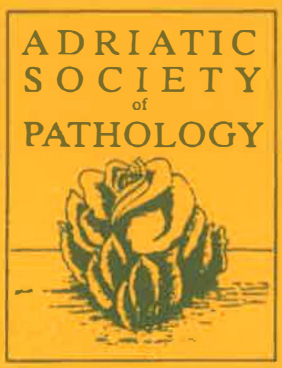
Adriatic Society of Pathology
20th International Meeting

Strunjan
June 25 - 26, 2005

Book of Abstracts



Institute of Oncology Ljubljana
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HEAD & NECK AND THYROID PATHOLOGY

FREE PAPERS

Cytogenetic analysis of premalignant and malignant lesions of the oral cavity

A. Farnedi[*], E. Magrini[*], L. Montebugnoli[°], C. Marchetti[§], A. Pession[*], MP. Foschini[*]

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Purpose of the study: The present is a prospective study based on 3 groups of patients (Group 1: patients showing clinical features of leukoplakia; Group 2: Oral Cavity Lichen Planus (OLP); Group 3; Squamous Cell Carcinoma of the oral cavity – (OSCC), to determine if chromosomal alterations can be helpful in the diagnosis of pre-neoplastic lesions. 9 cases of normal gingival mucosa were enrolled as control group.

Methods used: Biopsies were subdivided into 2 parts: one was formalin fixed and the remaining, after enzymatic digestion, was seeded for a primary short term culture. G-banded chromosomes were described according to the ISCN 1995 Guidelines for Cancer.

Results:

Group 1: "*clinical leukoplakias*", 13 cases. On histology, hyperkeratosis of the squamous epithelium was observed. One case showed dysplasia. Cytogenetic results showed the presence of clonal alteration (CA) in 3/13 cases and the presence of non clonal alteration (NCA) in 7/13 cases. Total cases with alterations: 10/13.

Group 2: *OLP*. 17 cases presented typical histological alterations as lymphoid infiltration, cytoplasmatic vacuolization of basal keratinocytes and apoptotic bodies. Cytogenetic results showed the presence of CA in 3/17 cases and presence of NCA in 13/17 cases. Total cases with alterations: 16/17.

Group 3: 7 cases of *OSCC*. All the patients underwent a biopsy of the lesion and a biopsy from clinically normal oral mucosa. Cytogenetic results showed the presence of CA in 1/7 cases (both tumour and clinically normal area) and the presence of NCA in 5/7 cases (both tumour and clinically normal area). Total cases with alterations: 6/7.

Group 4: *"negative controls"*, 9 cases. 3 cases presented a mild chronic inflammation. The remaining showed normal mucosa features. Cytogenetic analysis was normal in all cases (46,XX or 46,XY).

Discussion: Recent data demonstrate that mucosa presenting chromosomal instability shows high risk for malignant transformation. The present data show that karyotypes obtained from OSCC cultures frequently present NCA in both specimens (neoplasia and clinically normal area). This feature may be useful to the evaluation of field cancerization. In addition, the present results suggest that, on occasion, oral mucosa, even if free from dysplastic features, presents chromosomal instability. Further follow up of the patients will define if chromosomal instability is a risk factor for neoplastic transformation.

Intratumoral microvessel density in papillary thyroid carcinomas with and without metastases

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*"Ljudevit Jurak" University Department of Pathology and *University Department of ENT, Head and Neck Surgery, "Sestre milosrdnice" University Hospital, Zagreb, Croatia*

Purpose of the study: Papillary carcinoma of the thyroid is biologically relatively indolent neoplasm characterized by a favorable outcome. However, about 30% of the tumors follow unexpected course and behave in a malignant fashion. In order to investigate whether microvessel density (MVD) could serve to identify subgroup of patients with more aggressive behavior of the tumor we analyzed intratumoral microvessel count (MVC) and MVD in 50 localized papillary carcinomas (LPC), 50 papillary carcinomas with metastatic involvement of regional lymph nodes (PCMLN), and normal thyroid gland tissue. We also compared intratumoral MVD and tumor histological grade, between LPC and PCMLN. Finally we analyzed the relationship between intratumoral MVD and clinical parameters including age, sex, and tumor size.

Methods used: The study was carried out by immunohistochemistry on paraffin embedded material with monoclonal antibody to human Von Willebrand Factor (Dako, Denmark) following Microwave Streptavidin ImmunoPeroxidase protocol on DAKO TechMate^{TM} Horizon automated immunostainer. To determine MVD, sections were examined at low magnifications (x40, x100) to identify most vascular area of the tumor ("hot spot"). Within these "hot spots" counting was done in 10 non-overlapping consecutive high power magnifications fields (x400/0.144mm^2). The average MVC was calculated from 10 vascular "hot spots", and was also expressed as MVD/mm^2 of the tumor area. Statistical analysis was performed using Student T-test, Mann-Whitney U-test, χ^2-test, and Pearson correlations. The level of significance was set at $P<0.05$ in all cases.

Results: We observed statistically significant difference in the MVD between LPC and PCMLN ($p<0,001$) showing higher values of MVD in PCMLN group (118.0/mm^2 in LPC versus 201.29/mm^2 in PCMLN) and between G1 and G2 papillary carcinomas ($p<0,001$) (average MVD in G1 group – 132.14/mm^2 versus 208.53/mm^2 in G2 group).

Conclusion: Our results suggest that MVD in papillary carcinomas of the thyroid gland may help to identify a group of patients at high risk, associated with more aggressive biological behavior of these tumors, who can benefit from new therapies and careful follow up.

Correlations between colour Doppler sonography and three dimensional reconstruction of vessel distribution in thyroid nodules

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The evaluation of vascular changes is important in preoperative diagnoses using colour Doppler sonography (CDS). CDS assessment is classified into three types: type I: no vessels are detected inside the nodule; type II: vessels are seen at the periphery of the nodule; type III: vessels are present around and inside the nodules. Types I and II nodules are more frequently benign, while type III nodules are more frequently malignant. This classification is hampered by a high rate of false positive and false negative results (J Ultrasound Med 22: 127-133, 2003). In a preliminary study based on three dimensional (3D) reconstruction of thyroid nodules we demonstrated that each type of nodule has a characteristic vascular pattern (Virchows Archiv 445;189-198, 2004)

The purpose of the present study was to compare CDS features of thyroid nodules with the 3D reconstruction.

Materials and Methods: All patients underwent CDS before surgery. All thyroid specimens were serially sectioned and all nodules were processed for routine histology. After diagnosis based on haematoxylin-eosin, selected blocks were deparaffinized, cleared to methyl salicylate, and 3D examined using a stereomicroscope (Nikon, Japan), as previously described (2). Cases were classified according to the CDS pattern and were compared to the histological diagnosis and 3D features.

Results: 28 nodules from 17 patients (14 female, 3 male, aged from 35 to 71 years, mean 53 years) were observed.

Type I nodules (8 cases): all cases were diagnosed as colloid goiter. On 3D reconstruction the nodules showed only rare and thin vessels.

Type II nodules (3 cases): two cases were colloid goiters and at 3D were surrounded by vessels; the third case was a papillary carcinoma, follicular variant, that at 3D showed numerous thin anastomosing vessels.

Type III nodules (17 cases): seven cases were colloid goiter. Their 3D reconstruction showed intralesional hemorrage.

Ten cases were neoplastic: two papillary carcinomas, follicular variant, seven follicular adenomas (one with oxyphilic changes), and one follicular carcinoma. At 3D level papillary carcinomas showed numerous fine vessels variously anastomosing.

Six of the 8 follicular lesions were centered by a large vessel. Rare thin anastomosing vessels were observed in the adjacent tissue.

Conclusions: The present data show that CDS is a useful tool in the pre-operative diagnosis of thyroid nodules. Specifically type I nodules correspond to benign lesions. Type III nodules includes benign and malignant lesions. Follicular lesions present a large central vessel. This pattern of vascularization is not seen in colloid goiter or in papillary carcinoma.

Malignant lymphomas of the thyroid gland: a report of two cases

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Primary lymphomas of the thyroid gland are rare and frequently produce alterations of the underlying glandular parenchyma that may represent a challenge to the correct diagnosis.

We report on two cases of primary thyroid gland lymphomas (PLTs) in the setting of autoimmune thyroiditidis (Hashimoto's disease).

