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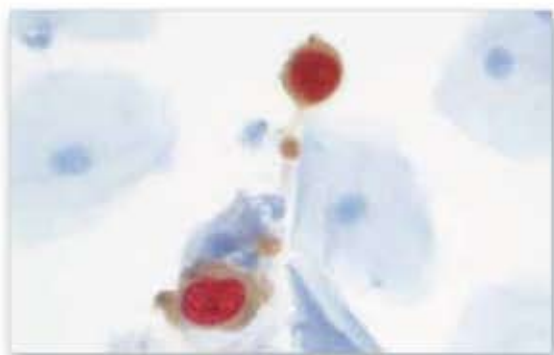
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*F. Angiero, V. Fesslova, T. Rizzuti, M. Stefani*

**Objectives.** Congenital heart defects may be associated with various extracardiac and chromosomal anomalies, and complex cardiac defects may occur in the presence of heterotaxy syndromes, in which both lungs are bilobate, in left isomerism, or both trilobate, in right isomerism. Lung lobation defects are otherwise very rare. Lung lobation is recognisable only at autopsy; however, its definition is fundamental for evaluation of the viscerotrial arrangement, together with other characteristic signs.

**Method.** We report seven cases of congenital heart defects diagnosed prenatally at 14-31 weeks of gestation (wg), 5 females and 2 males, in which autopsy revealed lung lobation defects in the presence of normal viscerotrial arrangement, in association with other extracardiac anomalies or dysmorphism.

**Results.** Three fetuses had hypoplastic left heart syndrome, one had corrected transposition of great arteries, one had tricuspid atresia, one Ebstein's anomaly and one had ventricular septal defect in trisomy 21. In six cases, pregnancy had been terminated, while the foetus with Ebstein's anomaly died in utero at 32 wg for supraventricular tachycardia. Monolobate, bilobate, trilobate and quadrilobate lungs were found in these fetuses, together with other minor extracardiac anomalies or dysmorphism.

**Conclusions.** Autoptic analysis in cases with prenatal diagnosis is needed to confirm echographic findings and reveal other minor anomalies, undetectable by ultrasound imaging that may complete the malformation pattern, which is useful to the couple for genetic counselling.

#### **Solitary extramedullary plasmacytoma of the thyroid gland associated with multinodular goiter: case report and review of the literature**

*G. Puliga, L. Olla, G. Bellisano, N. Di Naro, M. Ganau, M.L. Lai, G. Faa, G.A. Tolu*

Solitary extramedullary plasmacytoma (SEP) is a rare malignant neoplasm arising from plasma cells most commonly occurring in the nasal cavity, nasopharynx and larynx. Thyroid involvement is rare and less than 75 cases of SEP of the thyroid gland have been reported to date. A 74-year-old woman with an history of multinodular goiter presented with dysphonia and painful neck swelling, related to a rapidly growing nodule in the right thyroid lobe. Thyroid function tests showed subclinical hypothyroidism; no evidence of Hashimoto's disease was found. Ultrasound confirmed the presence of an isoechoic nodule, 35 mm in diameter, with a CDIII vascular pattern. FNAC showed a monotonous population of atypical cells, interpreted as suspicious for malignant neoplasia (Thyr. 4). The patient underwent total thyroidectomy. Histopathological examination showed a unencapsulated neoplasm composed of atypical tumour cells characterized by abundant cytoplasm and eccentric nuclei. At immunohistochemistry, tumour cells revealed diffuse reactivity for CD138 and CD45RB and predominant staining for kappa chains. Pan-cytokeratins, TTF1, thyroglobulin, calcitonin, CD20 and CD79a were negative. Clinically, a complete multiple myeloma workup was negative. On this basis, a definitive diagnosis of SEP was made. At 16 months follow-up, the patient showed good clinical conditions without evidence of multiple myeloma. In conclusion, SEP should be considered in the differential diagnosis of a rapidly enlarging thyroid nodule. Clinical correlation and immunocytochemistry are crucial in avoiding pitfalls. Surgery remains the best modality of treatment whenever the lesion is localized and easily removable.

#### **Sebaceous carcinoma of the vulva: critical approach to grading and review of the literature**

*T. Pusiol, D. Morichetti, M.G. Zorzi*

**Background.** Sebaceous glands are abundant on the vulva, but vulvar sebaceous carcinoma (SC) is an uncommon neoplasm.

**Methods.** We report a case of SC of the vulva in a 51 year-old woman.

**Results.** The patient presented a 6-month history of an asymptomatic 2.5 × 1.5 cm exophytic tumour localized on the left labium majora. Tumorectomy was performed. Histologically, the lesion had an irregular lobular growth pattern composed of lobules or sheets of malignant cells separated by fibrovascular stroma. There was a mixture of sebaceous-type differentiation, small ducts and areas showing basaloid or squamous features. Centrally-located tumour cells showed moderate EMA immunoreactivity, especially enhancing cytoplasmic "bubbliness". Tumour cells were immunoreactive for CAM 5.2. The immunoreactivity for intranuclear p53 staining was > 10%. Southern blot hybridization and PCR studies did not detect HPV DNA. Hemivulvectomy was performed. After 18 months of follow-up, the patient has no evidence of recurrence, metastases or other malignant tumours.

**Conclusions.** The grading of cutaneous SC proposed by Rutten et al. (World Health Organization Classification of Skin Tumours) and Patterson & Wick (Nonmelanocytic Tumours of the Skin. Armed Forces Institute of Pathology) is based on patterns of tumour growth rather than cytological features. Such grading of skin SC, including vulvar SC, should not be used since its prognostic value has not been sufficiently documented. As the number of reported vulvar SCs is very limited, their natural history is unknown and the optimal treatment has not been established. The follow-up of 7 reported cases supports the general opinion that the tumour may be aggressive. SC groin node metastases carry a devastating prognosis, and unrecognized disease in the inguino-femoral lymph nodes is nearly always fatal. The use of sentinel lymph nodes (SLN) has evolved as an effective surgical technique for identifying early subclinical regional nodal involvement for many solid tumours throughout the body for staging disease; this is because extra-ocular SCs cause widespread metastatic disease. In our opinion, SLN should be used in conjunction with wide local excision of the primary tumour to investigate regional subclinical metastases. In the presence of a positive sentinel node, early lymphadenectomy with or without radiotherapy could be used to reduce tumour-related morbidity and mortality. The histopathologic differential diagnosis of SC is wide-ranging, including virtually all other malignant clear cell tumours of the skin. The proliferative pattern, immunostaining and cytologic features permit exclusion of neoplasms that mimic SC, but a diagnosis of SC should be rendered only if the overall attributes of the lesion are appropriate for such an interpretation.

### CASE REPORTS

#### **Pleomorphic giant cell ductal carcinoma of the breast**

*D. Tacchini, M.G. Mastrogliulio, L. Vassallo, A. Ginori*

Pleomorphic ductal invasive carcinoma is a very rare, high-grade breast cancer with unfavourable prognosis. It contains highly pleomorphic giant cells, which represent more than 50% of the cancer cells. One such case is described herein, focusing on its morphological, histopathological and immunohistochemical patterns. It was multicentric, oestrogen and progesterone receptor negative and epidermal growth factor receptor type 2 positive.

#### **A solitary pilar leiomyoma of the trunk**

*R. Benmously-Mlika, F. Ishak, S. Ben Jennet, H. Hammami, T. Badri, I. Mokhtar, S. Fenniche*

Smooth muscle tumours arising in the skin are divided into angioleiomyomas, genital leiomyomas and pilar leiomyomas. Limited

data about solitary leiomyoma are available in the literature. We herein report a case of a 66-year-old man who presented to our department with a slowly progressing cutaneous tumour of the right scapular area that had developed over the past 12 years. Histopathological and immunohistochemical results were consistent with the diagnosis of pilar leiomyoma. Pilar leiomyoma is a benign smooth muscle tumour arising from arrector pili muscle. Tumours can be painful from compression of cutaneous nerves or because of fibre contraction within the tumour in case of cold weather or emotional stress. This case is noteworthy as the piloleiomyoma was solitary, located on the trunk and had an unusual nipple aspect.

**Malignant proliferating trichilemmal cyst of the scalp: histological aspects and nosology**

*A. Khaled, M. Kourda\*, B. Fazaa, J. Kourda, S. Ben Jilani, M. Ridha Kamoun, R. Zermani\*\**

**Background.** Malignant proliferating trichilemmal cyst is a rare tumour usually located on the scalp of elderly women. About 40 cases of malignant proliferating trichilemmal tumour have been documented.

**Case report.** We report a case of a malignant proliferating trichilemmal cyst of the scalp in a 57-year-old woman. On the vertex she had a voluminous vegetated and multinodular tumour measuring 7 × 5 cm with spontaneous and abundant bleeding, and another lesion of the scalp corresponding to a trichilemmal cyst. Based on histopathological findings, the case was diagnosed as malignant proliferating trichilemmal cyst.

**Conclusion.** Diagnostic, clinicoprognostic and histological features of this tumour are discussed. Treatment is not yet standardized given its rarity.

# Autoptic and echocardiographic findings in seven foetuses with congenital heart anomalies, lung lobation defects and normal viscerotrial arrangement

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## Key words

Lung lobation defects • Congenital heart anomalies • Extracardiac anomalies • Prenatal diagnosis • Foetal echocardiography • Autoptic examination

## Summary

**Objectives.** Congenital heart defects may be associated with various extracardiac and chromosomal anomalies, and complex cardiac defects may occur in the presence of heterotaxy syndromes, in which both lungs are bilobate, in left isomerism, or both trilobate, in right isomerism. Lung lobation defects are otherwise very rare. Lung lobation is recognisable only at autopsy; however, its definition is fundamental for evaluation of the viscerotrial arrangement, together with other characteristic signs.

**Method.** We report seven cases of congenital heart defects diagnosed prenatally at 14-31 weeks of gestation (wg), 5 females and 2 males, in which autopsy revealed lung lobation defects in the presence of normal viscerotrial arrangement, in association with other extracardiac anomalies or dysmorphism.

**Results.** Three foetuses had hypoplastic left heart syndrome, one had corrected transposition of great arteries, one had tricuspid atresia, one Ebstein's anomaly and one had ventricular septal defect in trisomy 21. In six cases, pregnancy had been terminated, while the foetus with Ebstein's anomaly died in utero at 32 wg for supraventricular tachycardia. Monolobate, bilobate, trilobate and quadrilobate lungs were found in these foetuses, together with other minor extracardiac anomalies or dysmorphism.

**Conclusions.** Autoptic analysis in cases with prenatal diagnosis is needed to confirm echographic findings and reveal other minor anomalies, undetectable by ultrasound imaging that may complete the malformation pattern, which is useful to the couple for genetic counselling.

## Introduction

Congenital heart defects have a prevalence in live-born infants, during the first year of life, of about 7-9/1000 births<sup>1</sup> and are reported to be found in utero in almost 2/1000 pregnancies<sup>2</sup>. In foetal life, the range of congenital heart diseases is different and more complex, and the association with chromosomal and extracardiac anomalies is higher than in postnatal life, both due to reasons of referral and because many of these foetuses die in utero<sup>3-5</sup>. Congenital heart defects contribute significantly to infant mortality, almost 50% of cases being due to cardiovascular malformations<sup>6</sup>, often associated with chromosomal anomalies and extracardiac malformations<sup>5-13</sup>. Chromosomal anomalies are reported in about 5-10% of live-born infants and in above 15% in foetal series, while extracardiac anomalies were found by Greenwood in 25% of cases in the first year of life, and more frequently (in 30-40%) in foetal cases<sup>4,12</sup>.

Congenital heart defects occur rarely (about 1 in 10-20,000 live births)<sup>12,13</sup> in cases with embryological defects of laterality or heterotaxy syndromes – with ambiguous viscerotrial arrangement – i.e. isomerism of the left or right (the so-called Ivemark syndrome) types<sup>14</sup>. In these cases, there is no distinction between right- and left-sidedness and the abdominal organs are abnormally disposed, usually with spleen agenesis in right isomerism or Ivemark syndrome, while left isomerism is usually associated with polysplenia. In both types of isomerisms, the lungs are similar, both two-lobed in left isomerism and both three-lobed in right isomerism. Thus, bilateral lung lobation defects are an anomaly that, though rare, can be associated with cardiac malformations in the ambiguous visceral arrangement, and are even more rarely found with the normal viscerotrial arrangement. These defects cannot be determined through echocardiography; they can only be detected postnatally by thoracic X-ray or through autoptic examination.

