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Primary Cutaneous Leiomyosarcoma:
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Leiomiosarcoma cutaneo primitivo: studio istologico e immunoistocheimico di 4 casi

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Key words
Cutaneous leiomyosarcoma • Subcutaneous soft tissue

Parole chiave
Leiomiosarcoma cutaneo • Tessuto molle sottocutaneo

Summary
Primary cutaneous leiomyosarcoma is an uncommon malignant neoplasm with a predilection for the lower extremities. A retrospective study of 4 cases was undertaken to analyse the clinicopathological characteristics and immunohistochemical profile of these neoplasms with emphasis on prognosis. Two male and 2 female patients aged between 49 and 80 years presented with painless tumours involving the lower lip, the chin, the scrotum and the shoulder. Histological examination of the initial biopsy specimen established a diagnosis of cutaneous leiomyosarcoma. All cases co-expressed smooth muscle actin and vimentin regardless of primary tumour site. Wide surgical excision of the tumour was performed in only 3 cases, and the remaining patient refused further treatment. Of the patients undergoing surgical intervention, local recurrence occurred in one case. No metastases were observed. Long-term follow-up of patients with cutaneous leiomyosarcoma is mandatory to detect local recurrence and distant metastases that can occur even years after the initial excision.

Riassunto
Il leiomiosarcoma cutaneo primitivo è una rara neoplasia maligna con predilezione per le estremità inferiori. Uno studio retrospettivo di 4 casi è stato intrapreso per analizzare le caratteristiche clinicopatologiche e il profilo immunoistocheimico di queste neoplasie con enfasi sulla prognosi. 2 pazienti di sesso maschile e 2 di sesso femminile di età compresa tra i 49 e gli 80 anni si erano presentati con tumori senza dolore che riguardavano il labbro inferiore, il mento, lo scroto e la spalla. L’esame istologico di un primo campione biotico aveva stabilito diagnosi di leiomiosarcoma cutaneo. Tutti i casi coesprimevano actina e vimentina del muscolo liscio indifferentemente dal sito del tumore primitivo. Un’ampia escissione chirurgica del tumore è stata eseguita solo in 3 casi, il restante paziente ha rifiutato un ulteriore trattamento. Dei pazienti sottoposti all’intervento chirurgico, una recidiva locale si è verificata in un solo caso. Non sono state osservate metastasi. Un follow up a lungo termine dei pazienti con leiomiosarcoma cutaneo è obbligatorio per scoprire recidive locali e metastasi a distanza che possono presentarsi anche anni dopo l’asportazione iniziale.

Introduction
Primary cutaneous leiomyosarcoma (PCL) of the skin is a rare soft tissue tumour that accounts for about 2-3% of all superficial soft tissue sarcomas. It may occur anywhere on the body, but has a predilection for the lower limbs. Leiomyosarcomas of the face and the scrotum are exceedingly rare. We report 4 cases of PCL found in unusual locations and involving the face, scrotum and shoulder. Herein we highlight the histological features and immunohistochemical profile of this uncommon neoplasm with special emphasis on prognostic factors.

Patients and methods
Over the 7-year period from January 2000 to December 2006, 4 cases of primary cutaneous leiomyosarcomas were diagnosed at the Pathology Department of La Rabta Hospital. Medical records, histopathological reports and microscopic slides were available for all cases, and were retrospectively reviewed. Follow-up data regarding the clinical course was obtained from the patients’ records. The following histopathological features were evaluated: architectural pattern, extension to subcutaneous fat, cellularity, mitotic activity including atypical mitoses, presence of tumour necrosis and cell pleomorphism. Histopathological
grade was evaluated according to the National Federation of Centres Against Cancer (Fédération Nationale des Centres de Lutte Contre le Cancer) score, taking into account the percentage of necrosis (score 1 or 2), mitotic index (score 1-3) and tumour differentiation (score 1-3). Grades were obtained by adding the scores for each variable, Grade I – 2 or 3; Grade II – 4 or 5; Grade III – 6 to 8.