Case 1: An 82-year old male with a history of hypothyroidism and multinodular goiter presented in February 2003 with dysphonia, recurrent nerve paralysis, compression of trachea and cervical adenopathy. Two months later a fine needle aspiration (FNA) of the thyroid was performed and showed numerous lymphoid celis. A temptative cytological diagnosis of thyroiditis suggestive of Hashimoto's disease was rendered but further workup was recommended. A dominant thyroid nodule with indistinct margins and dishomogeneous structure was discovered by CT scan. The patient underwent total thyroidectomy with excision of cervical lymph nodes at the 4th and 6th levels. Histological examination was compatible with the diagnosis of extranodal marginal zone B-cell lymphoma (MALT-type lymphoma) with evolution to large B-cell lymphoma.

Case 2: A 45-year old woman with a history of hypothyroidism and Hashimoto's disease developed a thyroid nodule with an irregular echo pattem including hypoechogenic areas by ultrasonography. The FNA of this nodule revealed a large number of immature lymphoid elements, histiocytes, giant cells and epithelial cells with microgranulomas. On the basis of the cytologic findings surgical excision was recommended. A total thyroidectomy was performed. Histologic examination demonstrated diffuse large B-cell lymphoma (DLBCL) arising in the setting of Hashimoto's thyroiditis.

PTLs are uncommon tumors representing 5% of all thyroid neoplasms and 2.5% of extranodal lymphomas. These lymphomas usually arise in middle-to old age women in the setting of autoimmune thyroiditis and are extranodal marginal zone B-cell lymphoma (MALT-type lymphoma). Their evolution to DLBCL does not appear to be infrequent and is indicated by the presence of foci of large cell transformation intermixed with the low grade MALT-type lymphomatous infiltrate.

Case report: poorly differentiated carcinoma of thyroid gland combined with Hurthle cell carcinoma and well differentiated papillary carcinoma

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We describe an unusual combination of typical papillary carcinoma, poorly differentiated carcinoma and Hurthle cell carcinoma. In the literature we found two cases of mixed Hurthle cell and papillary carcinoma. Thyroid tumors of follicular origin are divided in 9 categories according to the WHO classification with papillary carcinoma being a most common of malignant tumors. The classical type of papillary carcinoma considered to have excellent prognosis unlike poorly differentiated variant of papillary carcinoma and Hurthle cell carcinoma.

Clinical data. Patient is a 77-old male with a nodule in the right lobe of thyroid gland that had been present for a year. The aspiration cytology showed a well differentiated follicular carcinoma. The both lobes of thyroid were resected. Positron emissive tomography was performed in order to search for possible primary tumor of unknown location but no abnormality was found. The patient underwent a 100mCi iodine 131 body scan and it demonstrated two foci of iodine uptake in the neck within the thyroid bed. Twenty two months after surgery the patient is well and disease free.

Pathologic findings. Material was a lobe of thyroid gland measuring 8:6.5:3 cm completely taken by grayish-white tumor. The tumor was restricted to the thyroid and there was no obvious invasion of surrounding structures. Histologically, the tumor was composed of large and irregular glands lined partly by the tall columnar cells with nuclei placed at the base of the cells and abundant clear cytoplasm and partly by the cuboidal cells some of which had eosinophilic granular cytoplasm with or without papillary projections. There were parts of tumor with a follicular and trabecular pattern and some solid areas as well composed of cells that partly showed oncocytic cytology but there were also solid areas of tumor cells without oncocytic cytology.

Immunohistochemical analysis showed no thyreoglobulin immunoreactivity in the papillary part and very weak and focal positivity in the oncocytic part of the tumor. The tumor showed no immunoreactivity to calcitonin, neuron specific enolase, synaptophysin or high molecular cytokeratin but was positive for TTF1 and low molecular cytokeratin.

Conclusion. In our case, it was expected that that the biology of the poorly differentiated part or the Hurtle cell carcinoma would dominate the disease course but the patient is alive and without disease progression 22 months after the surgery.

Oncocytic meningioma: a case with rapid progression after radio surgery

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Oncocytic meningioma is an uncommon variant of meningioma, characterised on histology by large, oxyphilic cells rich in mitochondria (1). This subtype of meningioma has been associated with a more aggressive behaviour and frequent recurrences.

We report a case of oncocytic meningioma that showed a dramatic progression after radiosurgery. A 49-year-old woman presented with a large basal-frontal tumour measuring 5 cm in greatest axis. On histology the tumour was composed by large polygonal cells, arranged in nests and sheets, showing finely granular eosinophilic cytoplasm. Mitoses were rare (2 per 10 high power fields) and necrosis was absent. Neoplastic cells resulted intensely positive with anti-mitochondrial antiserum. Ki67 antiserum stained nuclei of 3% of neoplastic cells. Ultrastructural examination revealed numerous, large, irregular mitochondria confirming the oncocytic features of the neoplastic cells. After one year, the patient was re-submitted for a second surgical resection of a residual lesion in the chyasmatic region. It was impossible to completely remove the lesion, so the patient was treated by radiosurgery one year later. The lesion recurred again and radiosurgery was repeated. Less than one year after the second radiotherapic treatment, the tumour recurred as multiple nodules. These recurrences shared similar histological, immunohistochemical and ultrastructural features as those observed in the primary tumour. Moreover, the Ki67 value was increased to 20%. The lesions did never show atypical meningioma features, according to the WHO classification (2). Nevertheless radiotherapy was performed because the original tumour was located in a site carrying high operative risks.

Today, 1 year after the last recurrence the patient shows a diffuse dissemination of intracranial nodules radiologically suggestive of disease regrowth.

The case here reported is a further example of the greater aggressiveness of oncocytic meningioma and stimulates discussion concerning the opportunity of radiotherapy in oncocytic tumours. The possibility that oncocytic meningioma is resistant to radiotherapy, as observed in other intracranial oncocytic tumours (3), should be taken into consideration.

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Otocephaly - a rare congenital malformation of the head and neck

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Introduction: Otocephaly is a causally heterogeneous, single developmental field defect that affects structures in the face and upper neck. Characteristic features are absence of the mandible and approximation of the ears in the midline region normally occupied by the mandible.

Case report: A 17-year old woman was admitted at 32+5 weeks gestation because of the onset of labor. It was her first, unregularly controlled pregnancy (elsewhere), and two ultrasonic examinations were allegedly normal. Her medical history was unremarkable, as well as that of the child's father. On amniotomy 6 liters of yellowish green amniotic fluid were found. Soon thereafter she gave birth to a malformed male child (1640g/43 cm). Intubation was attempted, but failed and death ensued after 5 min. Both placenta and the child were submitted for pathological examination. The child showed extreme microstomia and micrognathia, with ventrally displaced external ears. Radiograms showed no sign of the mandible. At autopsy, a blind ending oral cavity was found, together with bilaterally cleft palate and uvula. The pharynx also ended blindly (with a small nodule resembling abortive tongue) and was completely separated from the oral cavity. The nodule was microscopically made of three bundles of muscle covered with multilayered squamous epithelium and salivary gland tissue underneath. At serial cuts, immediately under the nodule, a calcified structure, probably hyoid bone was found. The oesophagus and trachea were patent, and all organs of the body showed normal gross morphology; microscopy revealed lung atelectasis and hemorrhage, hemorrhage in both adrenals and small hemorrhages in the epicardium.

Discussion: Otocephaly is the result of maldevelopment of the 1st and 2nd pharyngeal arches. Fetuses with otocephaly may have associated cardiac defects, renal anomalies, and bilateral pulmonary agenesis. Most patients die shortly after birth because spontaneous breathing as well as intubation is not possible. The ultrasound is the most important tool for antenatal recognition of this malformation.

Cornelia de Lange syndrome

C.I. Paulon[1], T. Rizzuti[2], L. Spaccini[3], L. Lalatte[3], G.P. Bulfamante[1]

[1]Unit of Human Pathology, D.M.C.O.- Medical School, University of Milan; [2]Unit of Human Pathology, I.C.P., Milan; [3]Unit of Medical Genetics, I.C.P., Milan, Italy

Purpose of the study: Cornelia de Lange Syndrome (CdLS) is a rare (1:10,000 live births) congenital syndrome depending on a combination of characteristics that may be recognized at birth or shortly after birth. The morphological and clinical phenotype is relatively consistent in all published cases. On the contrary, life expectance and quality remain unknown. Individuals with this syndrome have low birth weight, delayed growth, small stature, microcephaly, distinctive facial features (synophyrs, long eyelashes, short up-turned nose, thin down-turned lips), developmental delays, heightened sensitivity to touch, behavior difficulties (hyperactivity, short attention span, oppositional and repetitive behavior, and self-injurious behavior). Actually, only few cases of aborted fetuses with CdLS are reported. This paper describes fetal phenotype of CdLS and confronts it to the postnatal one.