## Correspondence

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With regard to the anatomical diagnosis of congenital heart diseases, we used the well known Van Praagh approach<sup>15-18</sup>. The guidelines established by this group, together with other contributions<sup>19-21</sup>, provide a clear definition of cardiac anatomy. The Van Praagh approach is also widely used in foetal echocardiography as second-step investigation in women with conditions at risk for congenital heart disease.

Autopsy is routinely performed in foetal cases undergoing termination of pregnancy, or after intrauterine or postnatal death, to verify the accuracy and the completeness of the prenatal diagnosis.

Our study reports the unusual finding of bilateral lobation defects at autopsy in seven foetuses with cardiac malformations outside the context of the heterotaxy syndromes, and stresses the importance of confirmation through post-mortem analysis in cases with prenatal diagnosis of cardiac and extracardiac anomalies.

## Materials and methods

We report the clinical and pathological data of seven cases referred to Policlinico San Donato IRCCS, Milan, between 2006 to 2010 for suspicious cardiac anatomy by obstetric scan in 6 cases, and due to a finding of

abnormal karyotype – trisomy 21 at amniocentesis – in the seventh. In all cases, diagnoses of congenital heart defects and extracardiac congenital anomalies were made by echocardiography in the antenatal period, and all were confirmed by foetal autopsy. Diagnosis of Down syndrome was made in cases 4 by cytogenetic analysis after amniocentesis. Some of the parents had not had genetic counselling during pregnancy. All foetuses underwent karyotyping.

Gestational age at diagnosis ranged from 14 to 31 weeks gestation (wg), with a median of 22. Maternal age was 20-35 years (median 29). In six cases, termination of pregnancy was decided by the couple and performed within one week after diagnosis. One foetus died at 31 wg due to supraventricular tachycardia. Autopsy was performed in all cases following standard criteria.

All cases were studied at the General Pathology Section, Milan University; all were reviewed for age, gender, mother's age, parity, history, type and number of cardiac malformations and extracardiac anomalies; the correlation between these parameters was investigated. All external and internal anomalies of the cases were carefully recorded and photographed. Following gross systematic examination, appropriate sections were taken from all organs and the work-up was completed by histopathological study.

Tab. I. Echocardiography data and week of gestation.

Case no/sex	Week of gestation	Echocardiography	Termination of pregnancy
Case 1 20-year old woman	Referred at 22 wg for foetal echocardiography for suspicious cardiac finding at obstetric scan	Diagnosis of hypoplastic left heart syndrome, small perimembranous ventricular septal defect with aortic arch interruption in female foetus was made	Termination of pregnancy at 22 wg
Case 2 29-year old woman	Referred at 22 wg for foetal echocardiography for suspected cardiac anomaly at obstetric echography	Hypoplastic left heart syndrome with interrupted aortic arch was diagnosed, in female foetus	Termination of pregnancy at 23 wg
Case 3 35-year old woman	Referred at 21 wg for foetal echocardiography	Corrected transposition of the great arteries was diagnosed, with ventricular septal defect and hypoplastic morphological right ventricle, in female foetus	Termination of pregnancy
Case 4 30-year old woman	Referred at 21 wg for foetal echocardiography due to an abnormal karyotype found at amniocentesis – trisomy 21	Diagnosis of perimembranous subaortic ventricular septal defect was made, in male foetus	Termination of pregnancy
Case 5 31-year old woman	Under phenobarbital treatment for epilepsy, at her second pregnancy, was sent at 31 wg for foetal echocardiography	Diagnosis of severe Ebstein anomaly was made, in male foetus	Six days later, supraventricular paroxysmal tachycardia occurred followed by endouterine death immediately after presentation
Case 6 25-year old woman	Referred at 19.4 wg for foetal echocardiography for suspected cardiac anomaly	Diagnosis of hypoplastic left ventricle with hypoplastic aorta in female foetus was made	Termination of pregnancy
Case 7 34 -years old woman	Referred at 14.0 wg for foetal echocardiography for suspected cardiac anomaly found during screening for nuchal translucency	Diagnosis of female foetus with tricuspid atresia, hypoplastic right ventricle with ventricular septal defect and mild pulmonary stenosis	After a second echocardiography at 18 wg the couple opted for termination of pregnancy, performed at 19 wg

## Results

Data of single cases are reported below and summarised in Table I. Echocardiography, performed in the prenatal period between 14 to 31 weeks of gestation, in all cases led to a diagnosis of congenital heart defects and extracardiac congenital anomalies (Tab. I). All foetuses had cardiac anomalies; of these, three had hypoplastic left heart syndrome, one had corrected transposition of great arteries, one had tricuspid atresia, one Ebstein's anomaly and one had ventricular septal defect in trisomy 21. At autopsy, the lung revealed lobation defects (Tab. II): monolobate, bilobate, trilobate and quadrilobate lungs were found in these foetuses, together with other minor extracardiac anomalies or dysmorphism. In all cases, the lungs were positive by the docimasia test, and the bronchial division appeared normal, except in case 2, in which the right bilobate lung appeared hypoplastic and poorly segmented and the left was bilobate, and in case 3, in which both bilobate lungs presented bronchial branching with one left principal bronchus and two right principal bronchi.

Histologically, in all cases the lungs appeared in the canalicular phase, some having glandular residues, with patches of lung congestion; in some bronchi we found rare endoluminal squamous cells, while in others there were patches with advanced autolysis.

## Case reports

### CASE 1

A healthy 20-year old woman, at her first pregnancy, referred at 22 wg for foetal echocardiography for a suspicious cardiac finding by obstetric scan; diagnosis of hypoplastic left heart syndrome, small perimembranous ventricular septal defect with aortic arch interruption in female foetus was made. Post-mortem examination after termination of pregnancy at 22 wg confirmed the cardiac diagnosis (in female foetus) in the presence of normal visceratrial arrangement and revealed other anomalies: 1) craniofacial anomalies: dysmorphic features, dolichocephaly, micrognathia and low-set ears, short neck; 2) musculoskeletal anomalies-agenesis of the tibia; 3) genitourinary anomalies: uterus arcuatus; and 4) lung anomalies: 2 monolobate lungs (Figs. 1A, 1B).

### CASE 2

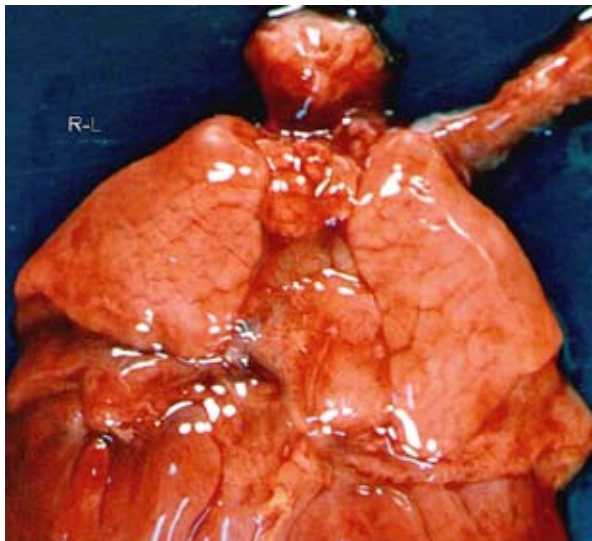
A 29-year-old woman, at her first pregnancy, was referred at 22 wg for foetal echocardiography for suspected cardiac anomaly by obstetric echography; hypoplastic left heart syndrome with interrupted aortic arch was diagnosed, in a female foetus.

At post-mortem examination after termination of pregnancy at 23 wg a normal visceratrial arrangement was found with hypoplastic left heart syndrome and interrupted aorta and other associated extracardiac anomalies:

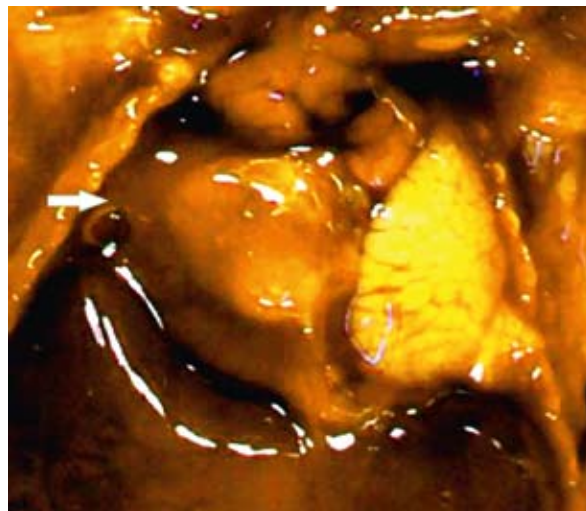
Tab. II. Autopsy data of foetuses.

Case no/sex	Pulmonary anomalies	Cardiac anomalies	Other extracardiac anomalies
Case 1 female	2 monolobate lungs	Hypoplastic left heart syndrome with ventricular septal defect, mitral hypoplasia and interrupted aortic arch	Craniofacial anomalies: dysmorphic features, dolichocephaly, micrognathia and low-set ears, short neck; musculoskeletal anomalies-agenesis of the tibia; genitourinary anomalies: uterus arcuatus
Case 2 female	Hypoplastic right lung with two small lobes and poorly segmented; left lung with two lobes	Hypoplastic left heart syndrome with interrupted aorta	Craniofacial anomalies: retrognathia; genitourinary anomalies: uterus and vagina didelphic, bicornuate, hypoplasia of ovarian and Fallopian tubes, ureteral dilatation, right kidney anomalies; intestinal anomalies: malrotation of the intestine
Case 3 female	2 bilobate lungs, incorrect subdivision of the bronchial tree	Corrected transposition of the great arteries, with ventricular septal defect and hypoplastic morphological right ventricle	Craniofacial anomalies (dysmorphism); hydrocephalus
Case 4 male	2 quadrilobate lungs	Perimembranous subaortic ventricular septal defect.	Craniofacial anomalies related to the trisomy 21 were observed: brachycephaly with flat occipital zone, hypoplasia of frontal bosses, rounded facies, depressed nasal bridge, microstomia, retrognathia, low-set ears
Case 5 male	2 quadrilobate lungs	Severe Ebstein anomaly of the tricuspid valve with a marked apical displacement of the anterior leaflet	Craniofacial anomalies: particular facies; genitourinary anomalies: absence of the fetal lobulations of the kidneys
Case 6 female	Right lung quadrilobate and left trilobate	Marked hypoplasia of the left ventricle, mitral atresia, small perimembranous ventricular septal defect, hypoplasia of ascending aorta	Craniofacial anomalies: particular facies, retrognathia, low-set ears
Case 7 female	Right lung monolobate, left lung bilobate	Marked hypoplasia of the right ventricle with ventricular perimembranous septal defect, tricuspid atresia	Craniofacial anomalies: particular facies

**Fig. 1A.** Autopsy image of 2 monolobate lungs in case 1 with hypoplastic left heart syndrome.



**Fig. 2A.** Autopsy image of case 2 showing hypoplastic right lung with two small lobes (see arrow) and left lung with two lobes in case 2 with hypoplastic left heart syndrome.



**Fig. 1B.** Foetal echocardiography shows hypoplastic left ventricle (LV) in the upper panel with echodensed wall due to endocardial fibroelastosis, and in the lower panel hypoplastic ascending aorta (Ao). RV: right ventricle, RA: right atrium, LA: left atrium.



**Fig. 2B.** Autopsy image of the same case that illustrates large pulmonary artery (P) arising from the large right ventricle and hypoplastic ascending aorta (A) and the hypoplastic right lung.



1) craniofacial anomalies: retrognathia; 2) genitourinary anomalies: uterus and vagina didelphic, bicornuate, hypoplasia of ovarian and Fallopian tubes, urethral dilatation, right kidney anomalies; 3) intestinal anomalies: malrotation of the intestine; 4) pulmonary anomalies: hypoplastic right lung with two lobes; left lung with two lobes (Figs. 2A, 2B).

### CASE 3

A healthy 35-years old woman at her second pregnancy was referred at 21 wg for fetal echocardiography for suspected cardiac anomaly at obstetric scan: corrected transposition of the great arteries was diagnosed, with ventricular septal defect and hypoplastic morphological right ventricle, in female foetus. At post-mortem

after termination of pregnancy, cardiac anomalies were confirmed, in the presence of normal viscerotrial arrangement and: 1) craniofacial anomalies (dysmorphism); 2) hydrocephalus and 3) pulmonary anomalies: 2 bilobate lungs with one bronchial tree with a left principal bronchus and two right principal bronchi (Fig. 3).