**Results**

**Clinical Findings**
The clinical findings of cutaneous leiomyosarcoma in our study are summarised in Table I. There were 2 male and 2 female patients with an age from 49 to 80 years (mean age 63 years). Two lesions were located in the head region (lower lip and chin), whilst the others involved the shoulder and scrotum. The lesions measured from 2 to 4 cm in greatest diameter, and mainly occurred as a solitary painless nodule. Ulceration was noted in 2 cases (cases 2 and 3). All lesions primarily involved the skin since clinical examination and radiological investigations did not disclose a tumour elsewhere. Following biopsy wide surgical excision of the tumour was performed in 3 cases. One patient refused further surgical treatment (case 1).

**Histological Findings**
The histological findings of our 4 cases are summarised in Table II. Histological examination of the biopsy specimen established a diagnosis of cutaneous leiomyosarcoma in all cases. All lesions showed a nodular growth pattern. The tumour was confined to the skin and occupied predominantly the superficial and reticular dermis in 3 cases (cases 1, 2 & 3), but extended into the subcutaneous tissue in one case (case 4). The diagnosis of leiomyosarcoma was established based on cellularity, increased mitotic activity and focal areas of necrosis. The tumours were highly cellular and showed

| Tab. I. Clinical data and follow-up in 4 patients with cutaneous leiomyosarcoma. |
|-----------------|-----------------|-----------------|-----------------|
|                 | Case 1           | Case 2           | Case 3           | Case 4           |
| Age/Sex         | 80/F             | 69/M             | 49/M             | 55/F             |
| Location        | Chin             | Scrotum          | Lower lip        | Shoulder         |
| Diameter (cm)   | 2                | 3.5              | 2                | 4                |
| Clinical presentation | Painless nodule beneath normal epidermis | Painless nodule with ulceration | Painless nodule with ulceration | Painless erythematous nodule |
| Treatment       | Refused treatment| Wide local excision | Wide local excision | Local excision |
| Follow-up       | Lost to follow-up| 8 months         | 24 months        | 12 months        |
| Evolution       | unknown          | No recurrence    | No recurrence    | Recurrence 12 months after surgery |

| Tab. II. Histological Findings in 4 cases of cutaneous leiomyosarcoma. |
|-----------------|-----------------|-----------------|-----------------|
|                 | Case 1           | Case 2           | Case 3           | Case 4           |
| Growth pattern  | Nodular          | Nodular          | Nodular          | Nodular          |
| Cellularity     | +++              | +++              | +++              | +++              |
| Atypia          | Moderate         | Marked           | Mild             | Moderate         |
| Giant multinucleate tumour cells | - | + | - | + |
| Mitotic index/10 HPF | 15 | 25 | 4 | 17 |
| Necrosis        | + (< 50%)        | -                | + (< 50%)        | -                |
| Ulceration      | -                | +                | +                | -                |
| Extension to subcutaneous fat | - | - | - | + |
| Histological Grade (FNCLCC) | Grade 2 | Grade 2 | Grade 2 | Grade 2 |

+++: high cellularity
densely packed spindle-shaped and oval cells arranged in transverse and longitudinal intersecting fascicles (Figs. 1 and 2). Cytomorphologically, the spindle cells showed blunt-ended nuclei and eosinophilic cytoplasm. Atypia was mild in case 1, moderate in cases 3 and 4 and marked in case 2 (Fig. 3). Generally, the neoplasms revealed numerous mitotic figures, some of which were abnormal. In addition, several single necrotic cells and occasional extensive necrotic areas were also present (cases 1 and 3).

**Immunohistochemical Findings**

In all cases, the tumour cells were immunoreactive for smooth muscle actin (SMA; Fig. 4) and vimentin, but were negative for cytokeratin and CD 34. In cases 2 and 4, there was a focal positive reaction for desmin. In case 3, some tumour cells expressed S-100 protein.