Methods: We reported two cases of CdLS in 22nd and 23rd week aborted fetuses. Autoptic examination and microscopic slides were performed and evaluated. The features seen in our fetuses were compared to those previously observed in individuals with CdLS.

Results: The fetuses phenotypes consisting in facial dismorphism, IUGR, hypertrichosis, moderate microcephaly, resemble the characteristic features of the CdLS in living individuals. In one of the fetuses we observed an infrequent finding consisting of bilateral agenesis of radius, first metacarpus and first finger.

Conclusions: Our first case was characterized by bilateral agenesis of arm and hand bones that allow us to circumscribe the differential diagnosis to a limited group of syndromes. Additional characteristics of the fetus helped to establish the diagnosis of CdLS.

On the contrary, the second case was characterized by clear typical facial features of CdLS which were suspected in ultrasound 3D performed before the death of the fetus. The autopsy was crucial for the diagnosis.

Actually there are in course molecular studies in order to identify mutations in NIPBL gene which characterize 60% of CdLS cases.

DERMATOPATHOLOGY

FREE PAPERS

Biopsies of the skin, a seven years retrospective study

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Aim: In the last period occurrence of different types of skin lesions changed due to sun exposure, UV exposure in solariums and some other environmental and modish influences as well as due to new diagnostic and treatment possibilities. We compared incidence of different types of skin lesions during the last seven years and their sex distribution.

Material and methods: We analyzed "Thanatos" data base from the "Ljudevit Jurak" University Department of Pathology during the period 1998-2004. We divided skin biopsies into three groups: tumors, non-tumorous lesions and the lesions with descriptive diagnosis.

Results: A total number of skin biopsies made in the last seven years were 8767. In the 1998 there were 248 and in the 2004 there were 1861 skin biopsies. The incidence of skin tumors increased from 1.2% in the beginning to 13.0% in the end of the period. The incidence of non-tumorous skin lesions also increased, from 24.6% to 51.7%. On the other hand we observed relative decrease of biopsy specimens with descriptive diagnosis, from 74.2% to 35.3%.

In the 1998 there were 116 (46.8%) skin biopsies taken from females and 132 (53.2%) from males and in the 2004 there were 1053 (56.6%) skin specimens from females and 808 (43.4 %) from males.

Conclusion: On the basis of this investigation we can conclude that the number of skin biopsies as well as the incidence of tumors and non-tumorous lesions showed significant increase. Increase is particularly present in females.

Pseudoepitheliomatous hyperplasia associated with cutaneous primary melanoma: report of 2 cases

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Purpose of the study: Pseudoepitheliomatous hyperplasia (PEH) is a benign proliferation of the epidermis into irregular squamous strands extending down into the dermis. It can closely mimic a squamous cell carcinoma. We report two cases of cutaneous primary melanoma associated with an extensive pseudoepitheliomatous hyperplasia.

Patients and methods: First patient was 38 years old male presented with polypoid, brown skin tumor in femoral region measuring up to 1.5 cm. Second case was a 75 years old female with elevated brown tumor, measuring 0.8 cm in largest diameter. Pathohistological analyses revealed in the first case primary melanoma Clark IV, Breslow V and in the second case primary melanoma Clark III, Breslow III. In each case, histological examination also revealed epidermal hyperplasia with irregular cords of well-differentiated epithelial cells extending into the dermis and infiltrating among and around the melanoma cells. Admixture of neoplastic melanocytic and the hyperplastic keratinocytic component led us in each case to reconsider diagnosis of malignant melanoma and simultaneous invasive squamous cell carcinoma. Additional immunohistochemistry (HMB45, cytokeratin) was performed that identified and separated neoplastic melanocytic and hyperplastic epidermal component.

Discussion and conclusion: PEH is a benign pathological reaction pattern associated with persistent inflammation of the subjacent dermis due to a chronic wound, retained foreign material or an infection. PEH is also seen overlying granular cell tumor and cutaneous T cell tumor. The association of PEH with melanoma is rare. PEH may mimic squamous cell carcinoma and may complicate the diagnosis of cutaneous primary melanoma. The histogenesis of PEH is speculated to be due to the proliferative effect of cytokines released by inflammatory or tumor cells within the subjacent dermis. Histologically, unlike a squamous cell carcinoma, PEH never has atypical mitotic figures, rarely has dyskeratosis or atypical nuclei, and is never involved in vascular, lymphatic or perineural invasion. The histological features of PEH may obscure an underlying malignant process.

An unusual combination of nevi

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A 7-year-old boy presented with a history of a slightly asymetric pigmented macula located on his left cheek measuring 2 mm. The lesion was excised. A standard HE tissue section, Warthin-Starry silver stain and immunochistochemistry were performed.

Microscopic examination revealed an ill-defined dermal lesion composed of elongated melanocytes with dendritic processes and oval melanocytes dispersed between collagen bundles. No cellular atypia or mitotic figures were observed. Overlying this lesion, in the dermoepidermal junction and within the epidermis there were nests of plump epitheloid cells with large nuclei and prominent nucleoli. Small nests and single epitheloid cells were detected also in the papillary dermis, around hair follicles and at the dermoepidermal junction of skin appendages. Regarding this observations the diagnosis of the combined nevus, consisting of a blue nevus with congenital compound Spitz nevus was established.

The combined nevus is characterised by the presence of two or more different types of melanocytic nevi in a single lesion. The combination of a common nevus of compound type with a blue nevus seems to be the most common, detected also in conjunctiva. Combined nevus consisting of blue nevus with Spitz nevus is extremely rare. In a series of 7733 pigmented lesions, only four cases of blue nevi combined with Spitz nevi were found. Combined nevi are considered congenital melanocytic nevi indicating phenotypic diversity and genetic lability of melanocytic nevus cells.

Hemosiderotic fibrohistiocytic lipomatous lesion – A precursor lesion of pleomorphic hyalinising angiectatic tumor?

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Background: Hemosiderotic fibrohistiocytic lipomatous lesion (HFLL) and early pleomorphic hyalinising angiectatic tumor (PHAT) are two rare entities that show very similar morphological features. They are both characterized by an unusual admixture of fat and moderately cellular fascicles of monomorphic hemosiderin-laden spindle cells growing in a perivascular, periadipocytic and septal pattern as well as the presence of macrophages and chronic inflammatory cells.

Case report: A 47-year-old female presented with a slowly growing painful lesion of the ankle's soft tissue following an ankle distortion. Three years after a non-radical excision, the lesion recurred. At surgery, the lesion appeared to be a soft brown-yellowish mass measuring 1.9x1.2 cm, located in the subcutis, without clear boundaries from the surrounding tissue. Histologically, the initial and the recurring lesions were composed of hemosiderin-laden spindle cells growing around mature fat cells, blood vessels and fibrous septa. The nuclei of spindle cells displayed pseudoinclusions and lacked mitotic activity. Immunohistochemically, spindle cells were CD34-positive. No hyalinized, ectatic or aneurismal blood vessels were found in either the primary or in the recurrent lesion. Based on the characteristic morphology, a diagnosis of HFLL/early PHAT was made. At present, the patient is well with local recurrence and without metastases.

Discussion: HFLL is regarded as a reactive lesion associated with a history of previous trauma in the majority of patients. In contrast, PHAT is considered a tumor of intermediate malignancy, because of the high rate of local recurrence and local invasive growth. Histologically, classic PHAT is composed of sheets and fascicles of spindle and pleomorphic cells displaying very low mitotic activity and abundant hemosiderin in their cytoplasm. Cells are situated around angiectatic vessels which sometimes show extensive perivascular hyalinization. Areas of early PHAT are usually located at the periphery of the lesion, but can also be found admixed with classic PHAT.

