can be harbingers of angiotropic lymphoma or facilitate its onset. To date, no testicular or epididymal primary site has been reported for angiotropic lymphoma.

PMID: 16640821 [PubMed - indexed for MEDLINE]

47. J Neurooncol. 2006 Apr;77(2):213-7. Epub 2005 Nov 29.

Human leukocyte antigen distribution analysis in North Italian brain Glioma patients: an association with HLA-DRB1*14.

Guerini FR, Agliardi C, Zanzottera M, Delbue S, Pagani E, Tinelli C, Boldorini R, Car PG, Veggiani C, Ferrante P.

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Human leukocyte antigens (HLA) are widely expressed cell surface molecules that present antigenic peptides to T-lymphocytes and modulate the immune response against inflammatory and malignant disease. Frequently, tumoral cells express antigens that are recognized by the immune system. Ineffective immune response could be the result of defects in antigen presentation in those subjects with peculiar HLA alleles, which, owing to mechanisms that are still unknown, are unable to carry out their function. Only a few studies on glioma and HLA association have been performed to date. The aim of our study was to characterize a group of Italian Caucasian patients with glioma, to investigate a possible association between HLA antigens and cerebral glioma tumorigenesis in Italian patients. HLA typing of class I and class II loci was done by molecular typing performed on blood DNA from 36 glioma patients from northern Italy. The data obtained were compared with HLA frequencies taken from the database of northern

Italian organ donors. A positive association between HLA-DRB1*14 and the presence of symptomatic cerebral glioma was observed ($p = 0.02$, odds ratio = 2.48, 95% confidence interval: 1.09-5.45). This is the first Italian report on a case-control data study of HLA distribution conducted on a group of glioma patients and a first step in defining a possible involvement of HLA in susceptibility to brain glioma in the Italian population.

PMID: 16314951 [PubMed - indexed for MEDLINE]

48. J Med Virol. 2005 Nov;77(3):447-54.

Distribution, characterization and significance of polyomavirus genomic sequences in tumors of the brain and its covering.

Delbue S, Pagani E, Guerini FR, Agliardi C, Mancuso R, Borghi E, Rossi F, Boldorini R, Veggiani C, Car PG, Ferrante P.

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The etiology of brain tumors and meningiomas is still unknown. Several factors have been considered, such as genetic predisposition and environmental risk factors, but the hypothesis that one or more infectious agents may play a role in tumor pathogenesis has also been investigated. Therefore, emphasis was placed on the neurooncogenic family Polyomaviridae and the presence of human polyomavirus DNA sequences and JCV mRNA were examined in malignant human brain biopsies. Italian patients affected with different types of neoplasias of the brain and its covering were enrolled. The patients underwent surgical tumor excision and the presence of the polyomavirus genome in biopsy and other body fluids was evaluated by PCR. In addition, the genomic organization of JCV was examined in depth, with the aim of providing information on genotype distribution and TCR rearrangements in the population affected with intracranial neoplasms. On the whole, polyomavirus DNA was found in 50% of the biopsy specimens studied, JC virus DNA and BK virus DNA were amplified in 40.6% mainly glioblastomas and 9.4% of the tissue specimens, respectively, while none of the biopsy specimens tested contained Simian virus 40 DNA. Genotype 1 and Mad 4 TCR organization were the most frequent in the population enrolled. Although a cause and effect was not demonstrated and the specific role of the viruses remains unknown, the findings appear to confirm the hypothesis that JCV and BKV could be important co-factors in tumor pathogenesis.

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PMID: 16173013 [PubMed - indexed for MEDLINE]

49. AJNR Am J Neuroradiol. 2005 Sep;26(8):2157-60.

Glioblastoma multiforme of the conus medullaris in a child: description of a case and literature review.

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We describe a case of glioblastoma multiforme of the conus medullaris in a child. MR imaging showed at the T12-L1 level an intramedullary mass with signal alteration, with only two nodules of contrast enhancement. The finding was consistent with astrocytoma. Pathologic evaluation was consistent with glioblastoma multiforme. Nine months after the surgical treatment, the patient showed leptomeningeal recurrence. This case appears to be unusual for both the hysto-type and the nonspecific MR imaging features.

PMID: 16155176 [PubMed - indexed for MEDLINE]

50. Ann Dermatol Venereol. 2005 Jun-Jul;132(6-7 Pt 1):540-3.

[Cutaneous spreading of a chordoma].

[Article in French]

Gattoni M, Astolfi S, Tiberio R, Boldorini R, Pia F, Leigheb G.

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INTRODUCTION: Chordomas are rare extradural bone tumors arising from notochord remnants, the embryonic structure forming the original axis of the spine. They represent 0.1p. 100 of all intra-cranial tumors. The chordoma is a locally malignant cancer that tends to invade the surrounding tissues. Its localization in the skin is exceptional.

OBSERVATION: A 56 year-old man developed a nut-sized vegetating nodule on the nasal groove. This lesion appeared a few months following surgery for a frontoglabbellar relapse of a chordoma that had developed six years earlier at the base of the skull.

DISCUSSION: We report this case because of the rareness of cutaneous involvement and the particular conditions in which it occurred. It may have been due to tumoral seeding during the previous surgical interventions.

PMID: 16142102 [PubMed - indexed for MEDLINE]

51. Am J Clin Pathol. 2005 Aug;124(2):303-12.

Are sequence variations in the BK virus control region essential for the development of polyomavirus nephropathy?

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BK virus replication is regulated by the noncoding control region (NCCR); major NCCR rearrangements could modify the strength of viral replication, having a role in the development of polyomavirus-associated nephropathy (PAN). Urine (n = 34), blood (n = 32), and renal biopsy samples (n = 13) from 5 transplant recipients with PAN underwent nested polymerase chain reaction to search for the NCCR region. Sequence analysis was performed on all NCCR fragments obtained. Decoy cells were evaluated semiquantitatively in urine and PAN staged in renal biopsy specimens; the results were related to the presence and type of NCCR sequence variations. Major NCCR rearrangements were found in urine (9/75 [12%]), blood (7/30 [23%]), and renal biopsy (4/15 [27%]) samples in 3 cases; 2 cases had only unrearranged strains. Neither the detection and number of decoy cells nor the PAN stage were related to the specific type of NCCR sequence rearrangements. NCCR rearrangements do not seem essential for the development of PAN.

PMID: 16040304 [PubMed - indexed for MEDLINE]

52. Acta Cytol. 2005 May-Jun;49(3):235-43.

Periodic assessment of urine and serum by cytology and molecular biology as a diagnostic tool for BK virus nephropathy in renal transplant patients.

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OBJECTIVE: To investigate the significance of polyomavirus (PV) viruria and viremia by morphologic, immunohistochemical and molecular analysis (multiplex nested-polymerase chain reaction) in renal transplant patients.

STUDY DESIGN: Urine (n=328), serum (n= 53) and renal biopsies (n=24) from renal transplant patients (n=106) were studied.

RESULTS: Decoy cells were found in 53 samples (16%) from 19 patients (18%); viral DNA was amplified in all urinary samples and disclosed BK virus (BKV) (n=24), JC virus (JCV) (n=16), and JCV and BKV DNA (n=13). BKV was the prevailing genotype in patients with a high frequency of decoy cell excretion (p = 0.001). JCV excretion correlated with a low number (p = 0.01) and BKV with a high number of decoy cells (p=0.003). PV DNA was amplified from 30/53 serum samples (56.6%); BKV was the prevailing genotype (p = 0.04). On 24 renal biopsies (18 from the decoy cell-negative and 6 from the decoy cell-positive group) PV nephropathy (PVN) was identified and BKV DNA amplified in 4 biopsies, all from the group with a high frequency of decoy cell excretion. PVN was not identified in renal biopsies from the decoy cell-negative group.

CONCLUSION: PV infection is frequent in renal transplant patients. The BKV genotype in urine and serum is significantly related to a high frequency and high number of decoy cells. PVN occurs only in patients with BKV viremia and a high number and frequency of decoy cell excretion in urine. In the absence of decoy cells, PVN can be excluded. Cytologic analysis of urine is an important

diagnostic tool for screening renal transplant patients at risk of PVN.

PMID: 15966283 [PubMed - indexed for MEDLINE]

53. Aliment Pharmacol Ther. 2005 Jun 15;21(12):1445-51.

Gender and liver fibrosis in chronic hepatitis: the role of iron status.

Rigamonti C, Andorno S, Maduli E, Capelli F, Boldorini R, Sartori M.

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BACKGROUND: The role of gender in the progression of fibrosis in chronic hepatitis C is still under investigation.

AIM: To investigate whether gender affects the progression of liver disease and/or hides other risk factors.

METHODS: A prospective series of 121 consecutive patients with chronic hepatitis C underwent liver biopsy. Grading and staging for chronic hepatitis were each evaluated according to Ishak's classification.

RESULTS: In univariate and multivariate analysis on the whole group of patients, male gender was not associated either with significant liver fibrosis (Ishak's score > 2) or with cirrhosis (Ishak's score > 4). On the contrary, in univariate analysis on patients aged < or = 50 years, male gender was nearly significantly (P = 0.06) predictive of liver fibrosis, whereas it was not in patients > 50 years. Hepatic iron grading, along with age, was an independent factor associated with fibrosis. Moreover, the values of all the variables which describe iron status were significantly higher in males aged < or = 50 years in comparison with females of the same age.

CONCLUSIONS: In chronic hepatitis C, male gender may be predictive of liver fibrosis only in patients aged < or = 50 years. Among fibrogenetic factors hidden by gender, iron status could play a major role.

PMID: 15948811 [PubMed - indexed for MEDLINE]

54. Acta Cytol. 2005 Mar-Apr;49(2):213-8.

Fine needle aspiration cytology in the diagnosis of non-Hodgkin's lymphomas of the muscle: a report of 2 cases.

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BACKGROUND: Primary skeletal muscle lymphoma has been reported in very few cases. Although such imaging techniques as computed tomography and magnetic resonance imaging can supply diagnostic indications, the most reliable data are obtained by means of muscle biopsy investigations. Fine needle aspiration cytology (FNAC) has

not been considered before for the diagnosis of muscle lymphoma.

CASES: In case 1, 60-year-old man presented with 2 masses in the pectoral muscle and neck. FNAC of the neck mass was performed. The diagnosis was non-Hodgkin's diffuse B-cell lymphoma of the muscle; the diagnosis was confirmed by surgical biopsy of the pectoral muscle. In case 2, a 70-year-old man presented with a mass in the quadriceps muscle. The results of FNAC aroused suspicion of lymphoma, and a muscle biopsy confirmed the presence of a non-Hodgkin's B-cell lymphoma. Immunohistochemistry identified it as non-Hodgkin's marginal zone B-cell lymphoma of MALT type.

CONCLUSION: FNAC can be a valuable starting point in muscle involvement by lymphoma because of the possibility of obtaining material by means of multiple aspirations without causing patients any discomfort.

PMID: 15839632 [PubMed - indexed for MEDLINE]

55. Arch Pathol Lab Med. 2005 Jan;129(1):69-73.

Kidney and urinary tract polyomavirus infection and distribution: molecular biology investigation of 10 consecutive autopsies.

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CONTEXT: Distinct human polyomavirus genotypes cause different diseases in patients with renal transplants: BK virus (BKV) causes tubulointerstitial nephritis and ureteral stenosis, whereas both JC virus (JCV) and BKV are responsible for hemorrhagic cystitis. These findings could result from a selective infection of kidney and urinary tract segments by JCV or BKV.

OBJECTIVE: To verify this hypothesis, 10 complete, unselected, consecutive autopsies from 9 immunocompetent patients and 1 patient affected by acquired immunodeficiency syndrome were investigated.

DESIGN: Samples from kidneys (n = 80), renal pelvis (n = 20), ureter (n = 40), and urinary bladder (n = 30) obtained from 10 consecutive autopsies were investigated by means of multiplex nested polymerase chain reaction to detect polyomavirus DNA and to distinguish different species of the Polyomavirus genus. In situ hybridization and immunohistochemistry were also carried out to define the viral status of the infected tissues.

RESULTS: Polyomavirus DNA was detected in all of the subjects (positive samples ranging from 2 to 7 samples), for a total of 43 of 170 samples (25.3%), distributed as follows: urinary bladder (10/30, 33%), renal pelvis (6/20, 30%), ureter (10/40, 25%), and kidney tissue (17/80, 21%). We found that JCV was most frequently detected overall (23/43 samples, 53.5%) and was also detected most frequently within the kidney (8/17 positive samples, 47%), the renal pelvis (5/6 positive samples, 70%), and the ureter (7/10 positive samples, 70%), whereas BKV was found in 14 samples (32.5%), and it was the prevailing genotype in urinary bladder (6/10 positive samples, 60%). Coinfection of BKV-JCV was found in 6 samples (14%). Immunohistochemistry and in situ hybridization returned negative

results.