**Follow-up**

Details of clinical follow-up were obtained in 3 patients. Only one patient was lost to follow-up (case 1). All patients were examined thoroughly for evidence of local recurrences and distant metastases. The mean follow-up period was 11 months. Cases 2 and 3 were alive and well with no evidence of recurrence or metastasis at 8 months and 24 months, respectively. One patient (case 4) developed local recurrence 12 months following surgical intervention. No metastases were observed during the follow-up period that ranged between 8 and 24 months. Notwithstanding, the follow-up period is likely too short to give a definitive appraisal of recurrence.

**Discussion**

Primary cutaneous leiomyosarcomas (PCL) are uncommon soft tissue tumours with more than 100 cases reported in the literature. They account for about
Cryosurgery has also been used in these difficult cases. Like desmin, this marker is not specific because it can stain myofibroblasts and striated muscle. In recent years h-caldesmon and calponin, two cytoskeleton-associated actin-binding proteins, have also been used to document myoid differentiation. PCL may occasionally present keratin-positive areas, or even weak EMA positivity. One case of our study was S100 protein positive. Swanson suggested that there is a correlation between the site of the tumour (dermal forms) and S100 positivity. Several benign or malignant tumoural lesions are difficult to distinguish from PCL, namely desmoplastic malignant melanoma (value of S100 and HMB45 staining), spindle-cell angiosarcoma, spindle-cell synovial sarcoma, malignant storiform pleomorphic histiocytofibroma, schwannoma or plexiform neurofibroma and atypical fibroxanthoma. Immunohistochemistry is a valuable diagnostic tool in these difficult cases.

Electron microscopy can reveal intracytoplasmic myofilaments in cases which are difficult to diagnose. The most effective treatment of cutaneous leiomyosarcoma is wide excision with a 3-5 cm lateral margin and a depth that includes subcutaneous tissue and fascia. Local excision without adequate margins leads to recurrence and increases the risk for metastatic and possibly fatal disease. It appears to be important in all cases to ascertain that excision is complete by pathology examination because the quality of the surgical treatment influences prognosis. An alternative method of treatment is Mohs micrographic operation to ensure complete tumour removal. Cryosurgery has also been used in elderly patients. Adjuvant therapies include radiation therapy, chemotherapy and supervoltage cobalt therapy.
However, leiomyosarcoma has been reported to be radioresistant; chemotherapy with doxorubicin is also unsuccessful

Recent studies have provided greater understanding of prognostic factors and the risk of recurrence. Several poor prognostic factors have been identified by Jensen, namely a tumour size $\geq 5$ cm, deep location with fascia involvement and high malignancy grade\textsuperscript{15}. Acral distribution also appears to have a poor prognosis. While cutaneous leiomyosarcomas have been reported to show local recurrence rates of 30-50% and rarely metastasise, subcutaneous leiomyosarcomas recur in up to 70% and the metastatic rate has been reported in 30-40% of cases\textsuperscript{16}.

In summary, we report 4 cases of PCL noteworthy for their unusual locations involving the face, scrotum and shoulder. In the presence of a small biopsy, PCL may be misinterpreted as a benign smooth muscle proliferation such as leiomyoma. Therefore, careful scrutiny of cytological details in multiple sections, clinicopathological correlation and immunohistochemistry are mandatory for definitive diagnosis. The importance of long-term follow-up must be emphasized because local recurrence and distant metastasis can occur even years after the initial excision.

References

Budget in Anatomia Patologica: il controllo di gestione per la valutazione di nuova tecnologia

Budget management in anatomical pathology: health technology assessment of new methodologies

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Parole chiave
Budget • Valutazione tecnologie mediche • Medicina predittiva • Appropriatezza