**CASE 4**

A healthy 30-year-old woman, at her first pregnancy, was referred at 21 wg for foetal echocardiography due to an abnormal karyotype found at amniocentesis – trisomy 21: a diagnosis of perimembranous subaortic ventricular septal defect was made in a male foetus. At post-mortem examination after termination of pregnancy, the cardiac defect was confirmed, with normal viscerotrial arrangement, and mild juxtaductal aortic coarctation. Craniofacial anomalies related to the trisomy 21 were observed: brachycephaly with flat occipital zone, hypoplasia of frontal bosses, rounded facies, depressed nasal bridge, microstomia, retrognathia, low-set ears and 2 quadrilobate lungs were also found.

**CASE 5**

A 31-year-old woman, under phenobarbital treatment for epilepsy, at her second pregnancy, was sent at 31 wg for foetal echocardiography due to abnormal cardiac findings by obstetric scan; a diagnosis of severe Ebstein anomaly was made in a male foetus. Six days later, su-

praventricular paroxysmal tachycardia occurred followed by endouterine death immediately after presentation.

Post-mortem examination confirmed the diagnosis of severe Ebstein anomaly of the tricuspid valve with marked apical displacement of the anterior leaflet. Two quadrilobate lungs were also found (Figs. 4A, 4B).

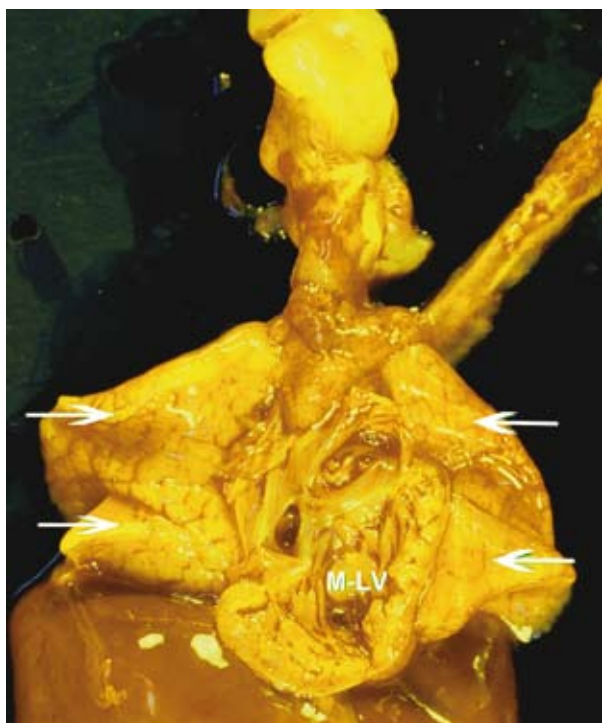
**CASE 6**

A healthy 25-year-old woman, at her first pregnancy, was referred at 19.4 wg for foetal echocardiography for suspected cardiac anomaly, and a diagnosis of hypoplastic left ventricle with hypoplastic aorta in female foetus was made. After termination of pregnancy at 21 wg autopsy confirmed: marked hypoplasia of the left ventricle, mitral atresia, small perimembranous ventricular septal defect, hypoplasia of ascending aorta and: 1) craniofacial anomalies: retrognathia, low-set ears; 2) pulmonary anomalies: right lung quadrilobate, left lung trilobate.

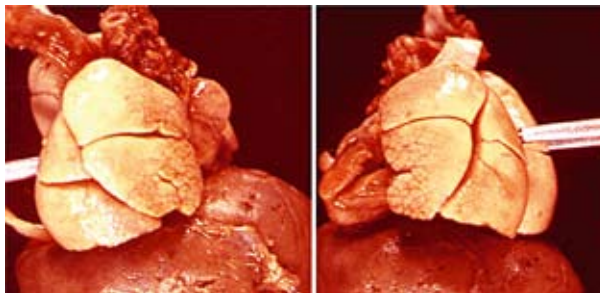
**CASE 7**

A healthy 34-year-old woman referred at 14.0 wg for foetal echocardiography for suspected cardiac anomaly found during screening for translucency of the nape (1.8 mm, with normal karyotype at chorial villi sampling 46XX) was diagnosed to have a female foetus with tricuspid atresia, hypoplastic right ventricle with ventricular septal defect and mild pulmonary stenosis. After a second

**Fig. 3.** Autopsy image of case 3 with corrected transposition of the great arteries showing two bilobate lungs (see arrows indicating the lobes) and open morfological left ventricle (MLV) with two papillary muscles.



**Fig. 4A.** Autopsy image of case 5 with Ebstein's anomaly showing two quadrilobate lungs.



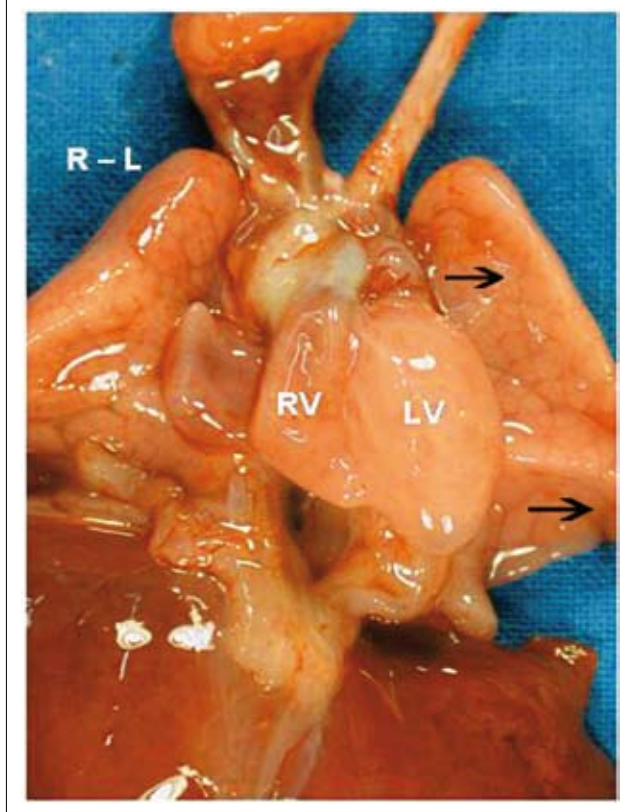
**Fig. 4B.** Foetal echocardiography showing Ebstein's anomaly in the left panel with a marked anterior displacement of the tricuspid valve and in the right panel a huge jet of tricuspid regurgitation at colour Doppler (M: mitral valve, T: tricuspid valve, RA: right atrium, LV: left ventricle).



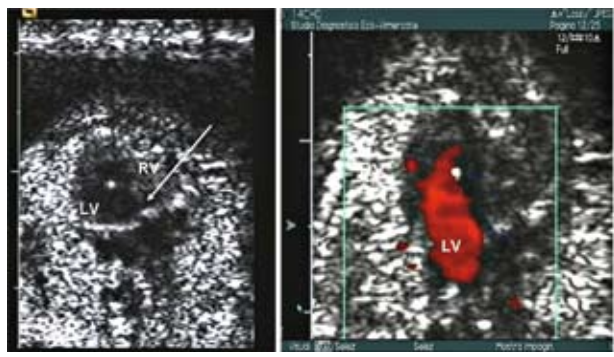
echocardiography at 18 wg the couple opted for termination of pregnancy, performed at 19 wg.

Autopsy confirmed cardiac anomalies: marked hypoplasia of the right ventricle with ventricular perimembranous septal defect, tricuspid atresia; and revealed other anomalies: 1) craniofacial anomalies; 2) lung anomalies: right lung monolobate, left lung bilobate (Figs. 5A, 5B).

**Fig. 5A.** Autopsy image of case 7 with hypoplastic right ventricle and tricuspid atresia demonstrating the right lung monolobate and the left lung bilobate, with the arrows indicating the lobes. R: right, L: left, RV: hypoplastic right ventricle, LV: large left ventricle.



**Fig. 5B.** Foetal echocardiography at 14 wg showing large left ventricle (LV) and hypoplastic right ventricle (RV) in the left panel, with an arrow indicating a small ventricular septal defect; right panel shows colour Doppler flow through the mitral valve and no filling of the right ventricle.



## Discussion

We report seven cases with prenatal echocardiographic diagnosis of complex congenital heart defects in which the autopsy revealed unusual findings of abnormal bilateral lung lobation in the presence of normal viscerotaxial arrangement. The association between congenital heart defects and abnormal lung lobation is found chiefly in heterotaxy syndromes, and sometimes in other forms<sup>22-24</sup>.

The anomalous arrangement of visceral organs is usually accompanied by isomerism at the level of the atria, with two morphologically “left” atria in cases of left isomerism, and two morphologically “right” atria in cases of right isomerism. Ambiguous arrangement of organs is manifested as asplenia, the spleen being predominantly absent in right isomerism (condition that has also been called the Ivemark syndrome or bilateral right-sidedness).

Among the forms in which lobation defects have been reported, there is Scimitar syndrome<sup>25 26</sup>, a congenital malformation characterized mainly by an anomalous venous return of the right lung into the inferior vena cava; Smith-Lemli-Opitz syndrome<sup>27</sup>, which is a multiple congenital anomaly/mental retardation syndrome with a distinct facial appearance; Fryns syndrome, which occurs in infants born to consanguineous parents; and tracheal agenesis, a rare syndrome, frequently associated with other respiratory, cardiovascular and genitourinary malformations with a very high frequency of abnormal lung lobation<sup>28 29</sup>. Koo et al. observed 49 cases with abnormal lung lobation in patients with congenital hydrocephalus<sup>30</sup>.

Frequently in these syndromes there are not only congenital heart defects, but also a series of anomalies ranging from the frequent abdominal abnormalities to craniofacial anomalies and others. In our series, various anomalies were present: craniofacial, genitourinary, abdominal, musculoskeletal and chromosomal. These cases are interesting, being quite variable, with different types of congenital heart defects. It is of interest that three of our cases, all female, had hypoplastic left heart syndrome, associated with other extracardiac anomalies and/or dysmorphism, apart from the lung lobation defects; this complex cardiac anomaly is only rarely associated with chromosomal anomalies<sup>31 32</sup> (1.5-4% in our experience) and more frequently with extracardiac anomalies (12-19%). In case 2, with hypoplastic left heart syndrome and associated genitourinary anomalies, at autopsy we also found malrotation of the intestines, which is usually present in heterotaxy syndromes. This foetus had hypoplastic right lung with two lobes; left lung with two lobes, in the presence of normal abdominal organs, abdominal vessels and atria. We can hypothesize mixed features of more than one syndrome.

The other congenital heart defects present in our small series - corrected transposition of the great vessels, tricuspid atresia and Ebstein's anomaly - are not usually associated with other extracardiac anomalies. Ebstein's

anomaly is known for possible complications due to arrhythmia, caused by an abnormal course of the conduction system, as in our case. The foetus with trisomy 21 had perimembranous subaortic ventricular septal defect, which is present in a small proportion of cases with this chromosomopathy, but again, bilateral lung lobation defects have not been reported in this setting.

Abnormal lobation of the lung may involve only one lung, left or right, or both, and instead of regular lobation the lungs may present more or fewer lobes than normal. The condition may be complete or partial, and in 20% of cases lobes are multiple<sup>25</sup>. At necroscopic examination of 100 lungs, Langlois & Henderson found a 45% incidence of altered fissuring of the pulmonary lobes, 33% of these consisting of single and 6% of double anomalies. These were chiefly bilobate lungs or lungs with additional or deficient fissures<sup>32</sup>.

Although lobation defects in most cases have no clinical relevance, it should be considered that the partial absence of a fissure produces a bridge of parenchyma between two contiguous lobes and permits the spread of disease across anatomical boundaries. Conversely, accessory fissures may limit disease, either to the additional lobe thus produced or to other lobar segments, sparing the separate lobe. The most significant problem, however, occurs when bronchial branching is also disordered, which only happens rarely<sup>32</sup>.

In our cases, as is usual in cases of complex cardiac anomalies, the exact visceral and atrial situs was determined, as well as the intracardiac anatomical details, and thus even where there were defects in lung lobation we ruled out isomerism. However, our cases indicate the presence of bilateral lung lobation defects, apparently with no particular significance or alteration of the bronchial branching, except in case 3 associated with lung hypoplasia, in which the right lung was hypoplastic and bilobate and the left lung was bilobate. Generally, the number of principal bronchi corresponds to the number of lobes, while in our case we found an incorrect subdivision of the bronchial branching, both lungs being bilobate, with one left principal bronchus and two right principal bronchi.

The pathogenetic mechanism underlying this defect is unknown, but it appears probable from the embryological development of the lung that during the pseudoglandular phase, when the lobes are formed, from the 5<sup>th</sup> to 16<sup>th</sup> week of development of the embryo with a differ-

ence of 2 weeks between upper lobes and lower lobes, genetic or other factors might intervene to produce a faulty subdivision in the lobes of the lung, which would then continue its growth, passing through the canalicular phase, the saccular and lastly the alveolar stage, reaching full maturity in postnatal life.