CONCLUSIONS: The viruses JCV and BKV latently persist randomly in kidney and urinary tract. Distinct diseases induced by them could be related more closely to molecular viral rearrangements than to the topographic distribution of latent viruses.

PMID: 15628910 [PubMed - indexed for MEDLINE]

56. Gynecol Oncol. 2004 Dec;95(3):724-8.

Aggressive angiomyxoma of the vulva.

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BACKGROUND: Aggressive angiomyxoma is a rare soft tissue tumour that carries a high risk of local relapse. It is a slowly growing and locally infiltrating tumour.

CASE: We describe the case of an aggressive pelvic-perineal angiomyxoma arising in a 36-year-old woman. The patient had a mass that grew before, during and after her pregnancy. Transperineal surgery was performed. The resection margins were free of disease.

CONCLUSION: Our case confirms what has previously been published concerning the possible hormone-dependence of this neoplasm. Given the positive estrogen and progesterone receptor status of this tumour, we will consider hormonal treatments in the case of a future relapse.

PMID: 15581991 [PubMed - indexed for MEDLINE]

57. Acta Cytol. 2003 Nov-Dec;47(6):985-90.

Sequence analysis of the JC virus transcriptional control region detected in urine from HIV-positive patients.

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OBJECTIVE: To investigate the correlation between transcriptional control region (TCR) types and virus replication and the role of decreased host immunity in inducing TCR changes.

STUDY DESIGN: In a previous study, urine specimens from 78 unselected HIV-positive patients were independently evaluated by cytology, immunohistochemistry and nested polymerase chain reaction (n-PCR) to detect the presence of polyomaviruses. The JC virus (JCV) large T region was positive in

44/78 (56%) urine specimens by n-PCR. In the current study, these cases further underwent to n-PCR to detect TCR, and the amplified products were sequenced. The JCV types identified were compared using: (1) morphologic evidence of replication (decoy cells and/or immunohistochemical staining of cells detected using anti-SV 40 antiserum), and (2) patients' immune status (CD4+ cell counts).

RESULTS: TCR was successfully amplified in 30/44 cases (68%). TCR sequence analysis disclosed 6/30 archetype (20%) and 24/30 archetypelike sequences, the latter distributed as follows: 4 G2 (4/30, 13%) with G-->A substitutions in the C sequence (nt 9), and 20 CY (20/30, 67%) with A-->G substitutions in the F sequence (nt 19). There were no correlations with morphologic evidence of viral replication or immune status.

CONCLUSION: The present study indicated that TCR in urine samples from PML-free HIV-positive subjects are archetypes or archetypelike. Immune suppression does not seem to influence minor changes in the TCR genome, and single by mutations do not change JCV replication activity.

PMID: 14674067 [PubMed - indexed for MEDLINE]

58. Lupus. 2003;12(11):851-3.

The two hit hypothesis in the antiphospholipid syndrome: acute ischaemic heart involvement after valvular replacement despite anticoagulation in a patient with secondary APS.

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A patient with the antiphospholipid syndrome (APS), in whom a nonfatal myocardial infarction ensued after valvular heart replacement despite anticoagulation, is described. The report further stresses the role of concomitant risk co-factors in inducing thrombotic events and points out that cardiosurgery might represent a potential major risk for myocardial ischaemic damage in APS.

PMID: 14667102 [PubMed - indexed for MEDLINE]

59. Pathology. 2003 Jun;35(3):248-53.

Molecular characterisation of JC virus strains detected in human brain tumours.

Boldorini R, Pagani E, Car PG, Omodeo-Zorini E, Borghi E, Tarantini L, Bellotti C, Ferrante P, Monga G.

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AIMS: The aim of this study was to evaluate the presence and significance of JC

virus (JCV) in human brain tumours.

METHODS: Histology, immunohistochemistry (IHC) and molecular biology techniques were employed to examine specimens of tumour tissue, peripheral blood and cerebrospinal fluid taken from 22 patients with primary neuro-epithelial tumours. Furthermore, the coding viral protein (VP1) region and non-coding transcription control region (TCR) of JCV genome isolated from the tumours were submitted to sequence analysis in order to detect viral rearrangements or mutations.

RESULTS: JCV genome was found in nine of the 22 tumour specimens (40.9%), including eight astrocyte-derived tumours (seven glioblastomas and one astrocytoma) and one oligodendroglioma, and in two of the 15 cerebrospinal fluid specimens (13.3%) with positive tumour tissue (one glioblastoma and one astrocytoma). Sequence analysis of JCV VP1, which was amplified in seven tissue samples and the two cerebrospinal fluid samples, revealed only genotype 1 (four 1a and three 1b), whereas TCR was amplified in six tissue samples and only one cerebrospinal fluid sample. TCR sequence analysis was possible in four cases and identified three Mad-4 and one type II sequences; the TCR genomic structures of JCV isolated from cerebrospinal fluid were the same as those sequenced from corresponding tumour tissue, thus indicating a possible cerebrospinal fluid dissemination of neoplastic cells carrying viral DNA.

CONCLUSIONS: Our results suggest a possible role of JCV in the induction of brain tumours, especially in those originating from brain cells normally targeted by JCV infection.

PMID: 14506971 [PubMed - indexed for MEDLINE]

60. Tumori. 2003 Mar-Apr;89(2):207-10.

Papillary thyroid carcinoma identified after Sistrunk procedure: report of two cases and review of the literature.

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Thyroglossal duct cysts represent the most common congenital cervical malformations. Carcinomas arising in the thyroglossal duct cysts are rare neoplasms characterized by a relatively non aggressive behavior with rare lymph node spread. Approximately 1% of thyroglossal cysts contain a carcinoma. The most frequent histological type is papillary carcinoma, accounting for about 80% of cases. Currently, most authors agree about their primary origin ex novo from ectopic thyroid tissue in the cyst. In most cases the diagnosis of thyroglossal duct carcinoma (TDC) is not made until histopathological examination has been performed on a resected cyst without any suspected clinical sign of malignancy. The definition of the correct surgical treatment for these carcinomas is still controversial; most authors maintain that resection of a TDC with the Sistrunk procedure can be considered oncologically adequate when dealing with a differentiated carcinoma without extracapsular invasion and/or lymph node metastases and with a normal thyroid. We present two cases of papillary thyroid carcinoma identified after resection of a thyroglossal cyst according to the

Sistrunk procedure and managed with different surgical approaches according to the different sites of the tumors. In addition, we discuss appropriate therapeutic strategies in light of the most recent data in the literature.

PMID: 12841674 [PubMed - indexed for MEDLINE]

61. Hepatology. 2003 Jul;38(1):42-9.

Moderate alcohol consumption increases oxidative stress in patients with chronic hepatitis C.

Rigamonti C, Mottaran E, Reale E, Rolla R, Cipriani V, Capelli F, Boldorini R, Vidali M, Sartori M, Albano E.

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The mechanisms by which alcohol consumption worsens the evolution of chronic hepatitis C (CHC) are poorly understood. We have investigated the possible interaction between hepatitis C virus (HCV) and ethanol in promoting oxidative stress. Circulating IgG against human serum albumin (HSA) adducted with malondialdehyde (MDA-HSA), 4-hydroxynonenal (HNE-HSA), or arachidonic acid hydroperoxide (AAHP-HSA) and against oxidized cardiolipin (Ox-CL) were evaluated as markers of oxidative stress in 145 CHC patients with different alcohol consumption, 20 HCV-free heavy drinkers (HD) without liver disease, and 50 healthy controls. Anti-MDA IgG was increased in CHC patients irrespective of alcohol intake as well as in the HD group. CHC patients with moderate alcohol intake (<50 g ethanol/d), but not HD, also had significantly higher values of anti-AAHP-HSA, anti-HNE-HSA, and anti-Ox-CL IgG ($P < .05$) than controls. A further elevation ($P < .001$) of these antibodies was evident in CHC patients with heavy alcohol intake (>50 g ethanol/d). Anti-AAHP and anti-Ox-CL IgG above the 95th percentile in the controls were observed in 24% to 26% of moderate and 58% to 63% of heavy drinkers but only in 6% to 9% of the abstainers. The risk of developing oxidative stress during CHC was increased 3-fold by moderate and 13- to 24-fold by heavy alcohol consumption. Heavy drinking CHC patients had significantly more piecemeal necrosis and fibrosis than abstainers. Diffuse piecemeal necrosis was 4-fold more frequent among alcohol-consuming patients with lipid peroxidation-related antibodies than among those without these antibodies. In conclusion, even moderate alcohol consumption promotes oxidative stress in CHC patients, suggesting a role for oxidative injury in the worsening of CHC evolution by alcohol.

PMID: 12829985 [PubMed - indexed for MEDLINE]

62. Ann Ital Med Int. 2002 Oct-Dec;17(4):242-7.

Evaluation of liver fibrosis in chronic hepatitis C with a computer-assisted morphometric method.

Maduli E, Andorno S, Rigamonti C, Capelli F, Morelli S, Colombi S, Nicosia G,

Boldorini R, Abate M, Sartori M.

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Objective methods are needed to quantitatively assess the burden of fibrous tissue in liver biopsy specimens and its changes after treatment. The aim of this study was to assess the validity of a computer-assisted morphometric method in the evaluation of liver fibrosis in patients with chronic hepatitis C. Sixty-nine liver biopsy specimens stained with Sirius red were evaluated by two independent observers with a computer-assisted morphometric method to measure the percentage of fibrous tissue in the optic fields examined (fibrosis ratio). Furthermore, 11 pairs of liver biopsy specimens obtained before and after treatment from patients with chronic hepatitis C were evaluated with morphometry by two independent observers in order to assess in which direction fibrosis changed. In the 69 patients, the correlation of the morphometry-measured fibrosis ratio pairs by the two observers was high ($r = 0.781$). However, the differences between paired values were large, reaching $\pm 5\%$ in 95% of instances. The fibrosis ratios observed with morphometry by the two examiners correlated poorly with the Ishak's staging score. The two examiners agreed in 10 out of 11 instances in judging in which direction fibrosis had changed. In conclusion, using our present technique of computer-assisted morphometry, the quantitative assessment of the percentage extension of fibrous tissue was not sufficiently accurate. However, computer-assisted morphometry proved to be useful when evaluating the direction of fibrous changes in pairs of liver biopsy specimens from patients with chronic hepatitis C before and after treatment.

PMID: 12532562 [PubMed - indexed for MEDLINE]

63. Mod Pathol. 2003 Jan;16(1):35-42.

Lytic JC virus infection in the kidneys of AIDS subjects.

Boldorini R, Omodeo-Zorini E, Nebuloni M, Benigni E, Vago L, Ferri A, Monga G.

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Our objective was to investigate the role of the human polyomavirus JC virus as a possible cause of renal damage in AIDS subjects. Histology, immunohistochemistry, and molecular biology were used to evaluate the frequency of viral infection, genotypes, viral status, and the presence of rearrangements or point mutations in specific genomic regions of strains isolated from renal tissue. Formalin-fixed, paraffin-embedded sections of postmortem renal specimens obtained from 111 unselected AIDS patients were stained for routine histology and with anti-SV40 antibody. The immunohistochemically positive specimens were further investigated by means of nested polymerase chain reaction for different polyomavirus genomic regions (large T, transcriptional control region, and viral protein 1). Furthermore, the sequences of transcriptional control region and viral protein 1

were also analyzed. Immunohistochemistry was positive in seven cases (6.3%), four of which showed morphological evidence of viral replication (intranuclear inclusion bodies and/or intratubular cellular casts): in all seven cases, only epithelial tubular cells (with and without inclusion bodies) and cellular casts were stained. The JC virus genome was identified by polymerase chain reaction in five of the seven immunohistochemically positive cases; transcriptional control region and viral protein 1 were amplified in, respectively, three and four cases. Transcriptional control region sequence analysis revealed major rearrangements in all three cases, with duplications of all the transcriptional factor-binding sites, whereas no point mutations were found in the viral protein 1 region, which was characterized as Type 1A in all cases. For the first time in AIDS subjects, this study shows that although rarely, JC virus can replicate in renal tissue. Molecular biology revealed major rearrangements in the transcriptional control region that, together with other unknown factors, could justify the increased pathogenicity of this human polyomavirus.