Riassunto
Viene presentata l’esperienza del Controllo di gestione dell’Anatomia Patologica dell’Ospedale di Trento per la valutazione dell’introduzione di nuova tecnologia nella routine diagnostica. A tal fine viene presentato il carico di lavoro del reparto assieme all’andamento annuale (dal 2000 al 2006) del budget dei vari centri di costi. Il controllo di gestione permette di imputare l’andamento della spesa all’attività sostenuta anche in rapporto all’introduzione di nuovi test che vengono sempre più frequentemente richiesti per personalizzare la terapia rispetto al profilo biologico del singolo paziente. Lo strumento dell’Health Technology Assessment attraverso approfondite analisi inerenti l’efficacia, la sicurezza, i costi, i benefici, la fruibilità nonché le misurazioni dell’effettivo miglioramento della qualità del lavoro o della vita stessa, permette all’anatomopatologo di essere uno dei principali attori di scelte ragionate in un sistema come quello sanitario che non dispone di risorse infinite.

Summary
The Author’s experience in health technology assessment of new methodologies for routine diagnosis at the Department of Anatomical Pathology at the Trento Hospital is presented. The workload of the department together with the annual budget trends (from 2000 to 2006) of the various costs is analysed. Budget analysis also allows evaluation of expenses relative to the introduction of new tests, which are increasingly requested in order to personalise therapy accordingly to the biological profile of individual patients. Health Technology Assessment permits in-depth analysis of the efficacy, safety, costs, benefits and feasibility in addition to providing a measurement of the contribution to improving the quality of work and life. This is an important tool in decision-making processes for pathologists, especially in consideration of the limited resources available in healthcare.

Introduzione
In poche specialità come quella dell’anatomia patologica è avvenuto un radicale cambiamento negli ultimi 10 anni. La necessità di integrare i progressi della medicina di base nella pratica diagnostica, l’introduzione di tecniche mini-invasive con necessità di ottenere sempre maggiori informazioni da frammenti sempre più piccoli, la crescente richiesta non solo di una diagnosi sempre più precisa, ma anche di indicazioni sull’espressione di marcatori di prognosi e di farmacodiagnostics individualizzata sul singolo paziente, in altri termini la “predictive medicine” di Dietel 1, hanno fatto esplodere la spesa in Anatomia patologica. Tale aumento esponenziale dell’attività a sostanziale pareggio del numero complessivo degli esami e la difficoltà di adeguare l’organico medico e tecnico del reparto alle nuove esigenze, hanno fatto crollare l’assonima che l’Anatomia patologica non può essere automatizzata come invece è ampiamente avvenuto con la Patologia clinica. L’automazione però ha costi cui la gran parte degli anatomopatologi non era abituata.
La SIAPEC ha istituito una commissione per adeguare le tariffe delle nostre prestazioni, ma vi sono ancora pochi dati per analizzare dettagliatamente i costi in un arco temporale piuttosto lungo. Scopo di questo lavoro è quello di valutare i costi prendendo come esempio l’analisi degli stessi in un Servizio ospedaliero di diagnosi e cura (e non con finalità di ricerca) in un arco di 7 anni, valutando quanto sia costata l’introduzione di nuovi test e di nuova tecnologia.

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Materiale e metodi

Nel servizio di Anatomia patologica dell’ospedale “S. Chiara” di Trento vengono effettuati annualmente circa 33.000 Pap Test, 23.000 esami istologici, 8.000 esami citologici extravaginali e 100 autopsie. Per quel che riguarda le tecniche speciali vi è un laboratorio di immunoistochimica automatizzata, uno di citometria a flusso, uno di biologia molecolare dotato di sequenziatore e di PCR quantitativa. La dotazione organica è costituita da 8 medici, 3 biologi, 18 tecnici di laboratorio/citotecnici, da 5 amministrativi, 1 operatore tecnico per la sala autoptica e 2 ausiliari specializzati. Il laboratorio serve una popolazione di circa 300.000 abitanti con ben 7 ospedali per un totale di 1.200 posti letto (ordinari e day hospital) per acuti. Come strutture ad alta specialità l’Ospedale maggiore offre la cardiochirurgia e la neurochirurgia.