Possible aetiological risk factors were also evaluated, but we had only one mother with pharmacotherapy during pregnancy (phenobarbital) and the foetus had Ebstein's anomaly, which is usually related to lithium therapy rather than to phenobarbital, in association with which lung lobation defects have never been reported.

Another peculiarity of our cases was the finding of associated minor extracardiac anomalies or facial dysmorphism, which could not have been diagnosed by ultrasonography and did not fit to any specific syndromes. Indeed, routine 2-D echocardiography cannot be exhaustive regarding minor anomalies; only the 3-D technique provides imaging of the foetal face and other morphological details that may lead to a suspicion of genetic syndromes. At present, prenatal screening (obstetric echography and foetal echocardiography) can detect major malformations of all organs with certainty, but is limited regarding minor abnormalities.

In conclusion, autopsy is extremely useful in foetuses with congenital heart defects and in all other malformations after therapeutic abortion or intrauterine death, at times discovering unusual associations with other malformations: this information is important for future genetic counselling of parents, in order to establish possible recurrent risks for future pregnancies.

Furthermore, given the small number of cases we reported here and the rarity of reports in the literature (probably due to the impossibility of diagnosing this condition echographically in utero), the association of abnormal lobation and cardiac defects in cases with usual viscerotrial arrangement is far from being clarified. Thus, the number of cases actually occurring may be assumed to be considerably higher than reported up to now, and it may be that improvements in diagnostic imaging techniques will help to clarify this type of defect and its relation with other syndromes. At present, anatomopathological evaluation plays a crucial role in clarifying the final complete diagnosis of affected foetuses, a fact that is very important in genetic counselling of couples considering future pregnancies.

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# Solitary extramedullary plasmacytoma of the thyroid gland associated with multinodular goiter: case report and review of the literature

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## Key words

Solitary extramedullary plasmacytoma • Multinodular goiter • Thyroid gland • Hashimoto's disease • CD 138 • Kappa chains

## Summary

Solitary extramedullary plasmacytoma (SEP) is a rare malignant neoplasm arising from plasma cells most commonly occurring in the nasal cavity, nasopharynx and larynx. Thyroid involvement is rare and less than 75 cases of SEP of the thyroid gland have been reported to date. A 74-year-old woman with an history of multinodular goiter presented with dysphonia and painful neck swelling, related to a rapidly growing nodule in the right thyroid lobe. Thyroid function tests showed subclinical hypothyroidism; no evidence of Hashimoto's disease was found. Ultrasound confirmed the presence of an isoechoic nodule, 35 mm in diameter, with a CDIII vascular pattern. FNAC showed a monotonous population of atypical cells, interpreted as suspicious for malignant neoplasia (Thyr. 4). The patient underwent total thyroidectomy. Histopathological examination showed a unencapsulated

neoplasm composed of atypical tumour cells characterized by abundant cytoplasm and eccentric nuclei. At immunohistochemistry, tumour cells revealed diffuse reactivity for CD138 and CD45RB and predominant staining for kappa chains. Pan-cytokeratins, TTF1, thyroglobulin, calcitonin, CD20 and CD79a were negative. Clinically, a complete multiple myeloma workup was negative. On this basis, a definitive diagnosis of SEP was made. At 16 months follow-up, the patient showed good clinical conditions without evidence of multiple myeloma. In conclusion, SEP should be considered in the differential diagnosis of a rapidly enlarging thyroid nodule. Clinical correlation and immunocytochemistry are crucial in avoiding pitfalls. Surgery remains the best modality of treatment whenever the lesion is localized and easily removable.

## Introduction

Solitary extramedullary plasmacytoma (SEP) is a uncommon plasma cell tumour that involves soft tissue, without any signs of systemic spread. It may originate in many sites, although it most frequently occurs in the upper respiratory tract, such as the oral cavity, nasal cavity, nasopharynx, larynx or conjunctiva. Its occurrence in thyroid gland is rare, and fewer than 75 cases of SEP of the thyroid gland have been reported to date. SEP is present in less than 5% of all plasma cell neoplasms, a percentage similar to that reported for solitary plasmacytoma of bone (SPB). Both these tumours are composed of sheets of plasma cell sat different stages of maturity, and both respond favourably to appropriate therapy. However, SPB evolves into multiple myeloma (MM) more frequently than SEP<sup>1</sup>.

## Materials and methods

A 74-year-old female with a history of multinodular goiter presented to the San Martino Hospital of Oristano in June 2009 for dysphonia and painful neck swelling related to a rapidly growing nodule in the right thyroid lobe. Histopathologic diagnosis was made from haematoxylin-eosin stained slides and confirmed by immunohistochemical demonstration of monoclonal cytoplasmic immunoglobulins. Initial work-up included thyroid ultrasonography, fine-needle aspiration cytology (FNAC), skeletal X-ray survey, serum electrophoresis, immunoglobulin quantification, immunoelectrophoresis or immunofixation of serum and urine, beta-2 microglobulin assay (the latter two tests were performed when they became available), chest X-ray, abdominal ultrasonography and CT-scan (when available). The diagnostic criteria were as follows:

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- 1) tissue biopsy showing monoclonal plasma cell histology;
- 2) bone marrow plasma cell infiltration not exceeding 5% of all nucleated cells;
- 3) absence of osteolytic bone lesions or other tissue involvement (no evidence of myeloma);
- 4) absence of hypercalcaemia or renal failure;
- 5) low serum M protein concentration, if present.

## Results

Physical examination revealed a 3.5 cm nodule in the thyroid gland. The mass was non-tender, elastic in consistency and movable while swallowing. All other physical examinations showed subclinical hypothyroidism; no evidence of Hashimoto's disease was found. Haemoglobin, serum calcium, phosphate, total protein (7.6 g/dl) and albumin (4.9 g/dl) levels, immunoelectrophoresis and chest X-ray results were normal. By ultrasound examination, the thyroid showed a non-homogeneous structure with multinodular features. Ultrasound scan confirmed the presence of an isoechoic nodule, 3.5 cm in diameter, with a CDIII vascular pattern. FNAC showed a homogenous population of atypical cells, interpreted as suspicious for malignant neoplasia (Thyr. 4). Subsequently thyroidectomy was performed. Histopathological examination showed an unencapsulated neoplasm composed of atypical tumour cells characterized by abundant eosinophilic cytoplasm and eccentric and atypical nuclei (Fig. 1) with abundant desmoplastic reaction; parenchyma with no extra capsular spread was present. Immunohistochemical staining revealed evidence of monoclonalism of plasma cells with diffuse reactivity for CD138 (Fig. 2), CD45RB and light chain restriction with predominant staining for kappa chains and minimal staining for lambda chain, which favours a diagnosis of plasmacytoma. Pan-cytokeratins, TTF1, thyroglobulin, calcitonin, CD79a (Fig. 3) and CD20 (Fig. 4) were negative. In addition, two small foci of papillary carcinoma of the left lobe were found, respectively, 2 and 4 mm in maximum diameter. A complete multiple myeloma workup was carried out including bone marrow biopsy, whole body CT scan, complete skeletal survey, MRI scan of thoracic lumbar spine, immunoelectrophoresis of serum and urine, urine for Bence-Jones proteins, quantitative serum immunoglobulin assay, serum biochemistry including calcium, renal function tests and FBC including platelet count which were all negative. The only abnormality found was a moderate increase in beta-2 microglobulin, which persisted even in subsequent follow-up investigations. Clinical follow-up for a 16-month period remained uneventful, and subsequent investigations including radiology, serum and urine for paraproteins remained negative.

## Discussion

Solitary extramedullary plasmacytoma is a rare and localised collection of monoclonal plasma cells. It is divided into solitary bone plasmacytoma and solitary extramedullary plasmacytoma involving the soft tissues excluding the bone. Solitary extramedullary extramedullary plasmacytomas are extremely rare and found principally in elderly people (5-6<sup>th</sup> decade) with a male predilection (3:1). They occur predominantly in head and neck region (> 90%) and account for 0.4% of all head and neck neoplasms<sup>1-5</sup>. It has a tendency to involve submucosal tissues of the upper aerodigestive tract in the majority of patients, which is probably related to long-term stimulation by inhaled irritants or viral infection<sup>4</sup>. Solitary extramedullary plasmacytoma is biologically and prognostically different from other plasma cell neoplasms. About 20% of solitary extramedullary plasmacytoma and > 50% of solitary bone plasmacytoma will eventually progress to multiple myeloma during long-term follow-up. About 20% of cases showed spread to the regional lymph nodes, and 14-25% had serum para protein detected; only fewer than 5% had urine Bence-Jones proteins<sup>6,7</sup>. In our case, neither was positive.

Concerning the aetiology of solitary extramedullary plasmacytoma, the proposed risk factors include chronic antigenic stimuli such as inhaled irritants, viral and other infections, smoking, radiation exposure and genetic predisposition. However, none of these were found in the present case. Solitary extramedullary plasmacytoma of the thyroid occurs most commonly in patients with Hashimoto's thyroiditis and must be distinguished from involvement of thyroid in multiple myeloma, inflammatory pseudotumour plasma cell variant, mucosa-associated lymphoid tissue lymphoma and medullary carcinoma<sup>8</sup>. Histopathological analysis alone is not sufficient to make a diagnosis of solitary extramedullary plasmacytoma as multiple myeloma has to be excluded through skeletal survey, bone marrow biopsy and serum and urine screen for paraproteins. Diagnosis by fine needle aspiration needs a high index of suspicion and often the material is insufficient for immunocytochemical analysis. Although FNAC has been widely used in diagnosing nodular thyroid disorders, limited experience exists for preoperative diagnosis of thyroid plasmacytomas. A thyroid plasmacytoma can be mistaken as thyroid lymphoma, medullary carcinoma and even thyroid lymphoma by FNAC<sup>9</sup>.

The treatment of choice is radiotherapy. However, if the lesion is localized and amenable to surgery, it could be the first choice since it is associated with less morbidity to the patient both in terms of duration of treatment and side effects. Regular follow-up with monitoring of serum and urine for para proteins and other appropriate investigations is necessary as there is a definite risk for progression to multiple myeloma in 5-20% of patients.

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# Sebaceous carcinoma of the vulva: critical approach to grading and review of the literature

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## Key words

Sebaceous carcinoma • Vulva cancer • Sebaceous neoplasm

## Summary

**Background.** Sebaceous glands are abundant on the vulva, but vulvar sebaceous carcinoma (SC) is an uncommon neoplasm.

**Methods.** We report a case of SC of the vulva in a 51 year-old woman.

**Results.** The patient presented a 6-month history of an asymptomatic 2.5 × 1.5 cm exophytic tumour localized on the left labium majora. Tumorectomy was performed. Histologically, the lesion had an irregular lobular growth pattern composed of lobules or sheets of malignant cells separated by fibrovascular stroma. There was a mixture of sebaceous-type differentiation, small ducts and areas showing basaloid or squamous features. Centrally-located tumour cells showed moderate EMA immunoreactivity, especially enhancing cytoplasmic "bubbiness". Tumour cells were immunoreactive for CAM 5.2. The immunoreactivity for intranuclear p53 staining was > 10%. Southern blot hybridization and PCR studies did not detect HPV DNA. Hemivulvectomy was performed. After 18 months of follow-up, the patient has no evidence of recurrence, metastases or other malignant tumours.

**Conclusions.** The grading of cutaneous SC proposed by Rutten et al. (World Health Organization Classification of Skin Tumours) and Patterson & Wick (Nonmelanocytic Tumours of the Skin. Armed Forces Institute of Pathology) is based on patterns of tumour growth rather than cytological features. Such grading of

skin SC, including vulvar SC, should not be used since its prognostic value has not been sufficiently documented. As the number of reported vulvar SCs is very limited, their natural history is unknown and the optimal treatment has not been established. The follow-up of 7 reported cases supports the general opinion that the tumour may be aggressive. SC groin node metastases carry a devastating prognosis, and unrecognized disease in the inguino-femoral lymph nodes is nearly always fatal. The use of sentinel lymph nodes (SLN) has evolved as an effective surgical technique for identifying early subclinical regional nodal involvement for many solid tumours throughout the body for staging disease; this is because extra-ocular SCs cause widespread metastatic disease. In our opinion, SLN should be used in conjunction with wide local excision of the primary tumour to investigate regional subclinical metastases. In the presence of a positive sentinel node, early lymphadenectomy with or without radiotherapy could be used to reduce tumour-related morbidity and mortality. The histopathologic differential diagnosis of SC is wide-ranging, including virtually all other malignant clear cell tumours of the skin. The proliferative pattern, immunostaining and cytologic features permit exclusion of neoplasms that mimic SC, but a diagnosis of SC should be rendered only if the overall attributes of the lesion are appropriate for such an interpretation.