The predominant localization of HFLL/early PHAT is the subcutaneous tissue of the ankle and the foot in middle-aged patients. Grossly, the lesions measure between 0.3 cm and 26.3 cm and are unencapsulated, although most commonly well circumscribed. Immunohistochemically, spindle cells are CD34-, vimentin- and calponin-positive and cytokeratin-, CD31-, desmin- and S100-negative. They are suggested to be uncommitted mesenchymal cells, possibly related to stromal fibroblasts.

Differential diagnosis of HFLL/early PHAT includes a variety of reactive and benign lesions, such as nodular fasciitis, benign fibrous histiocytoma, spindle cell lipoma and also dermatofibrosarcoma protuberans.

Conclusions: HFLL and early PHAT have similar, if not identical, histological appearance and probably represent the same lesion. Although both lesions may be characterized by invasive local growth and frequently recur following incomplete resection, metastases have not been described. Until more data become available on the biological potential of HFLL/early PHAT, e.g. reactive process or tumor, radical surgical excision and follow up of the patient remain the best treatment option.

Pacinioma of the cauda equina - a case report

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A male newborn presenting with a sacral red papule was diagnosed by ultrasound to have spina bifida occulta at the level of the 4th lumbar vertebra. Five months later, MRI revealed an oblongated lesion in the region of the filum terminale suspiciously connected to the subcutis, and tethered spinal cord. At surgery, a cord of yellow tissue was found at the level of L5-S1 and removed. The cord was running from the subcutis through the bone defect into the sacral spinal canal, where it entered the dura. Intradurally, it ran parallel to the filum terminale and was attached to the conus medullaris.

Histological examination of the cord showed adipose and fibrous tissue containing large and small nerve fascicles and several differentiated Vater-Pacinian corpuscles. The corpuscles contained a central axon, labelled with neurofilament, which was surrounded by S100 positive Schwann cells.

Vater-Pacinian corpuscles belong to the group of nervous end-organs found mainly in the subcutis, but detected also in the urinary bladder, pancreas and around joints. In the hand and foot, Pacinian hyperplasia, a painful lesion composed of differentiated, mainly hyperplastic Vater-Pacinian corpuscles must be distinguished from nerve tumors (Pacinian neurofibromas) harboring onion-bulb structure which closely resemble Vater-Pacinian corpuscles. Only two cases of multiple Vater-Pacinian corpuscles embedded in adipose tissue in association with spina bifida occulta have been reported. Due to their occurrence in the sacrococcygeal region, which is the primary site for congenital malformation, and their association with spina bifida occulta, the cords of differentiated Vater-Pacinian corpuscles seem to be more hamartomatous malformations than true neoplasms. In 1980, Bale proposed the term pacinioma to differentiate these probable malformations from pacinian neurofibromas.

Borrelia burgdorferi dissemination - detection of spirochetal DNA in skin, blood and urine from patients with erythema migrans

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Lyme borreliosis is a systemic infectious disease with a wide spectrum of symptoms affecting the skin, heart and musculoskeletal systems. In its initial stage its typical manifestation is the erythema migrans, a cutaneous lesion that occurs in up to 90% of patients.

In order to investigate the presence of the specific agent Borrelia burgdorferi in the early stages of the disease, DNA from paraffin embedded skin biopsies, urine and peripheral blood of 30 patients with clinically documented erythema migrans and without apparent systemic involvement was analysed by polymerase chain reaction.

Borrelia DNA in both blood and skin biopsies was detected in 23 patients, while in 9 patients it was discovered in urine and skin biopsies. These results demonstrate that Borrelia DNA is detectable systematically also in patients with early Lyme borreliosis. These findings strongly suggest a possible early dissemination of the causative agents even in the early phases of the disease when only a local infection is assumed.

Kaposi's sarcoma and Castleman's disease in a previously cystectomized and bilaterally nefrectomized, HIV-negative, 72 year-old man

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Castleman's disease - angiofollicular lymph node hyperplasia - is a rare disease with two identified forms: "localized", presenting as an isolated enlarged lymph node, and "multicentric", where several sites are involved. This second form is mostly found in HIV-positive patients where the possible etiopatogenetic agent HHV 8 is commonly detected with a Polymerase Chain Reaction test in peripheral mononuclear blood cells or in neoplastic tissue samples. Castleman's disease, particularly in this latter group of patients, is sometimes associated with Kaposi's sarcoma, which is a malignant skin tumour of vascular origin, strongly related to HHV-8 infection. Some authors have reported the association between these diseases also in immunosuppressed patients other than HIV-positive ones, such as transplanted patients, or in patients with severely impaired immunity . We report the case of a 72 year-old man, who, in his past history, underwent bilateral nefrectomy and cystectomy for recurrent urothelial papillary infiltrative neoplasm, and after a year of dialytic treatment developed Castleman's disease and Kaposi 's sarcoma, manifested as a swollen mass in the thoracic wall.

Squamous cell carcinoma of the breast

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Introduction: Pure squamous cell carcinoma (SCC) represents less than 1% of breast carcinomas. No definite prognostic criteria are available due to the rarity of this lesion and to the wide morphological spectrum of these lesions.

Purpose of the present study is to better define the morphological feature of SCC of the breast.

Materials and methods: eight cases of SCC of the breast were retrieved from the files of the Section of Anatomic Pathology of the University of Bologna at Bellaria Hospital and from the consultation files of one of us (VE). All the cases were formalin fixed and paraffin embedded. Serial sections were cut and immunohistochemically stained with antibodies against CK14, E-cadherin, estrogen and progesterone receptors, Ki67, p63 and CK7. In one case the specimen was received fresh, submitted to enzymatic digestion and cell suspensions were seeded for a primary short term culture.

Results: All the patients were female ranging in age from 44 to 80 years (mean 65.6 years). The lesions were located in the left breast in 7 cases, in the right breast in 1 case. All cases were monolateral and their size ranged from 1.5 to 24 cm (mean 6.5 cm). Five cases showed acantholytic features. On immunohistochemistry acantholytic features were highlighted by loss of E- cadherin expression. All the cases were CK 14 positive and lacked immunoreactivity for estrogen and progesterone receptors. P63 positivity was focally present in 3 cases and CK7 positivity was preserved in 2 cases. Ki67 positive cells were never less than 15% of the total neoplastic population (range 15-70% mean: 36%). Two cases presented lymph-node axillary metastases.

Cytogenetic analysis was performed in one case of acantholytic SCC, and showed numerical and structural alterations as: monosomy of chromosome 3, deletion of chromosome 16(q)(21.1-ter) and a translocation involving chromosome 16 and chromosome X.

Acantholitic SCC demonstrated an aggressive behaviour; follow-up was available in three of the five cases, two patients died of widespread metastatic disease four and twenty-four months after surgery, the third presented a local recurrence three months after surgery. Non acantholytic SCC: one of the five cases presented lymph-node metastases and local recurrences 18 months after surgery.

Conclusions: The present cases confirm that SCC can show a variety of morphological pattern. Acantholytic SCC are characterized by E-cadherin loss that in one case was sustained by loss of 16q. The present data confirm that acantholytic SCC shows a rapidly aggressive behaviour.

Myoepithelial markers are an important tool in the differential diagnosis of sarcomatoid metaplastic breast carcinomas

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Due to inconsistent cytokeratin (CK) expression in many sarcomatoid metaplastic breast carcinomas (MCs) and their histologic resemblance to various types of sarcomas or high grade phyllodes tumours (PTs) with stromal overgrowth, additional immunohistochemical markers play an important role in the differential diagnosis of these tumours. Although a myoepithelial immunophenotype of MCs has been reported in previous studies, a thorough immunohistochemical examination has not yet been performed.

We immunohistochemically assessed 20 MCs, the stromal component of 5 high grade PTs and 7 sarcomatoid tumours without panCK-expression ("NOS-type sarcomas") which histologically resembled spindle cell MCs with a fascicular growth pattern. Our immunohistochemical antibody panel included pan-cytokeratin (CK), low molecular weight CK (CK8/18), 4 basal cell type CKs (34βE12, CK5/6, CK14 and CK17), vimentin antibodies, as well as antibodies to established (SMA, CD10, p63, S100, maspin, calponin, GFAP, SM-myosin) and novel (CD29, 14-3-3σ) myoepithelial markers. Additional myogenic markers (caldesmon, desmin) were examined to exclude leimyosarcoma in the NOS-type sarcomas.