PMID: 12527711 [PubMed - indexed for MEDLINE]

64. *Recenti Prog Med.* 2002 Apr;93(4):247.

[BK virus encephalitis in an HIV-seropositive patient. Preliminary data].

[Article in Italian]

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The BK virus (BKV) belongs to the family of the polyoma group. Although up to 60% of AIDS patients excrete BKV in the urine, there have been few reports of infection of kidney, lung, retina, brain and peripheral blood mononuclear cells. We report the case of a 37 year-old male HIV positive patient with BKV encephalitis. This diagnosis should be considered in AIDS patients with signs of cerebral disease.

PMID: 11989130 [PubMed - indexed for MEDLINE]

65. *Am J Kidney Dis.* 2002 Apr;39(4):713-20.

Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies.

Mazzucco G, Bertani T, Fortunato M, Bernardi M, Leutner M, Boldorini R, Monga G.

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The frequency of various types of renal changes in patients with type 2 diabetes is not clearly defined in the literature. Reported discrepancies likely are

caused by ethnic and geographic factors. However, policies used in nephrological centers for the selection of patients to undergo renal biopsy also may have an influence. The present study reports 393 renal biopsies in patients with type 2 diabetes performed in a group of centers in northwestern Italy using different (restricted [CRPs] or unrestricted [CUP]) biopsy policies. On the basis of light microscopic, immunofluorescence, and ultrastructural findings, cases were subdivided into three classes characterized by the presence of diabetic glomerulosclerosis (class 1), prevailing vascular (arterioarteriolosclerotic) and ischemic glomerular changes (class 2), other glomerulonephritides superimposed on diabetic glomerulosclerosis (class 3a), or glomerulonephritides without the presence of diabetic glomerulosclerosis (class 3b). Although no significant differences were found for class 2 (detected in 15% and 16% of patients from CRPs and the CUP, respectively), the frequency of the other two classes was strongly biased by the biopsy policy. Class 1 was found in 29% and 51% of cases, and class 3 in 57% and 33% of cases from CRPs and the CUP, respectively. Moreover, class 3a was more common (67%) in the CUP, and class 3b (78%) in CRPs. Our findings may explain conflicting data from the literature and the influence that type of adopted biopsy policy may have on an epidemiological evaluation. This study helps clarify the frequency of renal changes in patients with type 2 diabetes and suggests more extensive use of renal biopsy to obtain reliable prognostic indications and plan a rational therapeutic approach.

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PMID: 11920336 [PubMed - indexed for MEDLINE]

66. Eur J Clin Invest. 2002 Mar;32 Suppl 1:28-35.

Iron, hepatic stellate cells and fibrosis in chronic hepatitis C.

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BACKGROUND/AIMS: In patients with chronic hepatitis C, hepatic iron concentration correlates with liver fibrosis. However, it is not clear whether this correlation merely reflects the presence of more active disease, or iron exacerbates chronic hepatitis C virus (HCV)-induced damage through activation of hepatic stellate cells and regeneration of hepatocytes.

MATERIALS AND METHODS: We studied 72 HCV-positive patients, staged according to the Ishak's score system. We measured hepatic iron concentration with spectrophotometry and evaluated the number of hepatic stellate cells (using monoclonal antibody against alpha smooth muscle actin) and proliferating hepatocytes (using monoclonal antibody against Ki67). Iron and ferritin serum levels were also determined.

RESULTS: Hepatic iron concentration correlated statistically with ferritin serum level ($r = 0.59$, $P < 0.001$), with grading ($r = 0.47$, $P < 0.001$) and staging ($r = 0.51$, $P < 0.001$) scores for chronic hepatitis in the whole group of patients.

Hepatic iron concentration correlated positively with stellate cell number ($r = 0.55$, $P = 0.004$) and Ki67-positive hepatocyte number ($r = 0.36$, $P = 0.08$) in patients with chronic hepatitis C and low grading score (< 3).

CONCLUSIONS: In patients with chronic hepatitis C and low grading score, hepatic iron could play a role in the activation of hepatic stellate cells and in the progression of fibrosis.

PMID: 11886429 [PubMed - indexed for MEDLINE]

67. Am J Clin Pathol. 2001 Oct;116(4):489-94.

Molecular characterization and sequence analysis of polyomavirus strains isolated from needle biopsy specimens of kidney allograft recipients.

Boldorini R, Omodeo-Zorini E, Suno A, Benigni E, Nebuloni M, Garino E, Fortunato M, Monga G, Mazzucco G.

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We retrospectively examined 29 renal allograft biopsy specimens from 42 kidney transplant recipients by means of molecular biologic techniques (nested polymerase chain reaction), immunohistochemical analysis (anti-SV40 antibody), and histologic examination to evaluate the presence of polyomaviruses (PVs), viral genotypes, genomic mutations, and their pathologic significance. PV genomes were found in six cases (21%); restriction fragment length polymorphism analysis characterized 4 as JC virus (JCV) and 2 as BK virus (BKV). The latter also were positively stained immunohistochemically and showed histologically typical intranuclear viral inclusions; JCV cases were negative. DNA sequence analysis revealed only minor changes in the 4 JCV cases (3 archetypes and 1 JCV type 3, not associated with a known pathogenic genotype) but identified 2 specific variants in the BKV isolates (AS and WW strains). Given the different histologic findings (mixed inflammatory infiltration in the AS and no inflammation in the WW strain), we speculate that different BKV strains may cause differential damage in transplanted kidneys. Finally, the negative histologic and immunohistochemical JCV results, as well as the absence of viral mutations, indicate that JCV renal infection is latent in transplant recipients.

PMID: 11601133 [PubMed - indexed for MEDLINE]

68. Recenti Prog Med. 2001 Sep;92(9):540.

[Hepatosplenic cat-scratch disease in the immunocompetent adult].

[Article in Italian]

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Atypical manifestations of cat-scratch disease have been described in children and immunosuppressed adults. We report the first case of hepatosplenic cat-scratch disease in an immunocompetent subject, demonstration of diversity of this infection. A 33-year-old man presented with prolonged fever, lymphadenopathy and multiple hypodense lesions of liver and spleen in ultrasonographic imaging. The hepatic biopsy showed non-specific inflammatory reactions including granulomata and stellate necrosis. Anti-Bartonella antibodies have been found. The therapy with clarithromycin and doxycycline for many weeks was effective for hepatic lesions. A month ago a history of a cat contact with the presence of a skin lesion has been reported.

PMID: 11552311 [PubMed - indexed for MEDLINE]

69. Pathology. 2001 Aug;33(3):390-5.

Multiple small intestinal stromal tumours in a patient with previously unrecognised neurofibromatosis type 1: immunohistochemical and ultrastructural evaluation.

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Neurofibromatosis type 1 could be associated with multiple gastrointestinal stromal tumours, although their presence is not considered among the major diagnostic criteria. We present here a case of a 50-year-old female complaining of abdominal pain, with about 100 small intestinal stromal tumours. This finding prompted us to suspect a neurofibromatosis which was clinically confirmed afterwards. Light microscopy examination revealed a low-grade stromal tumour with skeinoid fibres. Mixed neural-interstitial cells of Cajal origin or, alternatively, neural differentiation of interstitial cells of Cajal are discussed on the basis of immunophenotype (CD117+, CD34+) and ultrastructure. A 2-year follow-up did not indicate an aggressive course in the case of this neoplasm.

PMID: 11523947 [PubMed - indexed for MEDLINE]

70. Hum Pathol. 2001 Jun;32(6):656-9.

Molecular characterization and sequence analysis of polyomavirus BKV-strain in a renal-allograft recipient.

Boldorini R, Zorini EO, Fortunato M, Bernardi M, Suno A, Benigni E, Monga G, Mazzucco G.

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The significance of polyomavirus (PV) infection was investigated in a 53-year-old patient who underwent renal transplantation and was treated with triple immunosuppressive therapy (tacrolimus, prednisone, and azathioprine). A renal biopsy taken because of the suspicion of acute rejection showed focal inflammatory interstitial infiltration, tubulitis, and tubular cell nuclear changes consistent with the hypothesis of viral infection. Both the tubular and decoy cells identified by means of urinalysis positively stained for anti-SV40 antibody. Polymerase chain reaction performed on the DNA extracted from renal tissue and isolated from urine showed the presence of an antigenic variant (AS) of the BKV archetype after sequence analysis of the transcription control region (TCR). On the basis of the diagnosis of BKV infection, immunosuppressive therapy was reduced. The patient's renal function improved and was still stable 8 months later when urinalysis showed only a few decoy cells, which were found to be infected by JC but not BK virus. These data suggest that only the BKV, probably favoured by immunosuppressive therapy (tacrolimus), causes renal damage. It is worth underlining that even small and sporadic viral genome mutations may lead to pathologic effects.

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PMID: 11431722 [PubMed - indexed for MEDLINE]

71. Dig Liver Dis. 2001 Mar;33(2):157-62.

Chronic hepatitis C treated with phlebotomy alone: biochemical and histological outcome.

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BACKGROUND: In patients with chronic hepatitis C, the histological outcome of long term phlebotomy is unknown.

AIM: To investigate biochemical and histological findings before and after phlebotomy in chronic hepatitis C.

PATIENTS: Twenty-four non-haemochromatotic patients with chronic hepatitis C were treated with long-term phlebotomy alone.

RESULTS: Hepatic iron concentration had decreased in all patients who underwent a second liver biopsy, two years after iron depletion was attained and maintained. Histological grading score decreased in four patients, was unchanged in two, and increased in five. Histological staging score decreased in two patients, was unchanged in five, and increased in four. Pretreatment high serum selenium level predicted the reduction of the inflammatory grading score in univariate analysis ($p=0.008$, while low serum aspartate aminotransferase ($p=0.02$) and low propeptide of procollagen III ($p=0.08$) levels predicted the lack of progression of liver fibrosis. Furthermore, when iron depletion was reached, significant reductions of serum levels of aminotransferase, gamma glutamyl transferase (-47%), propeptide

of procollagen III, alpha foetoprotein, selenium were observed in 24 patients. No changes in serum hepatitis C virus-RNA levels were found.

CONCLUSIONS: Phlebotomy alone seems to be efficacious in suppressing progression of chronic hepatitis C in some patients. Phlebotomy not only induces iron depletion, but it even modifies serum levels of other trace elements involved in the balance between oxidant and antioxidant processes.

PMID: 11346145 [PubMed - indexed for MEDLINE]

72. Histopathology. 2001 Apr;38(4):344-54.

Dirofilariasis due to *Dirofilaria repens* in Italy, an emergent zoonosis: report of 60 new cases.

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AIMS: Sixty new cases of human dirofilariasis due to *Dirofilaria repens*, occurring in Italy between 1990 and 1999, are presented. This is the most extensive case study of this zoonosis reported worldwide by a single study group. The aim is to utilize this large experience to characterize the different histopathological findings in the parasitic lesions in man.

METHODS AND RESULTS: Diagnosis was performed on histological sections of the nematode enclosed in the nodules excised at biopsy or surgery. The nematode was located in the subcutaneous tissue (49 cases), the epididymis (two cases), the spermatic cord (two cases), the lung (two cases), the breast (two cases), the omentum (two cases) and under the conjunctival tissue (one case). The majority of cases (46) were from Piedmont; the remainder were from Emilia-Romagna, Sardinia, Sicily, Tuscany, Apulia and Lombardy. The histopathological features of the lesions are described and the clinical and epidemiological aspects of the zoonosis are discussed. The prevalence in Italy in general and in the area of Piedmont in particular, comprising the provinces of Alessandria, Asti, Novara and Vercelli, which is one of the most severely affected areas of the world, is emphasized. The evident increase in the number of cases in the last few years is a clear indication that it is an emergent zoonosis.

CONCLUSIONS: We recommend that each and every case observed be recorded, to enable the true extent of human dirofilariasis in Italy to be assessed, and that a reference centre be set up in the area to collate the data. The importance of the histopathologist's role in the diagnosis is stressed.

PMID: 11318900 [PubMed - indexed for MEDLINE]

73. AIDS. 2001 Mar 30;15(5):571-5.

Beta amyloid precursor protein and patterns of HIV p24 immunohistochemistry in different brain areas of AIDS patients.

Nebuloni M, Pellegrinelli A, Ferri A, Bonetto S, Boldorini R, Vago L, Grassi MP, Costanzi G.

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OBJECTIVES: To evaluate the correlation between immunohistochemical positive patterns (globular and filamentous structures) of beta-amyloid precursor protein (beta-APP), used as a marker of axonal damage, and the different distribution of HIV p24 antigens, in three different brain areas of AIDS patients.