## Introduction

In comparison to ocular sebaceous carcinoma (SC), extraocular SC is an uncommon neoplasm that usually presents as yellow-tan firm nodule, often ulcerated, measuring 1-4 cm or more in diameter. They are most commonly found on the head and neck of elderly patients. Sebaceous glands are also abundant on the vulva, but vulvar SC is an uncommon neoplasm<sup>1-7</sup>. SCs have been rarely associated with Muir-Torre syndrome<sup>8</sup> and organ transplant recipients<sup>9</sup>. To our knowledge, there are only six reported cases of vulvar SC. Herein, we report an

additional vulvar case of SC. A review of the literature is also presented to discuss prognostic parameters, management and differential diagnosis.

## Materials and methods

A 51-year-old woman presented with a 6-month history of an asymptomatic nodule localized on the left labium majora. Physical examination demonstrated a 2.5 cm × 1.5 cm exophytic red and white tumour. There was no history of any significant medical problems, and

## Correspondence

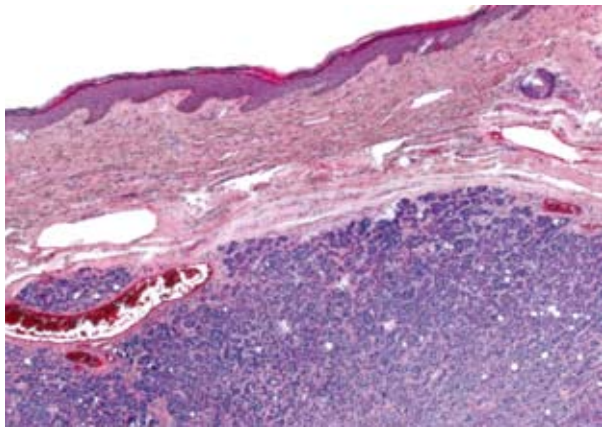
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her family history was unremarkable. A tumorectomy was performed. After diagnosis of SC, hemivulvectomy was performed. No additional areas of persistent SC were found in the specimen of hemivulvectomy. Whole body CT showed no evidence of metastatic disease or any other malignant neoplasm. After 18 months of follow-up, the patient has no evidence of recurrence, metastases or other malignant tumours.

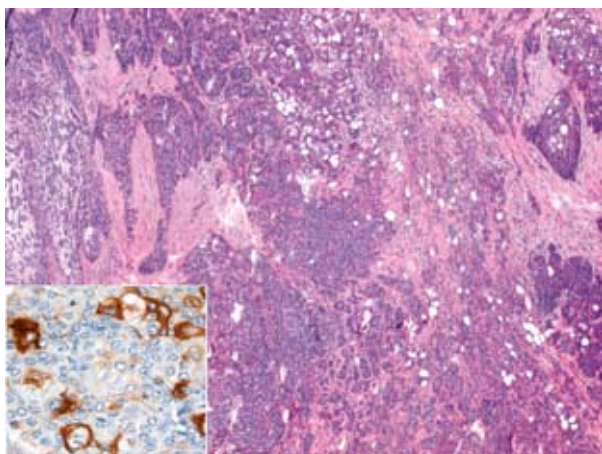
## Results

Histologically, the lesion had an irregular lobular growth pattern with clear evidence of cytologic atypia and was composed of lobules or sheets of cells separated by fibrovascular stroma. There was a mixture of sebaceous-type differentiation, with small ducts and areas showing basaloid or squamous features (Figs. 1-3). There

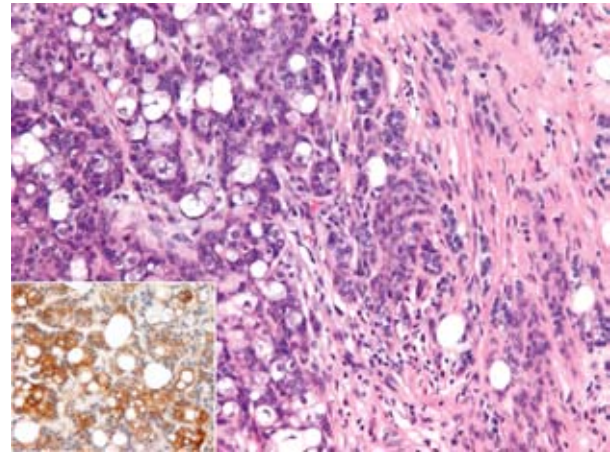
**Fig. 1.** The neoplasm within reticular dermis is a mixture of sebaceous-type differentiation, small ducts and areas showing basaloid features. (haematoxylin-eosin, 40 $\times$ ).



**Fig. 2.** The neoplasm has an infiltrative pattern with irregular nests of cells showing sebaceous differentiation. The cells at the periphery of the neoplastic nests were small and basaloid. (haematoxylin-eosin, 40 $\times$ ) (insert: Immunostaining for EMA: centrally located tumour cells showed moderate EMA immunoreactivity, enhancing the cytoplasmic "bubbliness" (200 $\times$ ).



**Fig. 3.** The sebaceous differentiation of neoplastic cells is evident. Basaloid tumour nests show an infiltrative pattern. (haematoxylin-eosin, 100 $\times$ ) (insert: Tumour cells were immunoreactive for Cam 5.2 (100 $\times$ ).



were scattered mitoses. The lesion did not involve the epidermis. The histological specimen was sent to Prof. Christopher D.M. Fletcher (Director of Surgical Pathology, Brigham and Women's Hospital, Boston, Massachusetts, USA) who confirmed our diagnosis. Sudan IV stain demonstrated positive globules in pale neoplastic cells, although occasional basaloid cells in the periphery of the nests were also positive. No Alcian blue-positive or PAS-positive intracytoplasmic mucinous substance or glycogen granules were identified in these cells. Centrally-located tumour cells showed moderate epithelial membrane antigen (EMA) immunoreactivity, enhancing the cytoplasmic "bubbliness". Tumour cells were immunoreactive for CAM 5.2. The immunoreactivity for intranuclear p53 protein was > 10%. Southern blot hybridization and PCR studies did not detect HPV DNA.

## Discussion

Both ocular and extra-ocular SCs have a 30-40% risk for local tumour recurrence, with a 20-25% risk for distant metastases and a 10-20% risk of tumour-related mortality<sup>10</sup>. Rutten et al.<sup>11</sup> and Patterson and Wick<sup>12</sup> have proposed a grading system for SC of the skin. The grading proposed by these authors (grades I through III) is based on tumour growth patterns rather than cytologic features. Lesions composed of rounded, well-demarcated, roughly equalized cellular lobules are graded as I. Those with an admixture of well-defined nests with infiltrative profiles or confluent cell groups are considered grade II lesions. Grade III SCs lesions demonstrate highly invasive cellular aggregates with irregular outlines or manifest a medullary sheet-like growth pattern. WHO and AFIP grading of skin SC have only a theoretical importance because the prognostic value has not been documented. In fact, Rutten et al.<sup>11</sup> and Patterson and Wick<sup>12</sup> mistakenly supported the grading of cutaneous SC based on the

study by Rao et al.<sup>13</sup>. These authors examined 104 cases of SCs of the ocular adnexa to establish prognostic factors. Rao et al.<sup>13</sup> have found various clinicopathologic features, that were associated with poor prognosis: vascular, lymphatic, and orbital invasion; involvement of both upper and lower eyelids; poor differentiation; multicentric origin; duration of symptoms greater than six months; tumour diameter exceeding 10 mm; a highly infiltrative pattern and pagetoid invasion of the overlying epithelia of the eyelids. Rao et al.<sup>13</sup> did not categorize ocular SCs into 3 grades. WHO and AFIP grading of the cutaneous SC should be not used to predict the outcome of skin SCs because the studies of Rao et al. were performed with ocular SCs. In the report by Hasebe et al.<sup>14</sup>, immunoreactivity for mutant p53 protein (> 10%) and proliferating cell nuclear antigen (> 25%) appears to be associated with adverse outcome. Only 3 cutaneous SCs were examined by Hasebe et al.<sup>14</sup>. Consequently, the conclusions of Patterson and Wick<sup>12</sup> and Rutten et al.<sup>11</sup> regarding the predictive value of p53 in cutaneous SC are not confirmed by Hasebe et al.<sup>15</sup> as only 3 skin SCs were studied. A total of 7 cases of SC of the vulva have been reported.

In our case, the infiltrative pattern of basaloid cells (Fig. 3) and the level of p53 were considered adverse prognostic features. Consequently, hemivulvectomy was performed.

Because of the small number of vulvar SC reported in the literature, optimal management of disease has been not established. Extraocular SCs causing widespread metastatic disease are rare, with only 9 recorded patient deaths as a result of visceral metastases<sup>2 15-21</sup>. When metastases from extraocular SC occur, only regional lymph nodes have been involved<sup>4 9 22</sup>. Patients with SC groin node metastases have a devastating prognosis and regional radiotherapy is reserved exclusively for those with positive groins. It is imperative that all possible steps are taken to avoid false positive results. For the majority of patients without groin node metastases, inguino-femoral lymphadenectomy is of unproven therapeutic benefit and carries a considerable risk of morbidity. In contrast, failing to resect metastatic disease in patients with malignant groins compromises their chance for cure. Unrecognised disease in the inguino-femoral lymph nodes is nearly always fatal. Sentinel node biopsy has evolved as an effective surgical technique for identifying early sub-

Tab. I. Vulvar sebaceous carcinoma: review of the literature.

Clinical features	Rulon and Helwing <sup>1</sup>	Ikuse et al. <sup>2</sup>	Jacobs et al. <sup>3</sup>	Kawamoto et al. <sup>4</sup>	Carlson et al. <sup>5</sup>	Escalonilla et al. <sup>6</sup>	Khan et al. <sup>7</sup>	Current case
Age	31	75	89	78	46	76	49	51
Site	Left labia minora	Labia majora	Left labia minora	Left labia minora	Left labia majora	Right labia majora	Right labia minora	Left labia majora
Duration of symptoms before diagnosis	6 months	2 years	1 year	6 months	NS	4 months	NS	6 months
Size (cm)	2 × 1.1 × 0.3	4 × 4	3 × 1.4 × 0.3	2.5 × 1.5 × 1.0	NS	4 × 3	0.5	2.5 × 1.5
Tumour appearance	Raw, yellow, slightly indurated plaque	Red, ulceration	Pink-white plaque	Yellow-white nodule	Sebaceous cyst	Exophytic red white tumour and small brown papules	Papilloma	Exophytic red and white tumour
Symptoms	NS	NS	Pain, dysuria	A	Pruritus	A	NS	A
Treatment	NS	NS	Left radical hemivulvectomy	Simple vulvectomy, left IL + radiotherapy for the left inguinal area	Left radical hemivulvectomy with left IL	Radical vulvectomy with IL	Wide local excision with bilateral IL + radiotherapy and chemotherapy	Left hemivulvectomy
Metastases	NS	Lung	NP	Left inguinal lymph nodes	NP	NP	Nodal left groin metastases	NP
Outcome	Alive (13 years, 7 months)	Dead	NS	Alive (17 months)	Alive (31 months)	Alive (12 months)	Vulvar skin of the right groin recurrence at 7 months after initial treatment. In the right groin, vulva and perineal region 1 year after initial admission	Alive (24 months)
Associated condition	NP	NP	Bowen's disease Muir-Torre syndrome	NP	NP	Bowen's disease	NP	NP

NS: not specified; NP: not present; IL: inguinal lymphadenectomy; A: asymptomatic.

clinical regional nodal metastasis for many solid tumours (mainly breast and malignant melanoma) throughout the body and for staging disease<sup>23 24</sup>.

We therefore believe that sentinel node biopsy should be used in conjunction with wide local excision of the primary tumour to investigate regional subclinical metastases. In the presence of a positive sentinel node, early lymphadenectomy with or without radiotherapy could be used to reduce tumour-related morbidity and mortality. Such a neoplasm has not been reported in a vulvar site. In conclusion, the natural history and optimal treatment of SC of the vulva are unknown. Grading and prognostic parameters are not available. Additional cases need to be reported in order to establish the treatment of choice. Sentinel node biopsy should be used in conjunction with

wide local excision of the original tumour to investigate regional subclinical metastasis. The histopathologic differential diagnosis of SC includes sebaceous tumours (sebaceous adenoma, sebaceoma), epithelial neoplasms with sebaceous differentiation (squamous and basal cell carcinoma) and virtually all other malignant clear cell tumours of the skin (ballon cell melanoma, clear variant of atypical fibroxanthoma, hydropic squamous carcinoma, clear cell basal cell carcinoma, clear cell eccrine adenocarcinoma, trichilemmal carcinoma, and metastatic clear cell carcinomas from the viscera). The proliferative pattern, immunostaining and cytologic features permit the exclusion of similar neoplasms, but a diagnosis of SC should be rendered only if the overall attributes of the lesion are appropriate for such an interpretation.