Dall’anno 2000 esiste una stretta collaborazione con l’istituto della pianta organica, nonostante l’aumento del carico di lavoro, ma all’applicazione dei contratti di lavoro della pianta organica, una di metodi, di trasversali, non hanno mostrato differenze significative, l’incremento maggiore riguarda i costi indiretti, cioè quelli legati al funzionamento dell’intera Azienda, con un $\Delta + 63\%$, e costi diretti dovuti ai consumi specifici del reparto, con un $\Delta + 60\%$. L’analisi più dettagliata di quest’ultimo capitolo di spesa è presentato nella Tabella II. Va comunque sottolineato che la voce “consumi” non raggiunge mai il 10% del totale del budget di reparto. Per cercare di individuare a che cosa fosse dovuto l’aumento della spesa dei consumi si sono presi in considerazione alcuni indicatori. Il più semplice è certamente quello relativo al numero delle diagnosi effettuate dal reparto, ma questo parametro si è rivelato del tutto inadeguato in quanto vi è una sostanziale parità di valori: infatti la numerosità delle richieste di esami è aumentata in misura minimale. È invece aumentata considerevolmente la complessità delle singole diagnosi e tale dato è documentata dalla numerosità e complessità dei test eseguiti nei singoli casi con conseguente incremento della spesa per effettuarli.

La Figura 1 mostra infatti la suddivisione della spesa dei consumi nei principali sottocentri di costo del Servizio di Anatomia patologica. La spesa per la normale routine istologica, evidenziata dalla voce Istologia, è rimasta complessivamente costante. La spesa per la citologia è aumentata in misura minima. È invece aumentata considerevolmente la complessità delle singole diagnosi e tale dato è documentato dalla numerosità e complessità dei test eseguiti nei singoli casi con conseguente incremento della spesa per effettuarli.

L’incremento maggiore riguarda i costi indiretti, cioè quelli legati al funzionamento dell’intera Azienda, con un $\Delta + 63\%$, e costi diretti dovuti ai consumi specifici del reparto, con un $\Delta + 60\%$. L’analisi più dettagliata di quest’ultimo capitolo di spesa è presentato nella Tabella II. Va comunque sottolineato che la voce “consumi” non raggiunge mai il 10% del totale del budget di reparto. Per cercare di individuare a che cosa fosse dovuto l’aumento della spesa dei consumi si sono presi in considerazione alcuni indicatori. Il più semplice è certamente quello relativo al numero delle diagnosi effettuate dal reparto, ma questo parametro si è rivelato del tutto inadeguato in quanto vi è una sostanziale parità di valori: infatti la numerosità delle richieste di esami è aumentata in misura minimale. È invece aumentata considerevolmente la complessità delle singole diagnosi e tale dato è documentata dalla numerosità e complessità dei test eseguiti nei singoli casi con conseguente incremento della spesa per effettuarli.

Tab. 1. Budget dell’Anatomia patologica di Trento.

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</thead>
<tbody>
<tr>
<td>Totale ammortamenti</td>
<td>68.067</td>
<td>81.737</td>
<td>87.181</td>
<td>85.372</td>
<td>90.453</td>
<td>99.698</td>
<td>99.622</td>
</tr>
<tr>
<td>Totale personale</td>
<td>1.826.493</td>
<td>2.096.764</td>
<td>2.162.869</td>
<td>2.399.775</td>
<td>2.452.965</td>
<td>2.389.405</td>
<td>2.514.676</td>
</tr>
<tr>
<td>Totale consumi</td>
<td>235.534</td>
<td>286.510</td>
<td>279.735</td>
<td>282.057</td>
<td>309.717</td>
<td>321.000</td>
<td>376.050</td>
</tr>
<tr>
<td>Totale altri costi</td>
<td>214.057</td>
<td>210.180</td>
<td>215.956</td>
<td>257.304</td>
<td>305.033</td>
<td>312.648</td>
<td>300.421</td>
</tr>
<tr>
<td>Totale costi diretti</td>
<td>2.344.151</td>
<td>2.675.191</td>
<td>2.745.741</td>
<td>3.024.488</td>
<td>3.158.168</td>
<td>3.122.941</td>
<td>3.290.768</td>
</tr>
<tr>
<td>Costi Indiretti</td>
<td>371.264</td>
<td>417.025</td>
<td>497.808</td>
<td>527.309</td>
<td>546.059</td>
<td>546.335</td>
<td>606.956</td>
</tr>
</tbody>
</table>
L’analisi ancora più dettagliata delle singole voci di spesa ha inoltre mostrato come i principali aumenti siano relativi ad acquisti per kit per la determinazione della amplificazione di Her-2 con tecnica FISH con relativo noleggio di un microscopio a fluorescenza, per i nuovi sistemi di rilevazione e perossidasi per l’immunoistochimica, per i kit HC2 HighRisk HPV DNA test per i Pap Test, per i kit del Papilloma Virus Typing fast, per i reattivi per analisi di clonalità di popolazioni linfoidi B e T per la citometria a flusso e i reattivi per la citologia (cervico-vaginale ed extra) in fase liquida.