METHODS: Eighteen AIDS patients with HIV-related brain lesions were included in the study. Forty-nine sections from basal ganglia, frontal cortex and hippocampus were selected. After microwave oven pre-treatment, the sections were incubated with anti-HIV p24 and anti-beta-APP monoclonal antibodies; the reactions were developed with peroxidase/3,3'diaminobenzidine. The positivity was graded by semi-quantitative scores. Double immunohistochemical staining was used to evaluate the co-localization of the antigens.

RESULTS: HIV p24 immunohistochemistry was positive in 44 of 49 sections (89%), with a prevalence of interstitial positive cells and positive microglial nodules in 27 and 13 sections respectively. beta-APP-positive structures were demonstrated in 23 of 44 sections (52%) with HIV-related lesions, and were absent from the five sections without viral expression. Globular and filamentous lesions were observed in 21 of 23 sections and 10 of 23 lesions respectively. Moreover, a high grade of globular type lesion was related to an elevated presence of diffuse interstitial HIV p24-positive cells in basal ganglia; double immunohistochemical reactions demonstrated the co-localization of beta-APP globules and HIV p24 antigens.

CONCLUSIONS: The data obtained confirm the coexpression of beta-APP and viral antigens in particular areas of the brain with HIV-related lesions; there is a strict correlation between beta-APP globules (indicating chronic cerebral damage) and the interstitial pattern of HIV p24 immunohistochemistry.

PMID: 11316993 [PubMed - indexed for MEDLINE]

74. Surg Neurol. 2001 Mar;55(3):163-8; discussion 168.

Primitive cerebral melanoma: case report and review of the literature.

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BACKGROUND: Central nervous system primary malignant melanoma accounts for approximately 1% of all the cases of melanoma; reports in the literature are relatively rare.

CASE DESCRIPTION: A 74-year-old man was hospitalized because of an episode of aphasia. The neuroradiologic examinations demonstrated a round homogeneous lesion extending near the left sylvian fissure. He had no extracranial abnormalities.

The patient underwent a neurosurgical procedure and the tumor was macroscopically totally excised. Pathological examination of the surgical specimen revealed a histological appearance similar to that of melanoma. A diagnosis of primary CNS melanoma was made after careful dermatologic and ophthalmologic examination, which ruled out presence of cutaneous or choroidal melanoma. The patient did not receive any further treatment and he is free of disease 2 years after diagnosis.

CONCLUSIONS: We report a case of primary cerebral melanoma of the left temporal lobe; clinical, neuroradiological, and histological findings are discussed with review of the literature. Primary melanoma of the CNS may present either with localized intra/extra-axial mass lesions or with meningeal spread, which carries a worse prognosis. The prognosis of cerebral primitive melanoma is variable, although it is common opinion that primitive cerebral melanoma has a better prognosis than cutaneous melanoma, with two cases in the literature surviving 9 and 12 years.

PMID: 11311915 [PubMed - indexed for MEDLINE]

75. J Gastroenterol Hepatol. 2000 Dec;15(12):1411-7.

Chronic hepatitis C is mild in menstruating women.

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BACKGROUND AND AIMS: Women with chronic hepatitis C may have a slower rate of disease progression than men. We have previously demonstrated a relationship between hepatic iron concentration and liver fibrosis in patients with chronic hepatitis C. Our aim was to compare hepatic histologic findings, iron status and other factors putatively capable of determining the severity of chronic hepatitis between menstruating women and men of comparable age.

METHODS: We studied 21 consecutive hepatitis C virus (HCV)-RNA positive menstruating women and 24 consecutive HCV-RNA positive men of comparable age, who underwent liver biopsy for chronic hepatitis C. Alcohol intake was recorded and blood tests, HCV genotyping, serum iron, unsaturated iron binding capacity, serum ferritin, hepatic iron concentration, and liver histology were evaluated.

RESULTS: Menstruating women showed lower grading (2.7 +/- 1.5 vs 3.6 +/- 2, P = 0.09) and significantly lower staging (1.38 +/- 1.11 vs 2.42 +/- 1.64, P = 0.037) scores than men of comparable age. Among the factors putatively capable of determining the severity of chronic hepatitis, only the hepatic iron concentration correlated with the hepatic histologic staging in a multivariate analysis. Iron-depleted women (transferrin saturation < 20% and/or serum ferritin < 9 micrograms/L) showed significant lower hepatic histologic grading (1.75 +/- 0.7 vs 3.23 +/- 1.55, P = 0.027) and staging (0.75 +/- 1.03 vs 1.77 +/- 1.01, P = 0.026) scores than women with normal iron status.

CONCLUSIONS: Menstruating women with chronic hepatitis C may have a milder disease compared to men of comparable age, possibly because of menstrual blood loss and lower hepatic iron concentration. Women with chronic hepatitis C and iron deficiency have a milder disease compared to women with normal iron status,

suggesting that iron deficiency results in a slower rate of disease progression.

PMID: 11197052 [PubMed - indexed for MEDLINE]

76. Virchows Arch. 2000 Aug;437(2):198-202.

Lymphoepithelioma-like carcinoma of the breast. An unusual pattern of infiltrating lobular carcinoma.

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A case of breast carcinoma, showing both lymphoepithelioma-like and lobular infiltrating carcinoma, is described, which must be distinguished from the medullary carcinoma with which it shares some features, such as the strong lymphocytic infiltration, but not sharp circumscription, syncytial growth pattern, nuclear pleomorphism, and high mitotic rate. Unlike the lymphoepithelial carcinoma of the nasopharynx and some lympho-epithelioma-like carcinomas of the lung, stomach, salivary glands, and thymus, it does not seem to be connected with Epstein-Barr virus (EBV) infection, as shown by negative results of both in situ hybridization and polymerase chain reaction. This neoplasia may be defined as a peculiar form of lobular carcinoma, therefore, more representative of an unusual microscopic pattern than a distinctive clinicopathologic entity in itself.

PMID: 10993283 [PubMed - indexed for MEDLINE]

77. Eur J Gynaecol Oncol. 2000;21(3):305-8.

Hormonal modulation of GM-CSF receptor alpha-chain in in vitro models of endometrial cancer.

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Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine that stimulates the proliferation and differentiation of bone marrow progenitors. Moreover, the presence and activity of GM-CSF and its receptor (GM-CSF-r) has been documented on tissues and cell lines of a non-hemopoietic origin. In this paper we studied the expression and putative role of GM-CSF and GM-CSF-r in endometrial cancer. The modulation of GM-CSF-r alpha-chain upon progesterone treatment suggests a role for GM-CSF and its receptor in the pathogenesis and development of endometrial cancer.

PMID: 10949402 [PubMed - indexed for MEDLINE]

78. Pathologica. 2000 Apr;92(2):132.

Intestinal stromal tumors with skeinoid fibers in patients with type I neurofibromatosis: histological and ultrastructural evaluation of a case.

[Article in Italian]

Boldorini R, Tosoni A, Ribaldone R, Surico N, Leutner M, Nebuloni M, Monga G.

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PMID: 10838889 [PubMed - indexed for MEDLINE]

79. J Neurovirol. 2000 Feb;6(1):46-50.

Etiology of microglial nodules in brains of patients with acquired immunodeficiency syndrome.

Nebuloni M, Pellegrinelli A, Ferri A, Tosoni A, Bonetto S, Zerbi P, Boldorini R, Vago L, Costanzi G.

L. Sacco Institute of Biomedical Sciences, University of Milan, L. Sacco Hospital, Italy.

Microglial nodules associated with opportunistic and HIV-related lesions are frequently found in the brains of AIDS patients. However, in many cases, the causative agent is only presumptively suspected. We reviewed 199 brains of AIDS patients with micronodular lesions to clarify their etiology by immunohistochemistry (to *Toxoplasma gondii*, cytomegalovirus, herpes simplex virus I/II, varicella zoster virus and HIV-p24 core protein), PCR (for herpetic viruses and *Mycobacterium tuberculosis*) and electron microscopy. Productive HIV infection was observed in 110 cases (55.1%): 30 cases with *Toxoplasma gondii* encephalitis, 30 with cytomegalovirus encephalitis, eight with multiple cerebral diseases, while in the remaining 42 cases HIV was the only pathogenetic agent. Multinucleated giant cells (hallmark of HIV infection) were found in the MGNs of 85/110 cases with HIV-related lesions; the remaining 25 cases had only p24 positive cells but no multinucleated giant cells. In these latter cases the micronodular lesions had been initially attributed to the main opportunistic agent found in the brain, or defined as subacute encephalitis. Individual microglial nodules positive for an opportunistic pathogen were generally negative for HIV antigens. In 13 cases no opportunistic agent or HIV productive infection was found. In these cases, PCR and electron microscopy examination for HIV and other viral infections were negative. Our data suggest that HIV-immunohistochemistry should be used for the etiological diagnosis of micronodular lesions in AIDS brains, even in the presence of other pathogens. After extensive search, the etiology of the microglial nodules remains unknown in only a small percentage of cases.

PMID: 10786996 [PubMed - indexed for MEDLINE]

80. J Exp Clin Cancer Res. 1999 Dec;18(4):567-9.

Mixed follicular and parafollicular thyroid carcinoma.

Vitri P, Galimberti A, De Pasquale L, Vago L, Boldorini R, Bastagli A.

II Dept. of General Surgery L. Sacco Hospital, University of Milan, Italy.
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A rare case of mixed follicular-parafollicular thyroid carcinoma which occurred in a 50-year-old man, is reported. The ultrastructural aspects of the tumor showed: a biphasic growth pattern with microfolliculi and solid areas; the coexpression of thyroglobulin and calcitonin antigens in the same follicle-like structures; the presence of neuroendocrine granules, microvilli and intracytoplasmic canaliculi bordered by microvilli. These characteristics lead us to a diagnosis of mixed follicular-parafollicular thyroid carcinoma.

PMID: 10746987 [PubMed - indexed for MEDLINE]

81. Hum Pathol. 2000 Mar;31(3):394-5.

JC virus in human glial-derived tumors.

Caldarelli-Stefano R, Boldorini R, Monga G, Meraviglia E, Zorini EO, Ferrante P.

Fondazione Don C. Gnocchi, IRCCS, Cattedra di Virologia, Università di Milano, Milan, Italy.

To investigate the presence and the role of polyomaviruses JC (JCV), BK (BKV), and the simian polyomavirus (SV40) in human brain tumors, samples from 25 glial-derived tumors (10 astrocytomas, 5 ependymomas, 5 oligodendrogliomas, and 5 glioblastomas) were examined by means of molecular biology and immunohistochemistry. Nested PCR of the large T (LT) region and its sequence analysis showed JCV in 6 cases (4 astrocytomas, 1 oligodendroglioma, and 1 ependymoma), while the transcriptional control region (TCR) was amplified only in 1 astrocytoma, the oligodendroglioma, and the ependymoma, one of which (astrocytoma) also stained positively by immunohistochemistry (JCV LT). TCR sequence analysis of the oligodendroglioma showed a JCV rearranged structure not related to a known viral strain, while the astrocytoma and the ependymoma disclosed a JCV Mad-4 strain that is known to induce brain tumors in animals. We suggest that JCV could have played a role in the pathogenesis of these brain tumors.

PMID: 10746685 [PubMed - indexed for MEDLINE]

82. Acta Cytol. 2000 Mar-Apr;44(2):205-10.

Cytologic and biomolecular diagnosis of polyomavirus infection in urine specimens of HIV-positive patients.

Boldorini R, Zorini EO, Viganò P, Nebuloni M, Mena M, Monga G.

Dipartimento di Scienze Mediche, Facoltà di Medicina e Chirurgia, Università del Piemonte Orientale Amedeo Avogadro, Novara, Italy.

OBJECTIVE: To evaluate the frequency of human polyomavirus reactivation in urine specimens from HIV-positive patients; compare the sensitivity of cytology, immunohistochemistry and molecular biology; differentiate viral genotypes; and correlate the results with urinary cytologic abnormalities.

STUDY DESIGN: Urine specimens from 78 unselected HIV-positive patients were evaluated by means of cytology, immunohistochemistry and nested polymerase chain reaction (n-PCR) to evaluate the presence of polyomaviruses. Restriction fragment length polymorphism (RFLP) was carried out in positive cases in order to differentiate BK virus (BKV) from JC virus (JCV). CD4 cells and serum creatinine levels were evaluated as indices of immune status and renal function, respectively, whereas the presence of red blood cells was used as an index of urogenital damage.