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# Pleomorphic giant cell ductal carcinoma of the breast

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## Key words

Breast • Ductal carcinoma • Giant cells

## Summary

Pleomorphic ductal invasive carcinoma is a very rare, high-grade breast cancer with unfavourable prognosis. It contains highly pleomorphic giant cells, which represent more than 50% of the cancer cells. One such case is described herein, focusing

on its morphological, histopathological and immunohistochemical patterns. It was multicentric, oestrogen and progesterone receptor negative and epidermal growth factor receptor type 2 positive.

## Introduction

Pleomorphic ductal carcinoma is a very rare high-grade breast cancer (0.5-1.2% of all breast cancers) which has been separated from ductal carcinoma NOS by the WHO tumour of the breast classification because of its aggressive behaviour and poorer prognosis<sup>1,2</sup>. To the best of our knowledge, 76 cases have been described in the breast to date. Similar tumours have been described in other organs such as the pancreas, liver, thyroid, prostate, lung, gallbladder, bile ducts, small intestine and colon<sup>3-8</sup>. The aim of the present study is to describe a case of multicentric, pleomorphic carcinoma of the breast in a woman aged 44 years, focusing on its morphology, immunohistochemical prognostic markers and differential diagnoses.

## Case report

A 44-year-old woman in good general health was subjected to a screening mammography that revealed two poorly circumscribed nodules (12 mm and 6 mm in their greatest axes, respectively) located in the two upper quadrants of the right breast. Ultrasonography showed two irregularly shaped, hypoechoic masses without posterior echo enhancement; many enlarged lymph nodes were seen in the right axilla. The lesions were highly suspicious for carcinoma at mammography; by fine needle aspiration cytology (FNAC) a "cellularity compatible with carcinoma"

was detected. The patient underwent biquadrantectomy with removal of the sentinel lymph node, whose positivity for cancer indicated the necessity for radical mastectomy with axillary lymphadenectomy. None of the 15 lymph nodes examined were invaded by cancer.

The patient had no complications during the postoperative course and is disease-free at 6 months after the diagnosis.

Samples were taken from both nodules. They were fixed in 10% buffered formalin, embedded in paraffin, routinely processed, cut in 4 µm-thick sections and stained with haematoxylin and eosin. Selected slides were used for immunohistochemical staining to better define the profile of the tumour and to evaluate selected prognostic markers.

Serial sections were obtained from the sentinel lymph node, which were stained with haematoxylin and eosin and tested for cytokeratins (CKAE1/AE3). Additional immunohistochemical features were analysed using the labelled streptavidin-biotin technique with mouse monoclonal antibodies against ER, PR, AE1/AE3, Her-2/neu, CD68, GCDFP-15, vimentin, EMA, P53, Bcl-2 and Mib 1. Axillary lymph nodes were routinely examined.

## Results

The surgical specimens contained two well circumscribed, white-greyish nodules with haemorrhagic ar-

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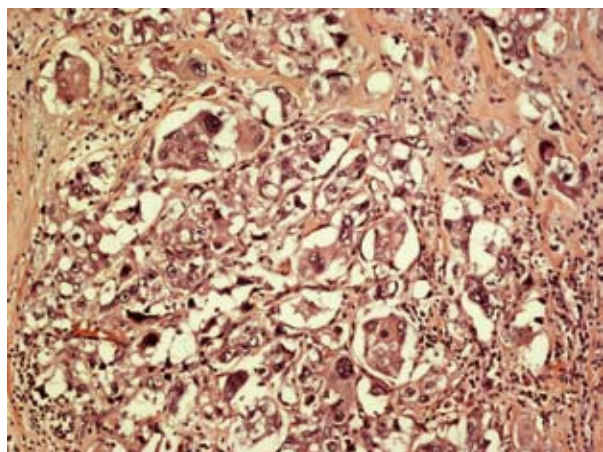
eas, measuring 12 and 6 mm at a distance of 15 mm each other. Microscopically, both nodules were diagnosed as high-grade, pleomorphic invasive ductal carcinoma with foci of pleomorphic ductal in situ carcinoma. The majority of neoplastic cells were large, multinucleated, with pleomorphic nuclei and coarse, smudged chromatin and multiple nucleoli. They were aggregated in sheets and cords or sparse, intermingled with few tubular structures, eosinophilic cells with rhabdoid features and spindle cells. The mitotic rate was > 20 mitoses/10 HPFs; mitoses were sometimes atypical. Many lymphocytes were present at the periphery of the nodules, together with foci of pleomorphic intraductal carcinoma. A few microcalcifications were detected inside the tumour nodules. All neoplastic cells were positive for cytokeratins AE1/AE3, E-cadherin and Her-2/neu, and negative for vimentin, oestrogen and progesterone receptors, GCDFP-15, CD 68 and p53. Giant anaplastic cells were also positive for CK5/6 and EMA. Mib 1 score was of about 35%. The sentinel lymph node was infiltrated by cancer, while all the axillary lymph nodes were negative.

**Discussion**

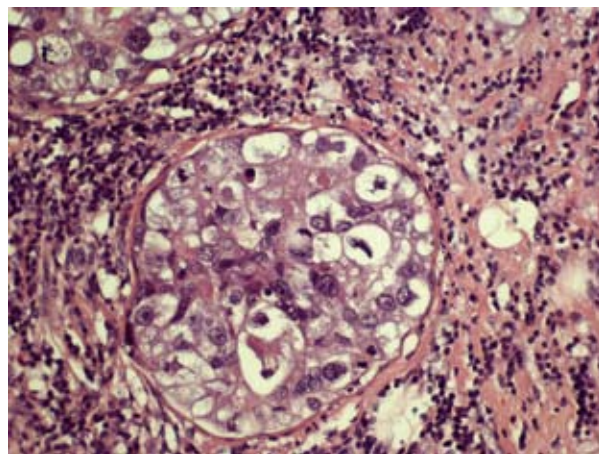
Pleomorphic invasive ductal carcinoma of the breast was recognized as an entity distinct from invasive ductal carcinoma NOS in 2003 (WHO classifications) because of its morphological features, rapid growth and aggressive behaviour<sup>19</sup>. It is predominantly composed of pleomorphic cells, many of which are giant and multinucleated (Fig. 1). The frequent presence of a ductal in situ component, as in our case, detected on the basis of E-cadherin positivity, definitely assigned this cancer to the ductal histotype. At the same time, its pleomorphic cellularity with many multinucleated giant cells, some spindle and some rhabdoid cells, as in

the present case, and sometimes squamous cells, as well as its rapid growth, testified by numerous mitoses and high Mib 1, are the reasons why the WHO classification of breast tumours removed invasive pleomorphic carcinoma from the invasive ductal carcinoma NOS. Breast pleomorphic carcinoma can relatively frequently pose problems for differential diagnosis. In particular, when the in situ component is absent, it is necessary to consider the possibility of a pleomorphic lobular carcinoma. However, pleomorphic lobular carcinoma does not contain as many giant cells, which is > 50% of the cellularity, its cells may show apocrine differentiation, absent in our case, and it tends to grow in linear arrays<sup>10</sup>. The cadherin positivity, as in our case, confirms that the tumour belongs to the ductal histotype. Metastatic carcinoma to the breast is a very rare event, often multicentric. In our case, the tumour was multicentric, although there were foci of in situ carcinoma (Fig. 2). Obviously, in the absence of any in situ component, it is important for diagnosis to exclude other primary tumours<sup>11</sup>. In the case under study, pleomorphic cells,

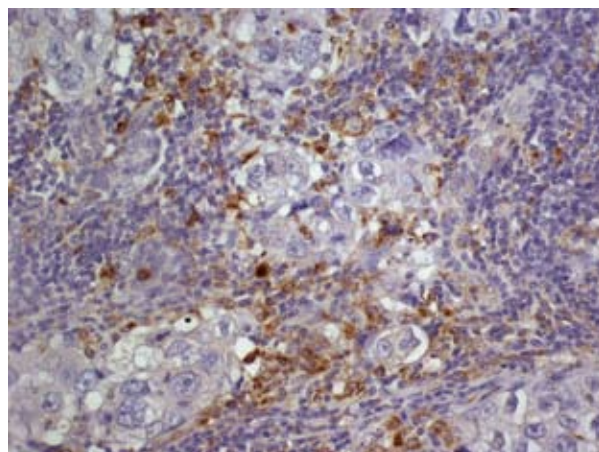
**Fig. 1.** Typical appearance of pleomorphic ductal carcinoma of the breast with a variable population of unusual giant tumour cells. Tumour cell multinucleation was present in the majority of the tumour, such as prominent nucleoli and high mitotic activity.



**Fig. 2.** In-situ component of pleomorphic ductal carcinoma.

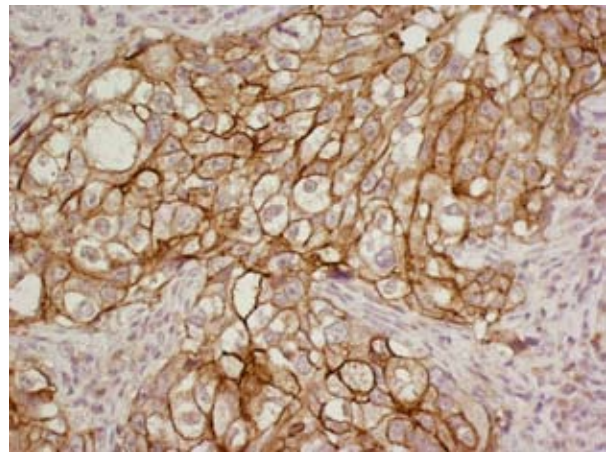


**Fig. 3.** CD68 negativity in multinucleated giant cells.

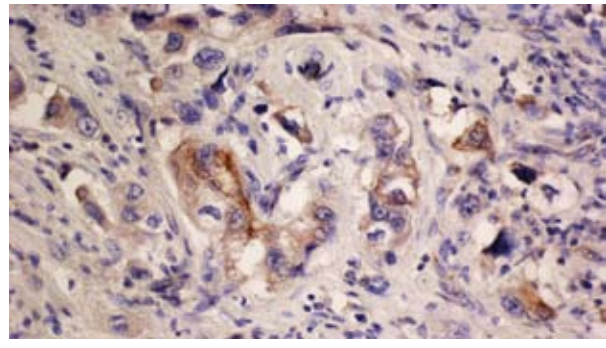


giant or not, were all CD68 negative and CK positive, excluding the possibility of osteoclastic-like cells, which, in contrast, are CD68 positive and CK negative (Fig. 3)<sup>12</sup>. The positivity of these cells for CK and their negativity for vimentin, even in the spindle cells areas, exclude sarcoma<sup>13</sup>. Notwithstanding their aggressive behaviour, ductal pleomorphic invasive carcinomas may be misdiagnosed at mammography and ultrasound because of their morphological appearance as well as circumscribed masses (from 35% according to Silver and Tavassoli, 2000<sup>9</sup>, to nearly 50%, according to Zhao et al., 2010<sup>11</sup>), as in our case. This is unexpected if one considers that most of the tumours described so far in the literature were high-grade and rapidly growing, and 61 of 75 were oestrogen and progesterone receptor negative and Her-2/neu negative (triple negative). Hence, histopathological and biological parameters, as explored by immunohistochemistry, are all indicative of a poor prognosis, in spite of the harmless macroscopic appearance of these tumours. Our case was oestrogen and progesterone receptor negative, but Her-2/neu positive, as were 15 of the 75 cases described in the literature (Fig. 4). Moreover, nothing can be affirmed about the behaviour of the tumour in the present case: the neoplastic invasion of the sentinel lymph node was not associated with invasion of the other axillary lymph nodes analyzed; the patient is disease-free at 6 months after diagnosis. However, the negativity for oestrogen and progesterone receptors, the high Mib 1 and the positivity for CK5/6 of anaplastic giant cells are indicative of poor prognosis (Fig. 5). In the literature, only one case has been tested for CK5/6 and was negative<sup>14</sup>. The positivity for Her-2/neu may add to the poor prognosis; however, it consents specific targeted therapy.