19 of the 20 MCs (95%) expressed at least 2 markers of the combination CD10/p63/SMA/S100. The novel myoepithelial markers CD29 and 14-3-3σ were positive in 18 (90%) and 11 MCs (55%), respectively. CK-antibodies were strongly reactive in 12 tumors (60%), but in 6 cases (30%) positivity for these markers was weak and only focal.

The 7 NOS-type sarcomas and the stromal component of all 5 PTs were positive for vimentin, but negative for all CKs. Whereas all myoepithelial markers were absent in the PTs, CD10, CD29 and SMA were expressed in 7 (100%), 5 (71%) and 3 (43%) NOS-type sarcomas, respectively. Caldesmon and desmin were negative in all NOS-type sarcomas.

We conclude that even sarcomatoid MCs with weak CK expression consistently exhibit a myoepithelial immunophenotype which is reliably detected by the combination CD10/p63/SMA/S100. PTs with stromal overgrowth and "classic" sarcomas can easily be ruled out by their negativity for myoepithelial markers. NOS-type sarcomas, however, represent a diagnostical challenge due to the frequent expression of CD10 and CD29, which suggest that at least some of them are of myoepithelial origin. As the treatment of MCs usually involves axillary lymphadenectomy, extensive immunohistochemical examination for CK expression and their distinctive myoepithelial immunophenotype should be performed before reporting a sarcomatoid tumour as NOS-type sarcoma.

Low grade DIN-flat type (DIN 1a, flat epithelial atypia) of the breast: An underdiagnosed entity commonly associated with lobular intraepithelial neoplasia

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Although low grade DIN-flat type (DIN 1a, flat epithelial atypia) is now recognized in the new WHO-classification of breast tumours (WHO, 2003), it is still easily overlooked in breast biopsies. Various synonyms such as "atypical columnar changes", "columnar alteration with prominent apical snouts and secretion (CAPSS)" and "atypical cystic lobules" prove the morphologic variety that complicates a widely accepted definition of this entity. A recent study has demonstrated that DIN 1a is in almost 30% associated with lobular intraepithelial neoplasia (LIN, "lobular carcinoma in situ"/"atypical lobular hyperplasia"). The aim of our study was to characterize the morphology of DIN-flat type and focus on selected archival cases with pure lobular intraepithelial neoplasia in order to evaluate possible association between LIN and DIN 1a.

Fifty-four cases containing LIN without classic "ductal carcinoma in situ" (DCIS) were obtained from our files. Using the WHO-criteria (WHO, 2003), all cases were reevaluated for the presence of LIN and possible association with DIN-flat type (DIN 1a, flat epithelial atypia). The distribution of LIN and DIN 1a was assessed by a semiquantitative method as focal (only rare microscopic foci, +), multifocal (multiple lobules or ducts in several sections, ++) and extensive (several lobules/ducts in more than 2/3 of the examined slides, +++).

Overall, 49 cases (91%) revealed an association between LIN and DIN 1a. There were 13 (24%), 32 (59%), and 9 (17%) cases with focal, multifocal and extensive LIN, respectively. The DIN 1a was identified as focal, multifocal and extensive in 18 (37%), 26 (53%) and 5 (10%) cases. The distribution of LIN and DIN 1a showed no statistically significant correlation (p=0,149; Pearson Chi-Square).

DIN 1a is a subtle intraepithelial lesion very frequently associated with LIN. As we focused on cases without associated DCIS or invasive carcinoma, this result supports the concept that DIN-flat type might represent an early precursor lesion like LIN. Recognition of DIN 1a is important, because it represents a possible risk factor and its presence should lead to thorough sampling of breast specimens for intraepithelial neoplasias such as LIN or more classic types of DIN (DCIS).

Breast carcinoma with features of polymorphous adenocarcinoma of salivary glands

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Purpose of the study: We describe three cases of carcinoma with features of polymorphous adenocarcinoma of the breast, a site, to the best of our knowledge, not hitherto reported in the literature for these tumours.

Material and Methods: All cases were retrieved from the consult files of one of us (VE). Patients were women aged 55, 37, and 84 years and they had no evidence of previous malignancy. Tissue was fixed in buffered formalin and routinely processed to paraffin. Slides were stained with haematoxylin-eosin (H&E) and for immunohistochemistry the ABC method was employed. Source, dilution and antigen retrieval of the antibodies used are listed in Table 1.

Results: Microscopically the neoplasms were unencapsulated and exhibited cells invading the surrounding breast tissue. All the tumours consisted of monotonous cells showing a wide spectrum of growth patterns: solid nests, trabeculae, tubules, cribriform structures, strands and fascicles reminiscent of the features seen in polymorphous low grade (PLGA) of salivary glands. Mitoses averaged 8/10 HPF (x400). No tumour necrosis was seen. The stroma within the tumours was collagenous but no in situ lesions were observed. No metastases were found in regional lymph nodes. All the tumours showed, with minor variations, similar immunohistochemical features (Table 2). Keratin 7 stained strongly and diffusely several areas of all the tumours. Keratin 14, smooth muscle actin was consistently absent in all cases as P63 was in case 1. The same antibody stained the nuclei of several neoplastic cellular nests while was absent in other areas in case 2. E-cadherin weakly stained most of the cells from all the cases ("fragmented" e-cadherin stain). Epithelial membrane antigen (EMA) was negative in all tumours as also were ER and PR.

Conclusions: The present study want to describe three cases of carcinoma with features of polymorphous adenocarcinoma of the breast, the last salivary gland-like tumour not yet reported in this site. It seems that the present report fills the gap.

Table 1. Antibodies used

Antibody	Clone	Source	Dilution
Keratin 7	OV-TL 12/30	Dako	1:100
Keratin 14	LL002	Biogenex	1: 100
SMA	1A4	Dako	1:100
P63	4A4	Neomarkers	1:200
ER	-	Dako	1: 50
PR	PgR636	Dako	1:50
E-cadherin	HECD-1	Zymed	1:1000
EMA	E 29	Dako	1:600

SMA= smooth muscle actin; ER= estrogen receptor; PR= progesterone receptor; EMA= epithelial membrane antigen

Table 2. Immunohistochemical results

Antisera	Patient 1	Patient 2	Patient 3
Keratin 7	+/-	+/-	+/-
Keratin 14	-	-/+	-/+
SMA	-	-	-
P63	-	+/-	-/+
ER	-	-	-
PR	-	-	-
E-cadherin	+	+ fragmented	+
EMA	-	-	-

TECHNOLOGICAL ADVANCES IN PATHOLOGY

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Molecular biological analysis in new-fixative treated tissues

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Most tissues from biopsy, surgery or autopsy origin are usually fixed and paraffin embedded as a routine procedure in hospital departments of pathology. Tissue storage is a fundamental step in the usual clinical procedure for histopathological investigations. The traditional method of tissue preservation is the fixation of tissues, mostly in formalin, followed by paraffin wax embedding. In this way, biochemical, molecular and structural integrity is ensured also for future retrospective analyses, because there is no further chemical degradation in paraffin. Usually, these tissues have been stored in the archives of pathology departments for decades.

Even if formalin fixation compromises the quality and intactness of nucleic acids, it has already been demonstrated that it is possible to recover and analyze DNA and RNA from formalin-fixed and paraffin-embedded post mortem tissues. The use of PCR-based techniques does not require intact nucleic acids for amplification; therefore even an increased degradation may not affect the outcome of the analysis. Protein analysis is on the contrary completely blocked, due the fact that formalin fixation creates metilenic covalent bridges between proteins.

In this study we present our results concerning the use of a new formalin free fixative. Bioptical and surgical tissues treated with this reagent were tested for conventional molecular biology examination, in comparison with formalin-fixed paraffin-embedded samples. PCR and RT-PCR analyses were performed on DNA and RNA, respectively, obtained from these samples, showing an interesting increase in nucleic acids intactness; for the DNA analysis it was possible to obtain an amp icon of 2400 bop, while in formalin-fixed ones the maximum length achieved was around 400 bop. RT-PCR analysis has shown that it was possible to obtain fragments of 600 bop from formalin free fixative treated tissues, against a maximum length of around 150 bop achieved by formalin-fixed tissues. Conventional proteomic analysis were tested on formalin-free fixative fixed, formalin-fixed and fresh tissues. These samples were analyzed with Western Blot, showing that it is actually not possible to extract proteins from formalin-fixed samples, while the proteins extracted from formalin-free fixative treated samples are comparable with those obtained from fresh tissues. Protein extracts from formalin-free fixative treated tissues were also compared by two dimensional electrophoresis with fresh tissues' lysates, with comparable results of protein spot number and distribution.