RESULTS: Cytologic evidence of polyomavirus infection was found in 17 samples and immunohistochemically confirmed in 9; another 6 cytologically negative cases were detected by means of immunohistochemistry. In all cases, only one or two cells showed typical viral inclusions or positive staining. n-PCR identified 44 positive samples, thus confirming all of the cytologically and immunohistochemically positive cases and detecting polyomavirus genome in a further 21. RFLP detected 39 JCV, 1 BKV and 4 JCV-BKV infections. No correlation was found between the presence or type of polyomavirus and immune status, but red blood cells were found more frequently in the positive than in the negative samples. Serum creatinine levels fell within the normal range in all cases.

CONCLUSION: Molecular biology is the most sensitive tool for detecting polyomavirus urinary infection in HIV-positive patients and the only reliable method of differentiating JCV and BKV viral genotypes.

PMID: 10740607 [PubMed - indexed for MEDLINE]

83. Arch Pathol Lab Med. 1999 Sep;123(9):807-11.

BK virus renal infection in a patient with the acquired immunodeficiency syndrome.

Nebuloni M, Tosoni A, Boldorini R, Monga G, Carsana L, Bonetto S, Abeli C, Caldarelli R, Vago L, Costanzi G.

L. Sacco Institute of Biomedical Sciences, Pathology Unit, Milan, Italy.

BACKGROUND: We describe herein a patient with the acquired immunodeficiency syndrome and renal failure due to biopsy-proven BK virus (BKV) infection. Three months after the diagnosis of the renal viral infection, his condition remained

unchanged. Although BKV has previously been shown to be associated with ureteral stenosis and renal damage in renal transplant patients, to our knowledge, the literature contains only 3 cases describing the presence of BKV lesions in the kidneys of immunosuppressed patients who had not undergone transplantation. METHODS: The presence of BKV infection was demonstrated by means of histology, immunohistochemistry with polyclonal anti-SV40 antibody, immunoelectron microscopy, polymerase chain reaction, and enzymatic cleavage with BamHI. RESULTS: Histologic examination revealed interstitial inflammatory infiltrates and tubules with enlarged and eosinophilic nuclei. CONCLUSIONS: The high frequency of latent BKV infection and its reactivation during immunosuppression suggest that the possibility of its involvement in renal damage should be considered in immunocompromised patients.

PMID: 10458828 [PubMed - indexed for MEDLINE]

84. Pathologica. 1998 Aug;90(4):412-3.

[Human microsporidiosis: emergence of a new opportunistic microorganism in patients infected with the human immunodeficiency virus (HIV)].

[Article in Italian]

Boldorini R, Tosoni A.

PMID: 9793405 [PubMed - indexed for MEDLINE]

85. Ital J Gastroenterol Hepatol. 1998 Aug;30(4):396-401.

Evaluation of iron status in patients with chronic hepatitis C.

Sartori M, Andorno S, La Terra G, Boldorini R, Leone F, Pittau S, Zecchina G, Aglietta M, Saglio G.

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Comment in

Ital J Gastroenterol Hepatol. 1998 Aug;30(4):402-4.

AIM: To evaluate the prevalence of iron overload in chronic hepatitis C and its relationship with liver histology.

PATIENTS AND METHODS: Serum iron, unsaturated iron binding capacity and ferritin levels were determined in 204 consecutive anti-hepatitis C virus positive subjects, whereas hepatic iron concentration, hepatic histological grading and staging, hepatitis C virus genotypes were further assessed in a subgroup of 50 patients who underwent liver biopsy for chronic hepatitis.

RESULTS: An increase in the serum markers of iron metabolism was more frequently found in subjects with aminotransferase activities above the normal range, whereas hepatic iron overload, established by direct hepatic iron determination,

was found only in 9/50 (18%) patients with chronic hepatitis C. No serum iron marker could reliably predict hepatic iron stores. Patients with mild iron overload usually showed active hepatitis and fibrosis, whereas iron overload was not present in patients without fibrosis or with very mild fibrosis. Two out of nine patients with iron overload were shown to be beta thalassaemia heterozygous, and two were heterozygous carriers of a putative haemochromatosis gene mutation (His63Asp).

CONCLUSIONS: Many anti-hepatitis C virus positive patients with elevated aminotransferase activities have serum ferritin levels above the normal range, but only a minority of patients with chronic hepatitis C have a mild iron overload. In chronic hepatitis C, a relationship does exist between hepatic iron content and liver fibrosis.

PMID: 9789136 [PubMed - indexed for MEDLINE]

86. Clin Infect Dis. 1998 Sep;27(3):504-8.

Microglial nodular encephalitis and ventriculoencephalitis due to cytomegalovirus infection in patients with AIDS: two distinct clinical patterns.

Grassi MP, Clerici F, Perin C, D'Arminio Monforte A, Vago L, Borella M, Boldorini R, Mangoni A.

I Clinica Neurologica, Clinica di Malattie Infettive, Anatomia Patologica-Istituto di Scienze Biomediche, Milano, Italy.

In patients with AIDS, cerebral infection due to cytomegalovirus (CMV) results in two distinct neuropathological patterns: microglial nodular encephalitis (MGNE) and ventriculoencephalitis (VE). In order to identify clinical features to facilitate the differential diagnosis of these two forms of CMV encephalopathy in living patients, we retrospectively reviewed the clinical records of 18 patients with MGNE or VE diagnosed at autopsy. We identified the following clinical features as distinguishing the two encephalopathies: (1) MGNE manifests earlier than VE; (2) the onset of MGNE is acute, whereas the onset of VE is insidious; (3) the onset of MGNE is marked by confusion and delirium, which do not occur in VE; (4) VE is frequently associated with radiculopathy, which is absent in MGNE; and (5) VE is associated with more marked alterations in cerebrospinal fluid (high protein levels and pleocytosis). The early neurological manifestations of MGNE should prompt a search for systemic CMV infection, which may lead to earlier treatment.

PMID: 9770148 [PubMed - indexed for MEDLINE]

87. Ital J Gastroenterol Hepatol. 1998 Jun;30(3):310-4.

Flutamide-induced acute hepatitis: investigation on the role of immunoallergic mechanisms.

Pontiroli L, Sartori M, Pittau S, Morelli S, Boldorini R, Albano E.

Institute of Medicine, University of Turin, Novara, Italy.

Comment in

Ital J Gastroenterol Hepatol. 1998 Jun;30(3):318-9.

Flutamide is a nonsteroidal antiandrogen drug used in the treatment of prostatic cancer. Hepatotoxic reactions due to flutamide have been reported with an incidence ranging from 1% to 5%. These reactions are usually reversible upon withdrawal of the drug but can occasionally be life-threatening. The mechanism of flutamide-associated hepatotoxicity is not well established. We report a case of a 69-year-old man with prostatic carcinoma in whom flutamide induced an acute hepatitis which resolved completely soon after drug withdrawal. In this patient, we have studied the possible involvement of an immunological mechanism in causing flutamide hepatitis by investigating the presence of circulating antibodies directed against reactive metabolites of flutamide bound to liver proteins with enzyme-linked immunosorbent assay technique. Although, in the present case, we have failed to detect IgG reacting with rat liver microsomes incubated in vitro with flutamide, this does not completely rule out the possibility of an immunological involvement in flutamide hepatotoxicity. The possibility of severe flutamide-related injury, independently of the underlying pathogenic mechanism, strongly suggests the need for careful monitoring of liver enzymes in patients taking this drug.

PMID: 9759603 [PubMed - indexed for MEDLINE]

88. J Neurovirol. 1998 Aug;4(4):457-60.

VZV fulminant necrotizing encephalitis with concomitant EBV-related lymphoma and CMV ventriculitis: report of an AIDS case.

Nebuloni M, Vago L, Boldorini R, Bonetto S, Costanzi G.

Pathology Unit, L. Sacco Institute of Medical Science, University of Milan, Italy.

A case of AIDS with varicella zoster virus fulminant necrotizing encephalitis associated with cytomegalovirus ependymitis-subependymitis and a periventricular Epstein-Barr virus-related lymphoma is described. The patient had no herpes zoster cutaneous eruptions and died three days after the onset of symptoms. Varicella zoster virus and cytomegalovirus antigens were found by immunohistochemistry in the same area around a necrotic periventricular lesion; a periventricular lymphoma, large B cell type, was also observed. In situ hybridization with Epstein-Barr virus-encoded- RNAs probe was positive in about 40% of the neoplastic cells. The association of herpes-related lesions in the same cerebral region should be consistent in AIDS cases with acute neurological symptoms.

PMID: 9718139 [PubMed - indexed for MEDLINE]

89. Acta Otorhinolaryngol Ital. 1998 Feb;18(1):30-3.

[Pleomorphic adenoma of the nasal septum].

[Article in Italian]

Pisani P, Dosdegani R, Ramponi A, Boldorini R, Pia F.

Clinica ORL 2 Facoltà di Medicina e Chirurgia, Università di Torino, Ospedale Maggiore di Novara.

Pleomorphic adenoma is the most frequent form of tumor in the major and minor salivary glands. It can occasionally appear in other sites corresponding to areas with ectopic salivary tissue. A case is presented of pleomorphic adenoma of the nasal septum recently observed by the authors. Complete removal of the tumor lesion, with the entire support base, careful histopathological evaluation, a battery of immunohistochemical tests and a long-term follow-up constitute the correct approach to this pathology.

PMID: 9707728 [PubMed - indexed for MEDLINE]

90. Virchows Arch. 1998 Jun;432(6):535-9.

Renal Encephalitozoon (Septata) intestinalis infection in a patient with AIDS. Post-mortem identification by means of transmission electron microscopy and PCR.

Boldorini R, Monga G, Tosoni A, Didier ES, Nebuloni M, Costanzi G, Mazzucco G, Orenstein JM.

Dipartimento di Scienze Mediche, Facoltà di Medicina e Chirurgia di Novara, Italy.

We describe the occurrence of renal Encephalitozoon (Septata) intestinalis infection in a 35-year-old AIDS patient who died with disseminated tuberculosis. The patient did not complain of specific symptoms involving the kidney or lower urinary tract during life, but at autopsy, light microscopic examination of the kidney revealed numerous small round or oval bodies in the tubules and tubular cell cytoplasm that were interpreted as intracellular protozoa. Transmission electron microscopy of tissue retrieved from paraffin-embedded samples identified these organisms as microsporidia belonging to the Encephalitozoonidae family, but did not allow definitive identification of the species of infecting parasite. This was made possible only by means of Southern blot hybridization after the polymerase chain reaction, which recognized the micro-organism as E. intestinalis.

PMID: 9672195 [PubMed - indexed for MEDLINE]

91. Recenti Prog Med. 1998 Mar;89(3):126-9.

[Post-infantile giant cell hepatitis. Clinical and histological response to immunosuppressive therapy].

[Article in Italian]

Pittau S, Morelli S, Venturini E, Boldorini R, Sartori M.

Dipartimento di Scienze Biomediche ed Oncologia Umana, Università, Novara.

Giant cell transformation of hepatocytes combined with variable degrees of hepatocyte necrosis and liver fibrosis is distinctly uncommon in adults. In this age group it has most often been associated with autoimmunity, drug reaction and viral infection. Prognosis is considered quite severe ranging from mild fibrosis to established cirrhosis. We report a case of giant cell hepatitis that occurred in a 30 yrs old man, who had been taking ticlopidine for 3 years. The causative role of the drug is uncertain because aminotransferase did not fall after withdrawal. The patient fulfilled most of the criteria for a diagnosis of autoimmune hepatitis and was treated accordingly with prednisolone and azathioprine. Immunosuppressive therapy led to a clinical, biochemical and histological response.

PMID: 9586424 [PubMed - indexed for MEDLINE]

92. J Neurovirol. 1998 Apr;4(2):242-5.

PCR detection of JC virus DNA in the brain tissue of a 9-year-old child with pleomorphic xanthoastrocytoma.

Boldorini R, Caldarelli-Stefano R, Monga G, Zocchi M, Mediatì M, Tosoni A, Ferrante P.

Department of Medical Sciences, University of Medicine, Novara, Italy.

Pleomorphic xanthoastrocytoma (PXA) is a rare cerebral tumor of young adults with a slow growth and a good prognosis. Due to its peculiar histopathological findings, the tumor resemble to the lytic phase of progressive multifocal leukoencephalopathy (PML), a JC Virus (JCV) induced disease. For these reasons, the presence of JCV genoma and viral particles were searched for by means of nested polymerase chain reaction (nPCR) and electron microscopy (EM) in a 9-year-old child with PXA. Although EM did not reveal any viral particles, nPCR did reveal genomic sequences of the LT, R, and VP1 regions of JCV. Sequence analysis showed that the R region was mutated with respect to the archetypal form thus yielding the Mad 4 variant of JCV previously reported as being oncogenic in animals. We suggest that JCV may have played a role in the development of this tumor.