**Fig. 4.** Immunohistochemical analysis for Her-2/neu showed intense and complete membrane immunoreactivity in pleomorphic giant cells.



**Fig. 5.** CK5/6 was intensely immunoreactive in pleomorphic giant cells.



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# A solitary pilar leiomyoma of the trunk

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## Key words

Pilar leiomyoma • Smooth muscle tumour

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## Summary

Smooth muscle tumours arising in the skin are divided into angioleiomyomas, genital leiomyomas and pilar leiomyomas. Limited data about solitary leiomyoma are available in the literature. We herein report a case of a 66-year-old man who presented to our department with a slowly progressing cutaneous tumour of the right scapular area that had developed over the past 12 years. Histopathological and immunohistochemical results were consis-

tent with the diagnosis of pilar leiomyoma. Pilar leiomyoma is a benign smooth muscle tumour arising from arrector pili muscle. Tumours can be painful from compression of cutaneous nerves or because of fibre contraction within the tumour in case of cold weather or emotional stress. This case is noteworthy as the piloleiomyoma was solitary, located on the trunk and had an unusual nipple aspect.

A 66-year-old man with a history of diabetes mellitus treated with insulin therapy presented to our outpatient department with a cutaneous tumour of the right scapular area that had developed over the past 12 years that slowly progressed (Fig. 1). The tumour was painful, especially in cold weather, but the patient was not taking any medications and has no history of trauma to the area. His family history was negative for similar pathologies. On cutaneous examination, there was a 2.5-3 cm erythematous papular well-circumscribed plaque with a reddish firm and smooth nodule having a nipple aspect. The plaque presented a slightly translucent appearance. Physical examination did not reveal any other abnormalities. Histological examination revealed a non-encapsulated tumour mass consisting of eosinophilic spindle cells extending irregularly in interweaving fascicles between bundles of collagen in the reticular dermis (Fig. 2a). Individual smooth muscle cells presented cigar-shaped nuclei on longitudinal sections (Fig. 2b). Immunohistochemically tumour cells stained strongly with smooth muscle actin antibodies (Fig. 3). No mitotic activity was identified. There was no reaction with CD34, S100 or CD68 antibodies. A diagnosis of pilar leiomyoma was made, and surgical removal of the tumour was performed. Smooth muscle tumours arising in the skin are divided into angioleiomyomas, genital leiomyomas and pilar leiomyomas. Pilar leiomyoma is a benign smooth muscle tumour arising from the arrector pili muscle<sup>1</sup>.

Only limited data about solitary leiomyoma is available in the literature. Solitary leiomyoma tend to be larger

than multiple lesions. Clinically, cutaneous pilar leiomyoma appear as multiple or solitary firm reddish to brown dermal papules or small nodules, ranging in size from several mm to more than 1 cm, and can coalesce to form plaques<sup>1,2</sup>. Diagnosis in our case was problematic, and other diagnoses were suspected such as B cell lymphoma, dermatofibroma and a supernumerary nipple, but the histological results confirmed a diagnosis of smooth muscle cell proliferation. Tumours can be painful from compression of cutaneous nerves or because of fibre contraction within the tumour in case of cold weather or emotional stress<sup>3</sup>. These tumours usually occur in adults with a wide age distribution on the trunk and on the extremities<sup>1</sup>. The available data suggest a variable sex distribution from 1:1 to a 3:1 female predilection. Most authors have reported a predominance of multiple lesions, although some noted an equal prevalence of solitary and multiple leiomyomas<sup>3</sup>. The trunk is mostly involved in multiple leiomyomas<sup>1</sup>. Piloleiomyoma can develop sporadically or can be transmitted genetically<sup>4</sup>, and familial involvement is only rarely found. In the familial form, transmission is through an autosomal dominant trait, and leiomyomas are usually multiple. Some diseases can be associated with piloleiomyomas such as Reed's syndrome, leukaemia and papillary carcinoma of the kidneys<sup>4,5</sup>. Histologically, pilar leiomyoma are composed of interlacing fascicles of well differentiated smooth muscle cells in the dermis. The tumour is usually well defined without a definite capsule and is separated from the epidermis by a thin layer of connective tis-

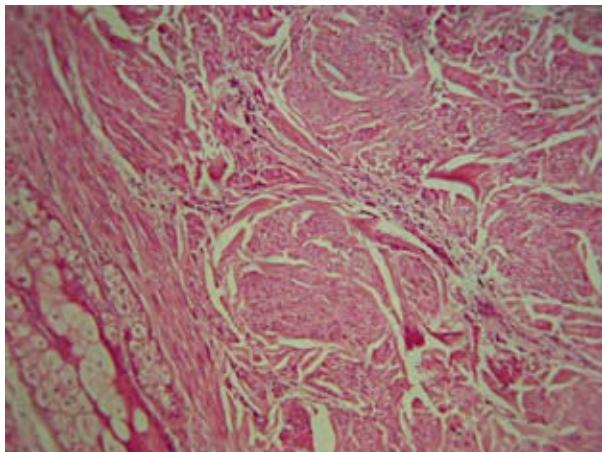
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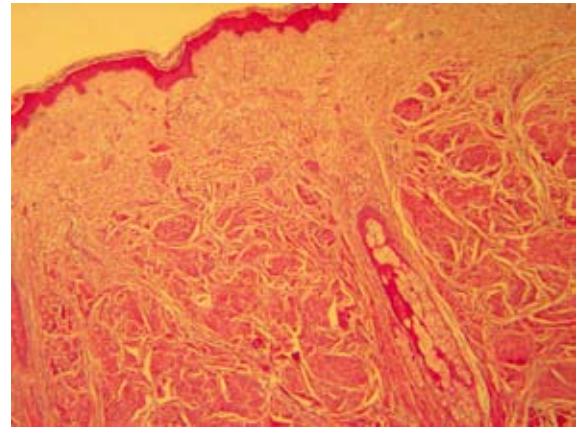
**Fig. 1.** A well circumscribed erythematous papular plaque with a reddish firm and smooth nodule having a nipple aspect.



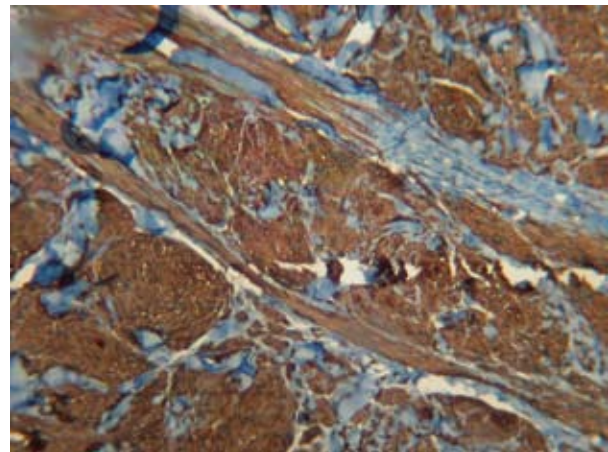
**Fig. 2b.** Individual smooth muscle cells presented cigar-shaped nuclei on longitudinal sections.



**Fig. 2a.** A non-encapsulated tumour mass consisting of eosinophilic spindle cells extending irregularly in interweaving fascicles between bundles of collagen in the reticular dermis.



**Fig. 3.** Tumour cells stained strongly with smooth muscle actin antibodies.



sue<sup>6</sup>. Solitary tumours can extend into the papillary dermis and subcutaneous fat. Raj et al. have demonstrated that the absence of cellular atypia and the presence of a low mitotic rate (< 1 mitosis per 10 high power fields; 1 HPF = 0.159 mm<sup>2</sup> on the microscope used) is necessary to eliminate malignancy<sup>3</sup>. In some cases, diagnosis can be difficult because of the presence of collagen bands. Immunohistochemical analysis is thus useful as it shows a strong positive reaction with smooth muscle actin antibodies. It is also useful to eliminate other neurologic tu-

mours through negative reactions with PS100, NSE and PGP antibodies<sup>6</sup>. Surgical removal of the tumour is the only curative option available to treat leiomyoma<sup>1</sup>. In our patient, the piloleiomyoma was solitary, located on the trunk and had an unusual nipple aspect (reddish nodule on an erythematous papular plaque). In conclusion, pilar leiomyomas are painful benign tumours presenting in most cases as multiple lesions, occurring over a wide age range in either sex with variable distribution. The only potentially curative option remains surgical excision.

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# Malignant proliferating trichilemmal cyst of the scalp: histological aspects and nosology

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## Key words

Malignant proliferating trichilemmal cyst • Malignant proliferating trichilemmal tumour

## Summary

**Background.** Malignant proliferating trichilemmal cyst is a rare tumour usually located on the scalp of elderly women. About 40 cases of malignant proliferating trichilemmal tumour have been documented.

**Case report.** We report a case of a malignant proliferating trichilemmal cyst of the scalp in a 57-year-old woman. On the vertex she had a voluminous vegetated and multinodular tumour mea-

suring 7 × 5 cm with spontaneous and abundant bleeding, and another lesion of the scalp corresponding to a trichilemmal cyst. Based on histopathological findings, the case was diagnosed as malignant proliferating trichilemmal cyst.

**Conclusion.** Diagnostic, clinicoprognotic and histological features of this tumour are discussed. Treatment is not yet standardized given its rarity.

## Introduction

Malignant proliferating trichilemmal cyst (MPTC) is a rare malignant tumour of elderly persons with a female predilection. We report here a case of MPTC of the scalp and discuss its pathophysiology and clinicopathological.

## Case report

A 57-year-old woman was followed-up in a psychiatric hospital for schizophrenia and had been administered antipsychotic agents for many years with no clear remission at the time of her referral to our hospital. For many years she had two nodules on her scalp that grew progressively. For the past 18 months, one of the two lesions had rapidly changed in aspect and had become the more important in size accompanied by spontaneous bleeding. Cutaneous examination showed on the parietal region of the scalp, a voluminous vegetated and multinodular tumour measuring 7 × 5 cm. There was spontaneous and abundant bleeding, but the tumour was not adherent to bone (Fig. 1). There was another subcutaneous nodule of the scalp measuring 3 cm with a firm consistency, probably corresponding to a trichilem-

**Fig. 1.** Voluminous vegetated and multinodular tumour of the scalp with spontaneous and abundant bleeding and a trichilemmal cyst near to the tumour.

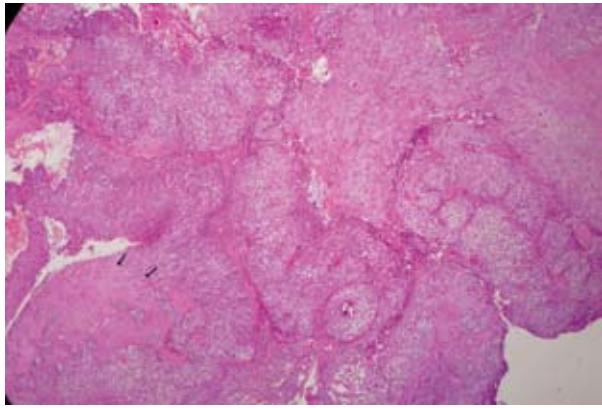


mal cyst (Fig. 1). Physical examination was otherwise normal with no palpable lymph nodes or visceromegaly. Histological examination of a biopsy specimen showed

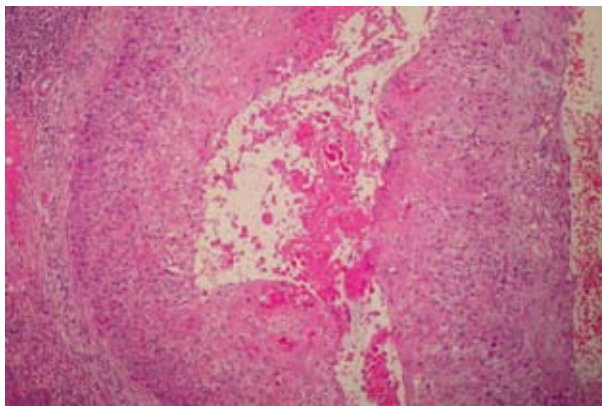
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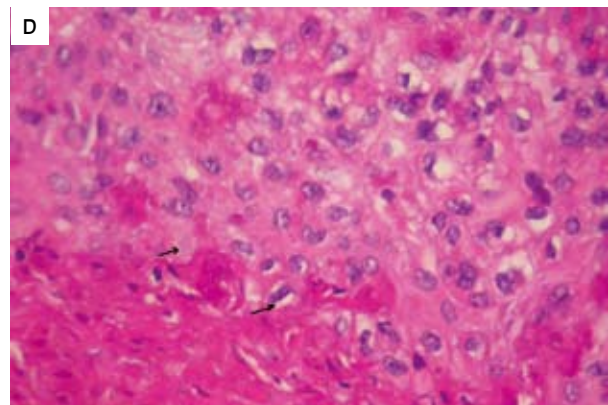
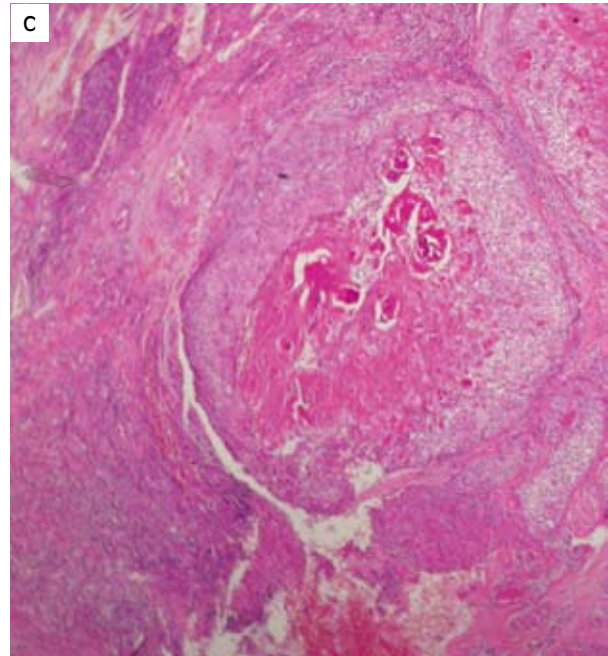
**Fig. 2a.** Tumour proliferation infiltrating the dermis with solid or central cystic epithelial lobules (H&E X 200).