Prospective isolation of bone marrow derived multipotent mesenchymal stem cells

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Background: it has recently been demonstrated that bone marrow contains a cell population that co-purifies with mesenchymal stem cells (MSCs) and displays a wide multipotentiality similar to embryonic stem cells (ES). So far, it is unknown which is the phenotype of this BM sub-fraction.

Aim: to identify, within the mononucleated fraction of the BM, the cell population enriched the most for multipotent progenitor cells.

Materials and Methods: BM (*n*=5) were obtained from the head of femurs of patients undergoing hip-replacement. BM mononucleated fraction was obtained by density-gradient centrifugation; subsequently, cells were stained with PE-conjugated monoclonal antibodies raised against CD105, CD117, CD90, ABCG2 and CD133. Cell viability was assessed by 7-AAD staining.

Positive and negative cell fractions (6000 cells/cm^2) for each of the tested antigens were sorted and cultured in a medium selective for the growth of MPCs.

Results: the fraction of peritrabecular BM expressing CD105, CD117, CD90, ABCG2 and CD133 was 15.5, 21.6, 16.7, 2.3 and 0.48%, respectively.

The frequency of clonogenic cells within this subpopulation was 28.3%, 5.33%, 0% and 0% respectively.

Once expanded, the selected cells expressed an immunophenotype typical of MPCs.

Conclusions: The results we obtained show that the CD105+ fraction is enriched for MPC culture initiating cells. This fact indicates that the in vivo counterpart of multipotent cells is a subset of CD105+ cells. We therefore suggest CD105 as a marker for the prospective isolation of multipotent cells.

Mesenchymal stem cells are mobilized, together with hematopoietic stem cells and endothelial progenitor cells, into the peripheral blood acutely after a myocardial infarction

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It has been shown that several stem/progenitor cell classes can be employed in cardiac cell therapy improving myocardial function after an acute ischemic event. It has also been shown that, one week after an MI, there is an increased myocyte proliferative activity that almost ceases during the chronic phase of a healed infarct.

Objectives: To identify whether:

- different classes of stem/progenitor cells (endothelial, hematopoietic and mesenchymal) are mobilized into the peripheral blood (PB) following an AMI;
- different stem cell (SC) classes are recruited into the PB with characteristic temporal kinetics;
- during the chronic phase of a healed infarct, SC mobilization ceases.

Materials and Methods: Patients with AMI (mean age, 60 years; 10 men and 4 women) and control subjects (mean age, 65 years; 6 men and 5 women) were enrolled. Patients with a previous AMI were excluded. The circulating SC classes were quantified on days 1 (T1), 7 (T2) and six months (T3) after the acute event. Peripheral white blood cells were stained with directly conjugated antibodies and analyzed by FACS. Mesenchymal stem cells (MSC) were identified as CD90+C45/CD34-/low, CD105+C45/CD34-/low, hematopoietic stem cells (HSC) as CD90+C45/CD34high, CD105+C45/CD34high, CD117+C45/CD34high, CD133+C45/CD34high and endothelial progenitor cells (EPCs) as VE-cadherin+CD117+/-, CD34+KDR+.

Results and conclusion: An increased circulating level of MSC, HSC and EPCs could be documented in the PB of patients suffering from an AMI.

MSCs were massively (7000 folds with respect to control, $P<0.01$) recruited to the PB at T1, persisted at a high concentration at T2 and decreased at control levels (CL) at T3. Although HSCs levels increased 40 folds ($P<0.01$) at T1, nearly doubled in concentration at T2 and decreased at T3, some differences could be notice in the HSC immunophenotype. The CD117+HSC mainly increased at T1 ($P<0.05$), whereas the CD105+ HSC at T2 ($P<0.05$) and the CD90+ HSC at T1 and T2. CD133+HSC levels did not significantly changed with time. Circulating EPCs peaked at T1 (6 folds), decreasing again at T2 and reaching CL at T3.

During the chronic phase of an healed infarct, the only SC subset resulting still significantly increased was the CD105+ HSC one (7 folds respect to CL, $p<0.05$).

In conclusion, the presence of different classes of stem cells into the peripheral blood that parallels the peak for myocyte proliferation observed acutely post-MI is in line with a possible role for blood-borne stem cells in myocardial healing.

Comparison between human atria and ventricles as possible stem cell sources

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Animal models show that atria are the heart region with the highest frequency in cardiac stem cell niches. From a clinical point of view, atrial biopsies with respect to ventricle ones are a safer procedure, that can allow to collect larger samples of tissue to be employed as a cell source for autologous transplantation.

Aim: To isolate, characterize and compare atrium-derived and ventricle-derived multipotent mesenchymal progenitor cells (MAPCs) obtained from explanted human hearts.

Methods and Results: Small cells (<30μm) were mechanically-enzymatically isolated from left atria and left ventricles of 15 explanted human hearts affected by ischemic cardiomyopathy, and grown in a selective medium. Cell lines were obtained from every isolated adult human atrium and ventricle, although the cloning efficiency was almost ten times higher for atrium derived cells with respect to ventricle derived cells (15±2.6 vs. 1.7±0.3). When compared with ventricle- derived cells, atrium-derived cells were characterized by a shorter population doubling time (36±3h vs. 51±6h).

Atrium-derived and ventricle-derived primitive cells share, instead, a similar mesenchymal immunophenotype: as evaluated by flow-cytometry (n=15), they were shown to be $CD45^{-}/CD34^{-}/CD38^{-}/CD117^{-}/CD133^{-}/HLA\text{-}DR^{-}/CD29^{lo}/KDR^{lo}/CD90^{hi}/CD13^{hi}/CD49b^{hi}$.

Both atrium- (n=10) and ventricle- derived (n=10) cell lines displayed a small but sharply defined population expressing high levels of MDR-1 and ABCG2; moreover, they possessed telomerase activity (n=6).

Cell lines obtained from the two different cardiac regions (n=6) did not differ ($p<0.001$) in cardiac-specific transcription factor expression, as evaluated by flow-cytometry and RT-PCR, displaying in both cases a small fraction (less than 10%) of cells positive for GATA-4, MEF2C, Nkx2.5 and Myocardin.

Moreover, when exposed to appropriate differentiation inducing conditions, both atrium-derived (n=5) and ventricle-derived (n=5) cell lines, were able to differentiate along an adipogenic, osteogenic, endothelial, and myogenic fate. Specifically, when cells were cultured in myogenic medium, they became strongly positive to GATA4, SMA, Troponin T and alpha-sarcomeric actin.

In conclusion:

1. multipotent cells can be isolated and grown from both atria and ventricles of human hearts;
2. atria- derived primitive cells did not differ from the ventricle derived ones in terms of phenotype, telomerase activity and multilineage differentiation capacity;
3. the highest cloning efficiency and shortest population doubling time displayed by atria-derived multipotent cells, appoint atria, respect to ventricles, as a more feasible cell source to be employed for autologous cell therapy.

Myocyte cell ploidy and CDK inhibitors as indicators of human cardiac growth reserve

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Aims:

1. To compare myocyte ploidy of normal and failing hearts;
2. To correlate DNA content, cell cycle associated proteins and age related antigens to myocyte hypertrophy and senescence.

Materials and Methods: Myocytes were enzimatically dissociated from left ventricles of 6 (3 per gender) ischemic dilated human hearts and from 4 control hearts (3 women, 1 men). A FISH staining for chromosome X,Y and 18 was utilized to estimate DNA ploidy. Ki-67 was utilized to evaluate, by means of immunofluorescence and confocal microscopy, the fraction of cycling myocytes, whereas p16 and p27 identified the fraction of senescent myocytes. Cell volume was evaluated by confocal microscopy and morphometry.