PMID: 9584961 [PubMed - indexed for MEDLINE]

93. J Clin Pathol. 1997 Sep;50(9):735-40.

Hepatic histology of patients with HIV infection and chronic hepatitis C treated with interferon.

Boldorini R, Viganò P, Monga G, Nebuloni M, Cargnel A, Gubertini G, Migliaretti G, Costanzi G.

Dipartimento di Scienze Mediche, Facoltà di Medicina e Chirurgia di Torino, sede di Novara, Italy.

AIMS: To evaluate the histological changes seen in liver biopsies after interferon (IFN) treatment in patients with chronic hepatitis C and human immunodeficiency virus (HIV) infection.

METHODS: Twenty four intravenous drug users with chronic hepatitis C were investigated histologically before beginning a 12 month course of IFN treatment and 18 months later. Twelve were HIV positive, without opportunistic or other viral infections (group A), and 12 were HIV negative (group B).

RESULTS: According to alanine amino-transferase concentrations, four sustained responders and eight non-responders were found in group A; six sustained responders, five relapsers, and one non-responder were found in group B. HCV RNA became negative in one sustained responder of group A and in the six sustained responders of group B. When histological findings of biopsies performed before therapy and 18 months later were compared, no significant changes in the mean value of Knodell's index and subindices were found in group A, whereas in group B Knodell's index, piecemeal necrosis, and focal hepatocellular necrosis decreased significantly.

CONCLUSIONS: In chronic hepatitis C, coinfection with HIV showed a tendency towards a lower response to IFN, although this did not reach statistical significance; however, none of the HIV positive patients developed cirrhosis during the follow up and this should be considered in clinical management of such patients.

PMCID: PMC500169

PMID: 9389973 [PubMed - indexed for MEDLINE]

94. Exp Hematol. 1997 Nov;25(12):1219-26.

GAS6, the ligand of Axl and Rse receptors, is expressed in hematopoietic tissue but lacks mitogenic activity.

Avanzi GC, Gallicchio M, Cavalloni G, Gammaitoni L, Leone F, Rosina A, Boldorini R, Monga G, Pegoraro L, Varnum B, Aglietta M.

Dipartimento di Scienze Mediche, Facoltà di Medicina di Novara, Italy.

GAS6, a gene previously identified as growth arrest specific, has been demonstrated to be the ligand of Axl, a novel tyrosine kinase receptor widely expressed in both normal and neoplastic hematopoietic tissue. We have observed previously that GAS6 mRNA was present in whole bone marrow. This preliminary

finding prompted us to investigate the presence of GAS6 in hematopoietic tissue and the possible role of this molecule in controlling the proliferation of hematopoietic precursors. We report here that the protein GAS6 is diffusely present in hematopoietic tissue, both in stromal and in hematopoietic cells, and that, among these cells, positivity is observed in megakaryocytes and myelomonocytic precursors. Furthermore, our data suggest that GAS6 is not a growth factor for hematopoietic progenitors or stromal fibroblasts. Despite the fact that both the Axl receptor and its ligand, GAS6, are expressed in hematopoietic tissue, the biological role of their interactions remains to be determined.

PMID: 9357964 [PubMed - indexed for MEDLINE]

95. Eur J Gastroenterol Hepatol. 1997 May;9(5):497-503.

Liver iron influences the response to interferon alpha therapy in chronic hepatitis C.

Fargion S, Fracanzani AL, Sampietro M, Molteni V, Boldorini R, Mattioli M, Cesana B, Lunghi G, Piperno A, Valsecchi C, Fiorelli G.

Institute of Internal Medicine and Medical Physiopathology, University of Milan, Maggiore Hospital IRCCS, Italy.

OBJECTIVE: To define whether there is any relation between the iron status of patients with hepatitis C virus (HCV) chronic liver disease and their response to interferon therapy.

DESIGN: To evaluate the long-term response to 1 year of interferon therapy with addition of phlebotomies after 3 months of treatment if at that time alanine aminotransferase (ALT) had not normalized in a group of patients with HCV-positive chronic liver disease whose iron status had been characterized.

SETTING: A northern Italian hospital.

PARTICIPANTS: Fifty-eight anti-HCV-positive patients (four HCV-RNA negative) with biopsy proven chronic hepatitis and no evidence of iron overload as indicated by normal transferrin saturation at the time of enrollment in the study.

INTERVENTION: Three times a week intramuscular injection of alpha interferon 3 MU for 1 year with addition of phlebotomies (350 ml/week) till iron depletion if after 3 months of interferon therapy ALT had not normalized.

RESULTS: A long-term response was observed in 19 of the 52 patients who completed the treatment, four HCV-RNA negative and 15 positive. The four RNA-negative and seven of the 15 RNA-positive long-term responders had been treated with interferon alone, and the other eight also with phlebotomies. At univariate analysis only HCV genotype, gamma-glutamyltranspeptidase and liver iron concentration were significantly associated with response whereas sinusoidal iron deposition was of borderline significance. No association was found with sex, age, duration of disease, histology, Knodell score, transferrin saturation %, serum ferritin, hepatocytic iron score, and portal iron score. HCV-RNA serum levels, measured in 29 patients, did not correlate with response. At multivariate analysis liver iron concentration was still significant and one unit reduction of liver iron concentration (natural logarithm transformed) was associated with 2.95

odds ratio of response.

CONCLUSION: These results indicate that iron in the liver is more closely related to response to interferon than the other variables considered, including HCV characteristics.

PMID: 9187884 [PubMed - indexed for MEDLINE]

96. AIDS. 1997 Apr;11(5):690-1.

HIV encephalitis and HIV leukoencephalopathy are associated with distinct clinical and radiological subtypes of the AIDS dementia complex.

Grassi MP, Clerici F, Boldorini R, Perin C, Vago L, D'Arminio Monforte A, Borella M, Nebuloni M, Mangoni A.

PMID: 9108957 [PubMed - indexed for MEDLINE]

97. Mod Pathol. 1997 Mar;10(3):159-67.

Renal changes in patients with acquired immunodeficiency syndrome: a post-mortem study on an unselected population in northwestern Italy.

Monga G, Mazzucco G, Boldorini R, Cristina S, Giacalone A, Fortunato M, Motta M, Campobasso O.

Dipartimento di Scienze Biomediche e Oncologia Umana, Sezione di Anatomia Patologica Torino, Italy.

The renal pathologic features of 120 consecutively autopsied patients affected by acquired immunodeficiency syndrome was investigated by light microscopic analysis. Various associated renal changes were found in 82 patients (68.3%). Glomerular changes were present in 25. The following diagnoses were made: mesangial glomerulonephritis (16 patients), defined by the presence of deposits in the mesangium and/or mesangial cell proliferation; membranous glomerulonephritis (4 patients), cirrhotic glomerulosclerosis (2 patients); and lupuslike glomerulonephritis (3 patients). Glomerular diseases seemed to be significantly associated with chronic hepatitis or liver cirrhosis. Interstitial inflammation was present in 19 cases: chronic pyelonephritis (2 patients), focal nephritis (5 patients), multiple cortical abscesses (7 patients), granulomatous nephritis (5 patients). Cryptococci were found in one and undetermined microorganisms in two cases of multiple cortical abscesses. Atypical mycobacteria were found in two cases of granulomatous nephritis. Mycotic infections were identified in another 6 patients, in whom they did not elicit any inflammatory response. It is worth stressing that, although various generalized infections are common in patients with acquired immunodeficiency syndrome, only cryptococci and atypical mycobacteria also frequently involve the kidney. Focal tubular necrosis was observed in 15 patients. Benign nephrosclerosis was the most common vascular change (27 patients). Changes recalling hemolyticuremic and localized intravascular coagulation were found in three and six patients, respectively. Our

data, dealing with a European Caucasian population, considerably differ from those reported in North American literature, in as much as we found no cases of human immunodeficiency virus nephropathy. Conversely, immune-mediated glomerular diseases were frequent, in agreement with recent studies on renal biopsy specimens from AIDS patients with acquired immunodeficiency syndrome. This type of infections, supplies multiple sources of antigens that may stimulate immune complex formation and, therefore, glomerular diseases.

PMID: 9071721 [PubMed - indexed for MEDLINE]

98. Ann Ital Med Int. 1997 Jan-Mar;12(1):35-8.

Systemic infection by JC virus in non-HIV induced immunodeficiency without progressive multifocal leukoencephalopathy.

Bordin G, Boldorini R, Caldarelli Stefano R, Omodeo-Zorini E.

Divisione di Medicina Interna, Azienda Ospedaliera Maggiore della Carità di Novara.

Reactivation of latent JC virus in immunodeficient subjects can lead to a demyelinating disease following lytic oligodendrocyte infection. It is known as idiopathic CD4+ lymphocytopenia and rarely occurs in immunosuppressed patients who are not infected by HIV. We describe a case of persistent idiopathic CD4+ lymphocytopenia in an HIV-negative 65-year-old woman. At autopsy, polymerase chain reaction analysis evidenced JC virus DNA in kidney, brain and liver although there were no signs of progressive multifocal leukoencephalopathy or evidence of oligodendrocyte infection. While her disease was not HIV-induced, it closely resembled AIDS in terms of the nature of the immune derangement and the clinical picture. The case also evidences the reactivation of JC virus infection in non-HIV-related immunosuppression in cerebral and/or extracerebral sites: liver infection seems to be particularly relevant since it has not yet been recognized as a common target of JC virus infection or a source of virus spreading. The absence of any sign of progressive multifocal leukoencephalopathy was remarkable: histological examination failed to disclose demyelination or other progressive multifocal leukoencephalopathy changes, and the search for JC virus DNA with in situ methods also gave negative results. The lack of lytic brain infection in this case would seem to support the hypothesis that the expression of progressive multifocal leukoencephalopathy is directly dependent on the presence of HIV infection.

PMID: 9284596 [PubMed - indexed for MEDLINE]

99. J Intern Med. 1996 Jul;240(1):37-41.

Idiopathic CD4+ lymphocytopenia and systemic vasculitis.

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The syndrome defined as 'idiopathic CD4 lymphocytopenia' (ICL) is a rare disease of unknown aetiology, often associated with severe depression of immune defences and the occurrence of opportunistic infections. A case is reported wherein a severe immunodeficiency syndrome with persistent idiopathic CD4+ lymphopenia developed in a woman suffering from systemic microscopic polyarteritis; no signs of HIV 1/2 or HTLV I/II infection were evident. The patient died of widespread opportunistic infections. The association of ICL with vasculitis has never been reported until now. A link between the two diseases cannot be ruled out.

PMID: 8708590 [PubMed - indexed for MEDLINE]

100. Nephrol Dial Transplant. 1996 May;11(5):857-9.

Immunoactoid glomerulopathy in a HIV-infected patient: a novel association.

di Belgiojoso GB, Genderini A, Bertoli S, Boldorini R, Tosoni A, Vago L.

Nephrology Service, L. Sacco Hospital, Milan, Italy.

PMID: 8671910 [PubMed - indexed for MEDLINE]

101. Pathol Res Pract. 1996 Mar;192(3):249-59.

Intracellular protozoan infection in small intestinal biopsies of patients with AIDS. Light and electron microscopic evaluation.

Boldorini R, Tosoni A, Mazzucco G, Cernuschi M, Caramello P, Maran E, Costanzi G, Monga G.

Dipartimento di Scienze Mediche, Facoltà di Medicina e Chirurgia di Novara, Italy.

Small intestinal biopsies of 21 patients with acquired immunodeficiency syndrome (AIDS) with light microscopic findings diagnostic or suspicious for parasite infection were investigated by transmission electron microscopy (TEM). TEM allowed us to identify and specify the genus and species of involved parasites in 16 out of the 21 cases: 7 *Cryptosporidium parvum*, 5 *Enterocytozoon bienewisi* and 4 *Isospora belli*. *Cryptosporidium* was easily identified on light microscopy (LM), and only slightly influenced by parasite burden in all the 7 cases; TEM confirmed LM diagnosis and made it possible to characterize the parasites as *C. parvum*. The identification of *Microsporidium* on LM in our cases was related to the burden of parasite; its presence was certainly identified in 2 cases and suspected in 3. TEM allowed to identify these parasites as *E. bienewisi*. Intracytoplasmic coccidia could be detected with certainty in semithin sections in all 4 cases, but TEM was always needed to specify the infectious agent as *I. belli*. In 5 cases the suspicious of protozoan infection on LM (3 microsporidia, 1 intracytoplasmic

coccidia and 1 *Cryptosporidium*) was not confirmed by TEM. Our data suggest that TEM is an appropriate diagnostic tool in this field of pathology and necessary in most of the cases.