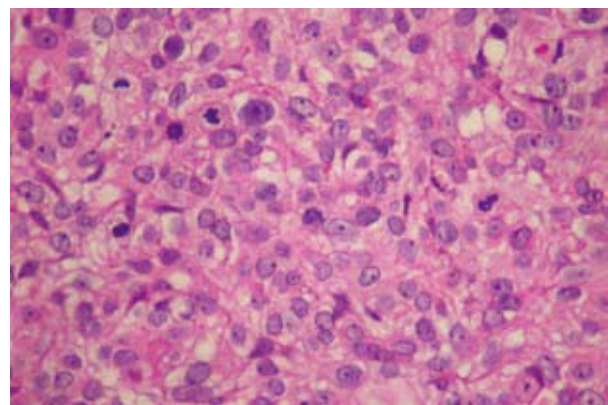
**Fig. 2b.** Multistratified epithelium of clear cells with a peripheral palisading circumscribed by a thick eosinophilic membrane (H&E X 400).



**Fig. 2c-d.** Central trichilemmal keratinisation (→) without interposition of a granular layer (H&E X 800).

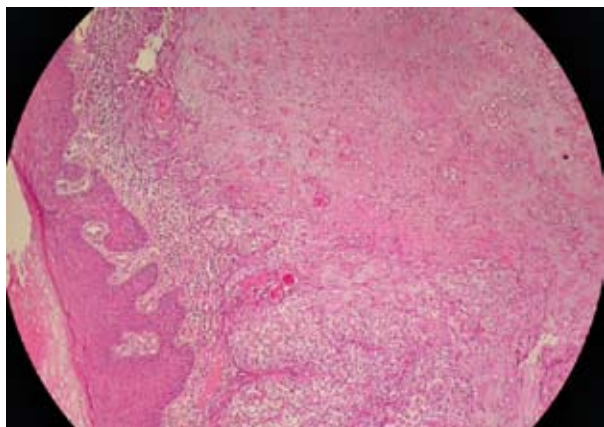


**Fig. 2e.** Numerous cytonuclear atypia and abnormal mitoses (H&E X 800).



that the tumour infiltrated the dermis (Fig. 2a) and was composed of solid or central cystic epithelial lobules (Fig. 2b). These consisted in a multistratified epithelium with clear cells having a peripheral palisading aspect circumscribed by a thick eosinophilic membrane and surrounded by a fibromyxoid stroma. Keratinisation was of a trichilemmal aspect devoid of a granular layer (Figs. 2c, 2d). There were numerous cytonuclear atypia and abnormal mitoses (Fig. 2e). The lower portion of the tumour was less circumscribed by small lobules infiltrating a sclerous stroma. Occasionally, the tumour had a striking resemblance to squamous cell carcinoma since there were dyskeratosis and cystic horns. However, the presence of clear cells evoked the trichilemmal nature of the tumour. Considering these aspects, a diagnosis of malignant proliferating trichilemmal cyst was made. Histological aspects of a proliferating trichilemmal cyst with a striking transitional zone between the benign well circumscribed contingent and the malignant ill-defined contingent were also present (Fig. 2f). A full body work

**Fig. 2f.** Transitional zone between the benign contingent (PTC) and the malignant ill-defined contingent (MPTC) (H&E X 200).



up (cerebral, thoracic and abdominal CT scan) showed no metastases. Most likely because of psychosis, the patient declined surgical excision. X-ray radiation was indicated, but the patient was lost to follow-up.

## Discussion

Malignant proliferating trichilemmal cyst (MPTC) is a rare tumour differentiating towards the follicular outer root sheath epithelium. About 40 cases have been reported in the literature<sup>1-5</sup>. The tumour is located on the scalp, usually in elderly female patients<sup>1</sup>. As there is debate about its pathophysiology, it has been described with various names. Indeed, it is known as “malignant proliferating trichilemmal cyst”, as “proliferating trichilemmal cystic carcinoma” and also as “malignant proliferating trichilemmal tumour”. The former terminology, used in the present report, is the most common. Several hypotheses have been forwarded concerning the origin of this tumour. It is considered as a malignant transformation from the capsule of a trichilemmal cyst with the existence of a continuum between trichilemmal cyst (TC), proliferating trichilemmal cyst and MPTC<sup>4,6</sup>. It is also thought to be a malignant variant of a proliferating trichilemmal cyst (PTC), or finally as a malignant trichilemmoma with cystic differentiation<sup>7</sup>. In reality, the first hypothesis seems to be the most well-accepted. Ackerman and Mones initially stated that PTC and MPTC are squamous cell carcinomas of proliferating cystic and follicular type<sup>8</sup>. Later, they considered the current hypothesis by acknowledging that proliferating trichilemmal cystic carcinoma derives from TC or PTC<sup>9</sup>. Our observation supports well this hypothesis. Indeed, in the present case the tumour likely derived from

a TC or PTC, since the patient had a TC on her vertex and in one side of the tumour there was a relic of TC or more probably of PTC. Furthermore, on histology the tumour contained two components, with a clear transitional zone between PTC and MPTC.

Considering frequent relapses and rare metastatic cases with no evident morphological anomalies, Noto stated that PTC are tumours with undetermined biological behaviour and should be considered as low grade malignant adnexal carcinomas<sup>10</sup>. Criteria of malignancy remain elusive since marked cellular atypia with high mitotic activity can be observed in benign PTC. Inversely, typical cases of apparently benign PTC have fatal progression<sup>11</sup>. The present criterion of malignancy remains the irregular and downward infiltrative growth toward the stroma<sup>4,6,12</sup>. This was histologically observed in our patient, confirming its malignant behaviour. Recently, Masui et al. demonstrated that immunohistochemical studies can distinguish between benign and malignant forms of PTC. Indeed, benign or tricholemmal cyst-like portions exhibited a high frequency of CK10 and involucrin expression, while the malignant area with disturbed epidermal differentiation exhibited a high frequency of proliferating cell nuclear antigen (PCNA)-positive cells and CK16<sup>12</sup>.

Squamous cell carcinoma (SCC) and trichilemmal carcinoma are differential diagnoses of MPTC. Localisation on the scalp, trichilemmal-type keratinisation and the absence of precancerous lesions, such as actinic keratoses in MPTC, are many criteria against the diagnosis of SCC. Moreover, and as stated by Ye et al., MPTC show positive staining for AE13 and AE14, monoclonal antibodies directed at pilar-type keratin polypeptides, while SCC shows no staining<sup>4,13</sup>. Trichilemmal carcinoma is distinguished from MPTC, because the latter shows a clear cell lobular proliferation with a peripheral palisading disposition, together with connection to the epidermis<sup>14</sup>.

The biological behaviour of MPTC is unpredictable, and some published cases remained disease free for many years after treatment, whereas in other cases, the tumour had aggressive behaviour and produced distant metastases<sup>14-17</sup>. Consequently, long-term follow-up is mandatory to detect relapses and metastases. Frequent clinical follow-up and lymph node examination are advised. A potential work-up for metastatic disease includes computed tomography of the head and neck, chest X-ray and positron emission tomography scan<sup>18</sup>.

Surgery remains the treatment of choice with one-cm-margins or Mohs micrographic surgery. For some authors, more aggressive therapies are necessary, by combining surgery with nodal dissection, chemotherapy and radiotherapy in order to decrease recurrence and metastases<sup>13,19-21</sup>.

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## Reliability of *K-ras* mutational analysis on cytological samples from metastatic colorectal cancer

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### Key words

*K-ras* • Colorectal cancer • Fine needle aspiration biopsy

*K-ras* mutations are emerging as a relevant predictive factor of response in patients with advanced colorectal cancer who are candidates for treatment with anti-epidermal growth factor receptor (EGFR) antibodies. It is still matter of debate whether *K-ras* mutational status should be assessed in the primary tumour or in metastatic lesions, as discordance rates ranging between 4% and 14% have been reported in paired-sample analyses<sup>1-4</sup>. Ultrasound-guided fine needle aspiration biopsy (FNAB) is a minimally-invasive technique that has increasingly become the modality of choice for tumour sampling as it provides a safe, convenient and reliable access to lymph nodes and deep tumour masses.

We investigated whether *K-ras* mutational status can be reliably evaluated on cytological material obtained by FNAB at metastatic sites by comparing 19 metastases and matched primary tumours. Secondary lesions were localized to the liver (n = 8), lung (n = 2), lymph nodes (n = 6) and other sites (n = 3). The aspirated material was smeared on glass slides, air-dried and stained with May-Grünwald-Giemsa (MGG) for routine cytology. DNA extraction and sequencing was performed either from cell suspensions obtained at the time of FNAB by needle washing in 0.9% NaCl (12 cases) or from scraping of MGG cytological destined smears (7 cases). *K-ras* status of the corresponding primary tumours was assessed on DNA obtained from microdissected formalin-fixed, paraffin-embedded tissue. *K-ras* mutations were detected by amplification and sequencing of exon 2 as previously described<sup>5</sup>.

*K-ras* analysis was informative in 18 cytological and 18 histological samples. *K-ras* mutations were found in 7 of 18 (39%) metastases and in 9 of 18 (50%)

primary tumours. The cytological specimen of one patient, showing a G13D mutation in the primary tumour, was not adequate for the mutational analysis in the liver metastasis due to the insufficient number of tumour cells. A second case, with a *K-ras* G12D mutated liver metastasis, was not adequate for molecular analysis of the histological specimen being a small endoscopic biopsy. In the remaining 17 matched cases, 15 (88%) were concordant for *K-ras* status (kappa coefficient = 0.761; p < 0.001): six cases had the same *K-ras* mutations and nine were *K-ras* wild type in both the primary tumour and matched metastasis. Two cases were discordant, one showing a G12R mutation and the other a G12V mutation in the primary tumour, and were negative in the paired metastatic lesion. No histological samples of the metastatic sites were available to confirm this discrepancy. The *K-ras* analysis of the two discordant metastases was performed in one case on a needle washing and in a second case by scraping of the cytological smear. In the first case, the electropherogram of the primary tumour showed a scarcely visible peak of the mutated allele that might have become undetectable on cytology possibly due to a lower proportion of tumour cells. In the second case, the cytological specimen was almost entirely composed of neoplastic cells. Therefore, the selection of a wild type clone might be hypothesized rather than a false negative result.

The majority of cytological smears included in the series were composed almost exclusively of neoplastic cells; non-neoplastic elements (i.e. hepatocytes and/or lymphocytes) represented less than 40% of the cell population in 4 cases (22%). The presence of necrotic debris did not affect the mutational analysis.

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Despite the low number of cases analyzed, the present findings indicate that cytological samples obtained by FNAB from metastatic sites are a reliable source for the assessment of *K-ras* mutational status. The best method to perform DNA analysis from cytological specimens is scraping of stained cytological slides as it allows deter-

mination of the cell composition and reduces the risk of false negative results. FNAB is a specific indication for *K-ras* mutational analysis in patients with advanced metastatic disease not eligible for surgery but who are candidate for anti-EGFR therapy.

## References

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