Results: Pathological hearts, in comparison with normal ones, were characterized by a significant increase in polyploid (77.4% vs. 44.4%, $p<0.001$), p16 positive (21.4% vs. 4.6%, $p<0.001$) and p27 positive (32.5% vs. 13.6%, $p<0.001$) myocytes. Both in control hearts and in failing human hearts, cell ploidy, p16 and p27 expression were associated with cell volume, being the larger myocytes polyploid and senescent ($p<0.001$). Although Ki-67 positive myocytes were significantly more numerous in failing hearts with respect to control ones (46.6% vs. 23.9%, $p<0.001$), pathological hearts displayed a larger fraction of Ki-67 positive myocytes arrested in G1 phase of the cell cycle, since they co-expressed p16 (33.6% vs. 11.5, $p<0.001$) or p27 (36.4% vs. 21.2, $p<0.001$).

Conclusion: In the myocardium we could identify two major classes of cells: a diploid one (constituted by small, p16, p27 negative cells) and a polyploid one (comprising the largest, p16, p27 positive cells). Cycling myocytes were identified in both groups, but in the latter, Ki-67 was preferentially expressed by cells arrested in the G1 phase. The recent demonstration of a cardiac stem cell pool (Beltrami et al., 2003) resident in the mammalian heart, supports the view of a cardiac hierarchical model of cellular differentiation and maturation that parallels the well established and characterized hematopoietic one. Under this light, the diploid cell compartment would be enriched in cells of the so-called transit amplifying pool, while the polyploid one would represent a population of cells that has reached growth arrest and terminal differentiation. This way, the proportion between diploid and polyploid cells would reflect the cardiac growth reserve and could be used as a marker of failing heart.

Two cases of myocarditis responsible for cardiac transplantation

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Myocarditis are inflammatory diseases of the myocardium, defined by the presence of an inflammatory infiltrate in the myocardium with necrosis or degenerative changes of the adjacent myocytes. Myocarditis are relatively rare; most of them are self-limited and full recovery is the expectation. However, some myocarditis can be sometimes devastating, resulting in severe and progressive heart failure and fatal arrhythmias. The diagnosis of myocarditis is based on immunological, histological and immunohistochemical criteria. We report two cases of myocarditis, a giant cell one and an eosinophilic one, leading to cardiac transplantation.

Case 1 is about a 39-year-old man with severe ulcerative colitis, diagnosed in 1987, treated with mesalazine. In June 2004, he evinced a refractory, rapidly progressive, heart failure, switching, in four mouths, from NYHA functional class II to NYHA functional class IV and so in October 2004 he underwent cardiac transplantation. *Macroscopic description:* the heart weighted 350 gr with external trasversal diameter of 95 mm and external vertical one of 120 mm. The left ventricle and the right ventricle wall thickness was 12 mm and 7 mm respectively. At section, the myocardium was diffusely marble. *Histological findings:* In atrial and ventricular myocardium we observed wide myocyte necrosis and diffuse inflammatory infiltrates forming non-caseating granulomas with giant cells, circumscribed by B lymphocytes and numerous CD8+ T ones. The diagnosis was giant cell myocarditis, a rare disorder characterized by irreversible, fulminant left ventricle dysfunction, congestive heart failure and conduction abnormalities. Giant cell myocarditis may occur with other autoimmune diseases, especially myastenia gravis and inflammatory bowel disease; the response to immunosoppressive treatment is poor and the cardiac transplantation represents the only therapeutic possibility.

Case 2 is about a 33-year-old man suffering from mild ulcerous colitis, diagnosed in 2000, treated with mesalazine, and presenting positiveness for anti-endomisium and anti-transglutaminase IgA antibodies. In 1999 he developed a dilated cardiomyopahty of unknown origin, reaching NYHA functional class III in 2003. In April 2005 the clinical status worsened, despite of an intense inotropic therapy (dobutamine), so he underwent cardiac transplantation pressingly (29/04/2005). *Macroscopic description:* the heart weighted 650 gr with external trasversal diameter of 150 mm and external vertical one of 130 mm. Lateral and posterior left ventricle walls were thinning (7 and 9 mm respectively) with sectum compensatory hypertrophy (18 mm). Left ventricular endocardium and mitral valve leaflets were thickening. At section, the left ventricular myocardium presented some white and firm areas. The right ventricle and atria did not have any macroscopic lesions. *Histologic findings:* in the left ventricule we observed an intense myocardial inflammatory infiltrate, predominantly eosinophilic, focal areas of myocyte necrosis and occasional granuloma-like formations with some giant cells. The predominantly eosinophilic inflammatory infiltrate also spread in the endocardium and in the pericardium where a non-necrotizing vasculitis was present. Intense fibrosis was observed in subendocardial and in subpericardial regions. The same histopathology was present in atria and in the right ventricle, although of milder entity. The diagnosis was eosinophilic pancarditis, of possible allergic origin (mesalazine, dobutamine).

Conclusions. The relative frequency of myocarditis causing severe heart failure and leading to cardiac transplantation as the only viable treatment option, emphasizes the importance of obtaining, from selected patients, endomyocardial biopsies, in order to place a correct diagnosis, before transplantation, allowing, therefore, to adress patient management in a more rational and successful manner.

Localized pulmonary form of light chain deposition: an autopsy case with ultrastructural examination

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Purpose: to determine the nature of amyloid-like pulmonary bilateral nodules found in an autopsy case of a 90-year-old man, admitted in the emergency unit of our hospital with gasping for breath. Chronic renal failure due to ischemic renal disease had been clinically documented.

Methods. The body was subjected to post mortem examination to ascertain the cause of death. Specimens of heart, liver, spleen, pancreas, thyroid, stomach, prostate, both kidneys and both adrenal glands were sent for histopathological study. Samples were fixed in formalin, routinely processed and stained with hematoxylin and eosin. Masson trichrome, periodic acid-Schiff (PAS), phosphotungstic acid-hematoxylin (PTAH), Congo red stains and immunohistochemistry for kappa light chains and for lambda light chains (Dako, dilution 1:200,000) were performed on lung specimens. Lung and kidney tissues were retrieved from paraffin blocks and processed for ultrastructural studies.

Results. Patient death is attributable to a state of diffuse sepsis with acute bronchitis, peritonsillar abscess, chronic gonarthritis and pericarditis. Other findings included diffuse dilation and blunting of renal calyces, glomerulosclerosis, pulmonary emphysema and 4 bilateral, subpleuric, pulmonary nodules, measuring 1-3 cm in greatest dimension. Pulmonary nodules were composed of eosinophilic, proteinaceous, acellular, granular, PAS positive, PTAH negative deposits, similar to amyloid, but lacking typical apple-green birefringence after Congo red staining. Immunoreactivity for kappa light chains was demonstrated within amyloid-like substance and in mature plasma cells surrounding it. Ultrastructural examination revealed a granular rather than fibrillar, electron-dense, extracellular material. Neither clinical history of plasma cells dyscrasia, nor elevation of M-component in the serum had been reported. No signs of amyloid-like material deposition were found in the kidney or in other organs.

Conclusions. Herein we describe a case of localized form of light chain deposition in the lung. Light chain deposition occurs more frequently in the context of systemic light chain deposition disease, but rare cases of localized pulmonary forms has been reported in literature.

The Fast Track Biopsy (FTB): Description of a rapid histology and immunohistochemistry method for evaluation of pre-operative breast core biopsies

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Purpose of the study: Here we describe a technique that employs a controlled microwave processing procedure lasting about 2 hours and 30 minutes, inclusive of fixation time through staining. This technique has been named fast track biopsy (FTB) to emphasize the fact that the diagnosis is obtained within a short period and that fast immunohistochemistry can be added to the diagnostic procedure.

Methods used: Thirty six core breast biopsies from 32 patients were paraffin- embedded using an automated microwave processor. In addition, a quick immunohistochemical method was used in selected cases. The quality of the hematoxylin and eosin (H&E) slides was very satisfactory, as were also the immunohistochemical stains for ER, PR and Ki67 when compared to those obtained with the use of a conventional automated immunostainer.

Results: Three cases were regarded as B1, and 13 cases were diagnosed as B2 ; these included fibroadenomas and epitheliosis (epithelial hyperplasia of usual type). Two cases were regarded as B3; these included a ductal adenoma and a cellular fibroadenoma that was not possible to distinguish from a phyllodes tumor. No case was considered B4, while B5 cases were the most numerous (18 cases). These included 12 invasive duct carcinoma NOS (10), 1 invasive mucinous carcinoma, 3 invasive lobular carcinomas, and 2 cases of in situ duct carcinoma. The time of the FTB ranged from 2 hours and 30 minutes to 4 hours (mean 2 hours and 54 minutes). During the last month of the study (January 2005) the processing time was stabilized at 2 hours and 30 minutes.