PMID: 8739472 [PubMed - indexed for MEDLINE]

102. J Endocrinol Invest. 1995 Dec;18(11):862-8.

Ultrastructural evidence of thyroid damage in amiodarone-induced thyrotoxicosis.

Cappiello E, Boldorini R, Tosoni A, Piraneo S, Bernasconi R, Raggi U.

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Amiodarone-induced thyrotoxicosis occurs in 2-12.1% of patients on chronic amiodarone treatment. In most cases its pathogenesis is related to iodine overload in the presence of preexisting thyroid abnormalities, such as multinodular or diffuse goiter or autonomous nodule. A minority of patients show apparently normal glands or pictures of non-autoimmune thyroiditis. However, there is recent evidence of a direct toxic effect of amiodarone, with consequent release of iodothyronines into the circulation. We report a patient with amiodarone-induced thyrotoxicosis with toxic thyroid effects demonstrated by electron microscopy in a fine-needle aspiration biopsy. There were three main pathologic findings: multilamellar lysosomal inclusions, intramitochondrial glycogen inclusions--both ultrastructural findings indicating thyroid cell damage--and a microscopic morphological pattern of thyroid cell hyperfunction. No inflammatory changes were found. Plasma thyroglobulin levels were high. The patient proved to be a non responder to simultaneous administration of methimazole (starting dose 30 mg/day) and potassium perchlorate (1000 mg/day for 40 days), while still taking amiodarone, thus providing evidence against a possible pathogenetic role of iodine overload. Dexamethasone (starting dose 3 mg/day) was added to methimazole. After three months euthyroidism had been restored and plasma thyroglobulin level substantially decreased. Subsequent subclinical hypothyroidism developed, which persisted after stopping antithyroid treatment and required substitution treatment with levothyroxine. In view of the primary role of lysosome function in the proteolysis of thyroglobulin molecules and of the energy-requiring carrier-mediated transport of monoiodotyrosine across the lysosomal membrane for iodine salvage and reutilization, we suggest that the pathological lysosomal and mitochondrial changes observed could be an ultrastructural marker for subsequent hypothyroidism in amiodarone-induced thyrotoxicosis. Our observations suggest the usefulness of ultrastructural thyroid evaluation and serial plasma thyroglobulin determinations to thoroughly evaluate the underlying pathogenetic mechanisms in amiodarone-associated thyrotoxicosis with apparently normal thyroid glands. Moreover, more knowledge of its pathogenesis could improve both prognostic stratification and treatment guides.

PMID: 8778159 [PubMed - indexed for MEDLINE]

103. Minerva Pediatr. 1995 Nov;47(11):489-91.

[The human tail. Report of a case of coccygeal retroposition in childhood].

[Article in Italian]

Falzone P, Boldorini R, Zilioli M, Sorrentino G.

Facoltà di Medicina, Università degli Studi - Novara.

The authors explain a little patient's case of coccydynia by back-position of the coccyx; the patient underwent an operation of partial resection with favourable clinical outcome. According to classification, the treated case corresponds to vestigial tail.

PMID: 8684345 [PubMed - indexed for MEDLINE]

104. J Med Virol. 1995 Nov;47(3):219-25.

PCR detection of JC virus DNA in brain tissue from patients with and without progressive multifocal leukoencephalopathy.

Ferrante P, Caldarelli-Stefano R, Omodeo-Zorini E, Vago L, Boldorini R, Costanzi G.

Institute of Medical Microbiology, University of Milan, Italy.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system, which is thought to be a result of the reactivation of JC virus (JCV), a human polyomavirus. The disease occurs in individuals with immunosuppression and in recent years there has been an increase in PML cases due to AIDS. A nested polymerase chain reaction (n-PCR) was employed to detect JCV and BK virus (BKV) DNA in brain tissue collected postmortem from 28 AIDS patients with PML and from 13 patients without PML, but with other diagnoses, including solid tumors, Alzheimer's disease, thromboembolism, myocardial infarction and acute cerebrovascular diseases. All 28 brain specimens from the patients with PML were positive for JCV DNA when tested by n-PCR and three of the latter were also positive for BKV DNA. These results were confirmed by an enzyme restriction analysis and a DNA hybridization assay. Interestingly, in this study, JCV DNA was also found in 6 brain tissue specimens from 4 subjects with diseases unrelated to PML or AIDS. All the brain specimens from the control group were negative for BKV DNA. The results confirm that the n-PCR is a useful tool for PML diagnosis. The presence of JCV DNA in the brain tissue of patients without PML is particularly important since it indicates that JCV could be latent in the brains of immunocompetent individuals. Moreover, detection of simultaneous presence of JCV and BKV in the brain tissue of the patients with PML demonstrates that BKV may also infect the human brain without causing any apparent neurological disease.

PMID: 8551272 [PubMed - indexed for MEDLINE]

105. Pathologica. 1995 Oct;87(5):534-38.

[Myoepithelial-epithelial carcinoma of the parotid: cyto-histological description of a case].

[Article in Italian]

Zocchi M, Nicosia G, Ramponi A, Pisani P, Boldorini R.

Servizio di Anatomia Patologica, Azienda Ospedaliera Maggiore della Carità di Novara.

We report a case of epithelial-myoepithelial carcinoma of the parotid gland arised in a 72 years-old woman, in which the diagnosis was suspected on fine-needle aspiration and confirmed on surgical specimen. Immunohistochemical evidence for the dual differentiation (glandular and myoepithelial) of the tumour was obtained both on surgical specimen and cytological inclusion. Morphological features and proliferating index (MIB1) analysis suggest that this case is an intermediate grade malignant neoplasm. Main differential diagnosis of the epithelial-myoepithelial carcinoma with predominantly clear cell tumours of the salivary glands were discussed.

PMID: 8868183 [PubMed - indexed for MEDLINE]

106. J Clin Pathol. 1995 Oct;48(10):975-8.

Acute hepatic and renal failure caused by Pneumocystis carinii in patients with AIDS.

Boldorini R, Guzzetti S, Meroni L, Quirino T, Cristina S, Monga G.

Dipartimento di Scienze Mediche, II Facoltà di Medicina e Chirurgia di Novara-Università di Torino, Italy.

Clinical and pathological findings are described in two AIDS patients with Pneumocystis carinii infection who received prophylactic treatment with nebulised pentamidine and developed unusual hepatic and renal failure. Histological examination showed clumps of P carinii massively obstructing hepatic sinuses and portal vessels in the first patient, and merular and intertubular capillaries in the second. These findings could explain the unusual clinical features, characterised by acute hepatic and renal failure.

PMCID: PMC502963

PMID: 8537506 [PubMed - indexed for MEDLINE]

107. Am J Kidney Dis. 1995 Sep;26(3):446-53.

Pattern of glomerular involvement in human immunodeficiency virus-infected patients: an Italian study.

Casanova S, Mazzucco G, Barbiano di Belgiojoso G, Motta M, Boldorini R, Genderini A, Monga G.

Laboratorio di Microscopia Elettronica, Ospedale M. Malpighi, Bologna, Italy.

Renal biopsy specimens from 26 adult human immunodeficiency virus (HIV)-infected patients with glomerular involvement were reviewed from the files of three hospital pathology services in Northern Italy. All the patients were Italian and most (19 of 26 patients) were intravenous drug addicts. The types of glomerular lesions were as follows: minimal-change glomerulopathy (two cases), mesangial proliferative glomerulonephritis (GN) with scanty immunoglobulin deposits (four cases), and various patterns of immune complex-mediated glomerulonephritis, including postinfectious GN (six cases), membranoproliferative GN (one case), membranous GN (three cases), immunoglobulin (Ig) A nephropathy (four cases), a mixed membranous and proliferative (three cases) and diffuse proliferative lupus-like pattern with subendothelial deposits, and intraluminal thrombi (two cases) or subepithelial and subendothelial deposits (one case). None of the patients had evidence of HIV-associated nephropathy. Our study confirms previous observations on the low incidence of HIV-associated nephropathy among white HIV-infected patients in Europe, where immune complex-mediated GN seems to predominate. Apart from the frequent electron microscopic observation of endothelial tubuloreticular structures, none of the reported lesions could be distinguished on morphologic grounds from those occurring in uninfected patients. The high variability of the glomerular lesions upholds the need for accurate diagnosis for the clinician confronted with an HIV-positive patient with suspected glomerular involvement.

PMID: 7645552 [PubMed - indexed for MEDLINE]

108. *Pathol Res Pract.* 1994 Dec;190(12):1208-11; discussion 1212-3.

Renal and hepatic angiomyolipomas in a child without evidence of tuberous sclerosis.

Monga G, Ramponi A, Falzoni PU, Boldorini R.

Dipartimento di Scienze Mediche, II Facoltà di Medicina e Chirurgia di Novara, Università di Torino, Italy.

A renal neoplasia, displaying the typical features of angiomyolipoma (an admixture of smooth muscle cells, mature adipocytes and tangles of thick-walled blood vessels) was found in a nine-year-old boy. In addition, cytoplasmic crystalloid structures and HMB 45 positivity were found in smooth muscle cells. Similar findings were also observed in a small nodule of the liver. According to literature data, angiomyolipoma is very rare in children and almost exclusively associated with tuberous sclerosis. Our case suggest that the diagnostic hypothesis of angiomyolipoma can not be disregarded when a renal mass is

identified in a young patient even in a clinical setting other than tuberous sclerosis.

PMID: 7792209 [PubMed - indexed for MEDLINE]

109. J Thorac Cardiovasc Surg. 1994 Aug;108(2):382-3.

Effects of storage with University of Wisconsin solution on human saphenous vein endothelium.

Santoli E, Vago T, Boldorini R, Sala E.

PMID: 8041188 [PubMed - indexed for MEDLINE]

110. Scand J Gastroenterol Suppl. 1994;201:28-34.

Effects of eradication of Helicobacter pylori on gastritis in duodenal ulcer patients.

Solcia E, Villani L, Fiocca R, Luinetti O, Boldorini R, Trespi E, Perego M, Alvisi C, Lazzaroni M, Bianchi Porro G.

Dept of Pathology, IRCCS Policlinico S. Matteo, Pavia, Italy.

The incidence and mean score of Helicobacter pylori-related, active antroduodenitis, lesions of superficial antral epithelium and duodenal gastric-type metaplasia were higher in endoscopic biopsies from a large series of patients with duodenal ulcer, when compared with asymptomatic patients or patients with non-ulcer dyspepsia. In 65 out of 73 patients with duodenal ulcer who could be followed up, H. pylori was eradicated using a combination of amoxicillin, 3 g daily, metronidazole, 1 g daily, and omeprazole, 20 mg daily. Rapid and permanent (6-month follow-up) abolition of both gastroduodenitis activity and lesions of the gastric surface epithelium was observed in these 65 patients. There was also a progressive decrease in total immune-inflammatory cells but without a substantial change in duodenal gastric-type metaplasia. Similar, but transient and quantitatively less prominent, improvements were observed in the antroduodenal mucosa, which had been temporarily cleared of H. pylori by treatment with omeprazole alone. Conversely, increased gastritis activity, epithelial lesions and immune-inflammatory cell scores were found in the short term in the corpus mucosa, which was not cleared of H. pylori after omeprazole treatment. It is concluded that, of the various H. pylori-related mucosal changes, antroduodenitis activity and antral epithelial lesions most closely reflect the severity of mucosal damage and are probably the most important factors in duodenal ulcerogenesis. Their complete and rapid suppression after bacterial eradication may be a key factor in preventing ulcer relapse.

PMID: 8047821 [PubMed - indexed for MEDLINE]

111. Ann Ital Chir. 1994 Jan-Feb;65(1):33-7.

[Incidentally discovered adrenal masses: a diagnostic and therapeutic protocol].

[Article in Italian]

Bastagli A, Boldorini R, De Pasquale L, Galimberti A, Piraneo S, Vitri P, Rovati V.

V Cattedra di Anatomia Patologica, Ospedale Luigi Sacco Università degli Studi di Milano.

PMID: 7978743 [PubMed - indexed for MEDLINE]

112. Ultrastruct Pathol. 1993 Nov-Dec;17(6):599-609.

Ultrastructural studies in the lytic phase of progressive multifocal leukoencephalopathy in AIDS patients.

Boldorini R, Cristina S, Vago L, Tosoni A, Guzzetti S, Costanzi G.

V Cattedra di Anatomia e Istologia Patologica, Istituto di Scienze Biomediche L. Sacco, Ospedale Sacco, Milano, Italy.

Brain fragments from eight cases (four autopsies and four biopsies) of patients with acquired immune deficiency syndrome (AIDS) with JC virus (JCV) lytic infections were examined ultrastructurally. Particular efforts were made to look for virions and their subcellular distribution in cells not usually involved by papovavirus infection. The cellular and subcellular distribution of virions was investigated with emphasis on cell types not normally associated with papovavirus infection. The pattern of JCV infection was as follows: 1) oligodendrocytes; nucleus only, 7 cases; cytoplasm only, no cases; 2) astrocytes (normal and "bizarre"); nucleus and cytoplasm, two cases; cytoplasm only, four cases; 3) macrophages; nucleus and cytoplasm, one case; cytoplasm only, four cases; and 4) neurons; nucleus and cytoplasm, two cases; cytoplasm only, three cases. Perivascular, endothelial, ependymal, and microglial cells were never infected. Our ultrastructural data indicate that cell types other than oligodendrocytes can be involved productively by JCV in the lytic phase of progressive multifocal leukoencephalopathy (PML) in AIDS patients. Neuronal cells, especially, can be infected productively by the JCV, and this should be considered in clinical interpretation of cortical symptoms and signs in suspected or proven cases of PML.

PMID: 8122326 [PubMed - indexed for MEDLINE]

113. J Pediatr Gastroenterol Nutr. 1993 Oct;17(3):255-9.

Ultrastructural changes in the duodenal mucosa of HIV-infected children.

Fontana M, Boldorini R, Zuin G, Tosoni A, Costanzi G, Principi N.

Fourth Pediatric Department, University of Milan Medical School, Italy.

We studied the ultrastructure of duodenal biopsy specimens from six HIV-infected children with chronic gastrointestinal symptoms. A monomorphic pattern of microvillar damage (short and irregular microvilli, joined at their bases) was seen in all cases, even when the mucosa was normal on conventional histology. Among nine HIV antibody negative children, a similar pattern was seen only in three out of four celiac children with severely atrophic mucosa. No viral, bacterial, or protozoan pathogen was found. In HIV-infected children tubuloreticular inclusions were also seen in endothelial cells. These ultrastructural changes could help to account for the gastrointestinal symptoms in HIV-infected children.

PMID: 8271123 [PubMed - indexed for MEDLINE]

114. Presse Med. 1993 Jun 12;22(21):1013.

[Disseminated pneumocystosis. 3 cases in HIV seropositive patients].

[Article in French]

Quirino T, Capetti A, Boldorini R, Iemoli E, Almaviva M, Vigevani GM.

PMID: 8367433 [PubMed - indexed for MEDLINE]

115. Pathologica. 1993 Jan-Feb;85(1095):17-30.

[Anatomo-pathological features of JCV infection in patients with acquired immunodeficiency syndrome (AIDS). Histological, immunohistochemical, and ultrastructural study including the in situ hybridization technique of 54 AIDS autopsies].

[Article in Italian]

Boldorini R, Cristina S, Vago L, Trabattoni GR, Costanzi G.

Cattedra di Anatomia patologica, Ospedale L. Sacco di Milano.

Anatomopathological aspects of the JCV infection in subjects with AIDS. An histologic, immunohistochemical, ultrastructural and in situ hybridization study of 54 AIDS autopsies. Among 700 AIDS autopsies performed in our institute from 1984 till 1991 54 brain tissue of definite PML cases were extensively studied. In 10 cases formalin-fixed paraffin sections were immunostained with genus-specific anti-simian virus (SV) 40 antiserum and hybridized in situ with DNA probes for JCV respectively. Labeling patterns were generally similar in ICC and ISH: in early and typical cases mainly oligodendroglia harbored virus, whereas labeling of neurons and endothelia was absent. Nuclei and cytoplasmic processes of bizarre

astrocytes were occasionally labeled by ICC and ISH in typical and lytic lesions. Electron microscopic study performed in 7 cases demonstrated round and rod-shaped particles of papovavirus in the nuclei of oligodendrocytes; membrane-bound cytoplasmic collections of papovavirus were seen in few astrocytes. In 4 brain biopsies of "possible" PML on histology, a definite diagnosis was performed only using ICC, ISH and EM: therefore, we stress the utility of all these techniques as a diagnostic tool in HIV-related brain lesions. Pathogenetic hypothesis on the development of PML in HIV-infected patients are also reported.

PMID: 8390637 [PubMed - indexed for MEDLINE]

116. Eur J Cardiothorac Surg. 1993;7(10):548-52.

University of Wisconsin solution and human saphenous vein graft preservation: preliminary anatomic report.

Santoli E, Di Mattia D, Boldorini R, Mingoli A, Tosoni A, Santoli C.

Department of Thoracic and Cardiovascular Surgery, L. Sacco Hospital, Milan, Italy.

Endothelial damage of human saphenous vein (HSV) during the preparation for bypass grafting could affect graft patency. Improving the preservation of HSV could provide a longer and better patency of coronary artery bypass grafts. An electron microscopic comparative analysis of the effects of three different preservatives on HSV morphology was carried on in order to determine the best method to prevent or minimize possible endothelial damage. Distal segments of HSVs were harvested from 15 patients with a "no-touch" technique. Each segment was divided into seven specimens after a low pressure distension with saline solution. The first of them was fixed immediately after harvesting with 2.5% glutaraldehyde solution, for basal evaluation. Three were fixed after 30 min and three after 5 h preservation at 4 degrees C in a) autologous, oxygenated, and heparinized blood (AOHB), b) heparinized saline solution with papaverine (HSSP) and c) University of Wisconsin solution (UWS). The specimens preserved in AOHB showed marked endothelial cell detachment and endothelial cell loss after both preservation times (30 min and 5 h). The specimens preserved in HSSP for 30 min showed no alteration in endothelium in 12 cases, while a partial endothelial detachment with intracellular edema was present in the last 3 cases; all 5 h specimens showed only a few remnants of endothelial cells. The specimens preserved in UWS for 30 min showed a morphology comparable to specimens preserved in the saline solution for the same time; in the 5 h specimens a well preserved endothelium was found in 11 cases and partial endothelial detachment and subendothelial edema in the other 4.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 8267997 [PubMed - indexed for MEDLINE]

117. Am J Clin Pathol. 1992 Oct;98(4):467; author reply 468-9.

Duodenal biopsy specimens in HIV-infected patients.

Boldorini R, Vago L, Zuin G, Fontana M, Principi N, Constanzi G.

Comment on

Am J Clin Pathol. 1992 Jan;97(1):21-8.

PMID: 1415027 [PubMed - indexed for MEDLINE]

118. AIDS. 1992 Oct;6(10):1159-64.

AIDS-defining diseases in 250 HIV-infected patients; a comparative study of clinical and autopsy diagnoses.

d'Arminio Monforte A, Vago L, Lazzarin A, Boldorini R, Bini T, Guzzetti S, Antinori S, Moroni M, Costanzi G.

Clinic of Infectious Diseases, L. Sacco Hospital, University of Milan, Italy.

OBJECTIVE: To evaluate the correlation between clinical and autopsy findings in 250 AIDS patients.

METHODS: Clinical and autopsy diagnoses of AIDS-defining diseases in 250 AIDS patients who died in Milan between May 1984 and February 1991 were compared.

RESULTS: Pneumocystis carinii (PCP) and oesophageal candidiasis were the most frequent clinical diagnoses, while cytomegalovirus (CMV) infection was observed in almost half of the autopsies. Forty-seven per cent of the diseases found at autopsy had not been diagnosed during life; CMV infection, mycoses, HIV-specific brain lesions, cerebral lymphomas and progressive multifocal leukoencephalopathy (PML) had a higher rate of non-diagnosis in life. CMV visceral infection accounted for the majority of the diseases not recognized in life. In contrast, clinically diagnosed PCP, oesophageal candidiasis and, to a lesser degree, brain toxoplasmosis were often not found at autopsy, possibly indicating a significant rate of recovery and prevention of relapse. Finally, bacterial pneumonia and sepsis, although not AIDS indicator diseases, were observed in approximately one-third of the autopsies.

CONCLUSION: Considerable differences in the frequency and type of the AIDS-defining diseases diagnosed during life and at post mortem were found.

PMID: 1334675 [PubMed - indexed for MEDLINE]

119. Pathologica. 1992 May-Jun;84(1091):403-9.

Primary papillary serous tumor of the peritoneum. Report of a case.

Boldorini R, Cristina S.

Servizio di anatomia patologica dell'Ospedale L. Sacco, Milano.

In the present report we describe a rare papillary serous tumor of the peritoneum occurring in a woman without evidence of ovarian neoplasia. Histochemical,

immunohistochemical and ultrastructural findings are reported, with particular emphasis on electron microscopic results and on their importance in the differential diagnosis with malignant mesotheliomas.

PMID: 1281538 [PubMed - indexed for MEDLINE]

120. *Histol Histopathol.* 1992 Apr;7(2):291-300.

Hypophyseal pathology in AIDS.

Mosca L, Costanzi G, Antonacci C, Boldorini R, Carboni N, Cristina S, Liverani C, Parravicini C, Pirolo A, Vago L.

3rd Chair of Morbid Anatomy and Histopathology, Faculty of Medicine, Milan University, Italy.

One hundred and eleven pituitary glands of patients (93 males, 18 females; mean age 32 years, 5 months) who died of fully developed AIDS or ARC were examined under light microscopy with the aid of immunohistochemistry. On post mortem (p.m.) examination a wide series of multiorgan alterations was noticed. Microscopically various lesions in both adeno- and neurohypophysis were seen. These ranged from vessel damage to secondaries to systemic infections, neoplasms and functional derangements. Necrotic lumps due to recent infarction could appear in both parts of the gland, while old fibrous scars sustained a previously overcome necrosis. Different pathogens (mainly fungi) could be seen either within the gland or arising from its meningeal surroundings. Examples of tumour pathology were provided by microadenomas, gliosis/gliomas; the frequency of adenomas (11.7%) was similar to that typical of senility. The functional impairment was mainly connected with ACTH cell hyperplasia, which seems in keeping with corticoadrenal or ACTH-receptor damage.

PMID: 1325230 [PubMed - indexed for MEDLINE]

121. *Acta Biomed Ateneo Parmense.* 1992;63(1-2):43-9.

Wernicke's encephalopathy: occurrence and pathological aspects in a series of 400 AIDS patients.

Boldorini R, Vago L, Lechi A, Tedeschi F, Trabattoni GR.

V Cattedra di Anatomia patologica dell'Università di Milano.

BACKGROUND: Wernicke encephalopathy (WE), acute (microhaemorrhages) and chronic (proliferation of capillaries) is actually considered as a not uncommon, and curable, condition in several diseases, and not only in alcoholic patients. Why serotonergic nuclei, and whether blood brain barrier (BB) are involved were our questions.

METHODS: In a dramatic series of AIDS cases we selected 380 brains, all belonging to drug addicted subjects. In all Thiamine administration had been under 20 mg

pro die and by oral way. In the cases considered, opportunistic infections were present in the 40%, and/or HIV specificity in the 35%.

RESULTS: "Acute" WE was found in nearly the 10%. All patients presented with CNS lesions, other than those of WE, but HIV specificity was found only in 5. They all showed changes in Choroid Plexus, namely alterations of various type of the cuboid epithelium, such as swelling, disruption, hyperplasia.

DISCUSSION: WE is set in connection with pyruvate accumulation at capillary level, likely bound to the Thiamine deficiency and to the lack of energy thus induced. Apart from obvious haemorrhagic aspects, CFS studies in WE are lacking. Choroid structure is not merely a permeable membrane (CSF is not a filtrate). Our findings would suggest that Thiamine plays a role in the energy supply to BB. Moreover, the existence of free nerve endings through the ependyma for the release and uptake of monoamines, allows to consider the elective involvement of serotonergic neurons as somehow connected to the choroid plexus changes described.

PMID: 1340667 [PubMed - indexed for MEDLINE]

122. Acta Neurol (Napoli). 1990 Feb;12(1):91-4.

Primary central nervous system lymphomas in AIDS.

Rizzardini G, Boldorini R, Vivirito MC, Berta L, Vigevani GM, Milazzo F.

I Divisione di Malattie Infettive, Ospedale L. Sacco Milano.

PMID: 2337002 [PubMed - indexed for MEDLINE]