For immunohistochemistry, 8 B5 cases were processed. The processing time of the fast immunohistochemical method ranged from 90 to 100 minutes, i.e., it was consistently shorter than that of the automated immunostainer, which ranged from 220 to 230 minutes.

When the quality and intensity of the staining obtained with the fast procedure were compared to those of the automated immunostainer, no difference between the two procedures were noted. ER was positive in 7 cases (range 70 to 90% of the total neoplastic proliferation), whereas PR was positive in 8 cases (range 20 to 90%). Ki 67 positivity ranged from 5% to 60% of the total neoplastic proliferation (mean 16.2%).

Conclusions: This procedure, which we named "fast track biopsy" (FTB) , is quick enough be competitive with FNAC (fine needle aspiration biopsy) in terms of turn-around-times.

The superiority of core biopsy over FNA in terms of the morphologic information provided is widely acknowledged, the only major argument currently mentioned in favor of FNAC being the shorter duration of the procedure. With the advent of FTB, it would appear that even this last remaining advantage has been erased.

Twenty meetings of the ASP (1986-2005)

1986 Portorož

Meeting of the founders

(M. Us-Krašovec, R. Golouh, J. Lamovec, V. Eusebi, G. Bussolati, C.A. Beltrami)

1987 Ancona

Organizer: C.A. Beltrami (Ancona)

Topics: Thyroid tumors *(M. Us-Krašovec, G.C. Zampi)*
Soft tissue and bone pathology *(M. Campanacci, M. Filotico)*
Technological advances in pathology *(G. Prodi, G. Coggi)*

1988 Cavtat

Organizer: R. Golouh (Ljubljana)

Topics: AIDS and related conditions *(G. Costanzi, C.D. Baroni)*
Breast pathology *(G. Bussolati, M. Us-Krašovec)*
Technological advances in pathology *(I. Nenci, G.M. Mariuzzi)*

1989 Ravenna

Organizer: E. Magni (Ravenna)

Topics: Gastroesophageal pathology *(J. Costa, C. Bordi)*
Pigmented skin lesions *(M. Cook, F. Rilke)*
Technological advances in pathology *(L. Rubbia, M. Papotti, B. Barbiroli)*
Paleopathology *(E. Fulcheri, E. Rabino Massa)*

1990 Split

Organizer: J. Bakotin (Split)

Topics: Neuropathology and neuromuscular diseases *(D. Schiffer, N. Grčević)*
Gynecological pathology *(S. Pilotti, S. Rainer)*
Technological advances in pathology *(P.C. Marchisio, P. Musiani, G. Mazzotti)*

1991 Grado

Organizer: C.A. Beltrami (Udine)

Topics: Lymph node pathology *(L. Fiore Donati, M. Dominis)*
Pediatric pathology *(F. Callea, M. Ščukanec)*
Technological advances in pathology *(G. Coggi, A. Scarpa, G. Viale, M. Loda, G. Stanta)*

1992 Trieste

Organizer: L. Di Bonito (Trieste)

Topics: Lung pathology *(T. Rott, F. Mollo, L. Di Bonito)*
Endocrine pathology *(R. Golouh, C. Capella, J.P. Camilleri)*
Technological advances in pathology *(H. Hofler, P. Vielh, M. Auersperg)*
Paleopathology *(C.D. Baroni)*

1993 Ascoli Piceno

Organizer: V. Mambelli (Ascoli Piceno)

Topics: Breast pathology *(M.D. Lagios, R.R. Millis, P.P. Rosen, C.D. Baroni)*
Skin pathology *(M.G. Cook, W. Gebhart, U. Magrini)*
Technological advances in pathology *(B. Palcic, G. Stanta)*
Paleopathology *(A. Capelli, R. Coda)*

1994 Portorož

Organizer: R. Golouh (Ljubljana)

Topics: Head and neck pathology *(H.B. Hellquist, C. Doglioni)*
Pathology of the mediastinum and retroperitoneum *(H.K. Muller-Hermelink, F. Menestrina)*
Technological advances in pathology *(A. Reith, C. Patriarca)*

1995 Venezia

Organizer: V. Stracca Pansa *(Venice)*

Topics: Paleopathology *(A. Guerci, E. Rabino-Massa, L. Fozzati, P. Scarani)*
Bone marrow pathology *(M. Dominis, A. Castello)*
Uropathology *(R. Montironi, G. Mikuz)*
Technological advances in pathology *(H. Battifora, A. Scarpa, G. Bussolati, V.E. Gould)*

1996 Grado

Organizer: G. Mikuz *(Innsbruck)*

Topics: Paleopathology *(C.D. Baroni, E. Fulcheri)*
Thyroid tumors *(K. Schmid, V.E. Gould)*
Gynecopathology *(S. Carinelli)*
Technological advances in pathology *(B. Palcic, G. Stanta)*

1997 Ostuni

Organizer: L. Pollice (Bari)

Topics: Paleopathology *(A. Ascenzi, G. Alciati, V. Pesce Delfino, E. Vacca)*
Pathology of the liver and biliary tract *(V. Desmet, H. Denk)*
Neuropathology *(H. Budka, F. Tagliavini, V.E. Gould)*

1998 Rijeka

Organizer: N. Jonjić *(Rijeka)*

Topics: Paleopathology *(C.D. Baroni)*
Dermatopathology *(M.G. Cook, B. Zelger)*
Pathology of the gastrointestinal system and pancreas *(R. Fiocca, C. Bordi, J. Luttges)*
Cytogenetics and transgenic technology *(A.P. Dei Tos, S. Jonjić)*

1999 Portorož

Organizer: R. Golouh (Ljubljana)

Topics: History of pathology *(P. Scarani)*
Gynecological pathology *(F. Nogales, S. Lax)*
Bone and soft tissue tumors *(F. Bertoni, T. Krausz)*
FISH and molecular fingerprints of tumors *(M.G. Tibiletti, W.J. Mooi)*

2000 Grado

Organizer: G. Mikuz (Innsbruck)

Topics: Paleopathology *(P. Scarani)*
Pathology of the lymphatic tissue *(S. Pileri, F. Facchetti)*
Transplantation pathology *(F. Wrba, F. Offner)*
Cytopathology and laser capture microdissection *(A. Pogačnik, F. Fend)*

2001 Rimini

Organizer: A. Bondi (Imola)

Topics: Paleopathology and history of medicine *(P. Scarani, E. Fulcheri)*
Prostate & Uterus *(R. Montironi, S. Jukić)*
Lung pathology *(H. Popper, T. Rott, A. Gschwendtner)*
Telepathology *(M. Dietel, C. Bifulco, J. Klossa)*

2002 Brijuni

Organizer: S. Jukić (Zagreb)

Topics: History of pathology *(B. Belicza)*
Soft tissue and bone tumor pathology *(F. Bertoni, R. Golouh)*
Perinatal - pediatric pathology *(M. Kos)*
Achievements of telepathology *(S. Seiwerth)*

2003 Mestre

Organizer: G. Mikuz (Innsbruck)

Topics: History of pathology and paleopathology
Lung pathology *(H. Popper, B. Murer, M. Dominis, A. Gschwendtner)*
Uropathology *(G. Mikuz, C. Mian, F. Visinoni)*
Recent advances in pathology *(G. Stanta, K. Zatloukal)*

2004 Opicina-Trieste

Organizer: G. Stanta (Trieste)

Topics: Breast pathology *(V. Eusebi, J. Lamovec)*
Soft tissue pathology *(R. Golouh, M. Us-Krašovec)*
Modern techniques in pathology *(A. Cavazzana, M. Chilosi, M. Dietel, A. Scarpa)*

2005 Strunjan

Organizer: S. Frković Grazio (Ljubljana)

Topics: Head & neck and thyroid pathology *(N. Gale, M. Papotti)*
Dermatopathology *(B. Zelger, M. Santucci)*
Technological advances in pathology *(R. Sciot, G. Stanta)*

The founders of ASP in Portotož, June 1986 ...

and in Opicina, June 2004: Janez Lamovec, Marija Us-Krašovec,
Carlo Alberto Beltrami, Vincenzo Eusebi, Gianni Bussolati and Rastko Golouh

AUTHOR INDEX

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