**Discussione**

In Italia, negli ultimi anni, si è spesso parlato della spesa della Sanità e molti Direttori hanno avuto tra gli obiettivi di budget quello di contenere, a volte abbassare, la spesa relativa ai consumi.

Il costo dell’Anatomia patologica sta aumentando con un indice molto maggiore rispetto al tasso inflazitivo. La maggior parte delle voci di costo (costo del personale, spese generali, ecc.) non sono sotto il diretto controllo degli anatomopatologi cui spetta principalmente il controllo dei consumi e delle attrezzature. Spesso si fa quanto viene richiesto, forse senza chiedersi se è sempre appropriato quanto si fa.

Dall’analisi del presente lavoro appare che più della metà dell’incremento della spesa alla voce reagenti è sostenuto dall’introduzione di test innovativi determinati dal passaggio da una diagnostica generalistica ad una sempre più personalizzata per il singolo paziente.

In una struttura complessa come quella della Sanità pubblica e più in dettaglio in quella di un ospedale sia
pure di grandi dimensioni, la realtà dell’Anatomia patologica è sempre stata considerata marginale per quel che riguardava il costo complessivo. Se paragonato ad altre strutture diagnostiche come la Patologia clinica, l’Ema- tologia e la stessa Radiologia, il budget dell’Anatomia patologica aveva storicamente un ruolo di “cenerentola” e l’entità del budget dipendeva essenzialmente dai costi del personale assegnato. Oggi, pur restando il costo del personale la voce di maggior peso economico, anche l’Anatomia patologica costa perché vengono richiesti esami sempre più costosi in termini di reattivi (come documentato più sopra) e perché frai le attrezzature iniziano a comparire strumenti nuovi e costosi, quali per esempio il sequenziatore pluricapillare o il lettore automatico dei Pap Test che richiedono impegni importanti.

In una recente pubblicazione è stato riportato come nel 2007 (dato non riportato nelle Tabelle presentate che si riferiscono ai valori fino al 2006) l’Anatomia patologica di Trento abbia acquisito proprio un lettore automatico per i preparati cervico-vaginali. Per tale acquisizione, dopo attenta valutazione secondo lo strumento del ‘break even point’ positivo attorno ai 45.000 preparati (il numero di test eseguiti in provincia di Trento in un anno). L’incremento di spesa per gli anni a venire è stato previsto in una media di 160.000 € all’anno il che porterebbe ad un ∆ di spesa per gli anni a venire è stato previsto per l’intero aumento dei costi. Infine l’introduzione dell’automazione deve essere attentamente valutata in un’ottica di HTA: ad un iniziale aumento dei costi deve corrispondere progressivamente una riduzione dei carichi di lavoro con conseguenti risparmi sul personale, il cui peso è di gran lunga il maggiore nel determinismo dei costi della nostra unità operative.

Occorre sottolineare che spesso le nuove tecnologie ed indagini che determinano i nuovi costi della Anatomia patologica rappresentano uno strumento ormai indispensabile per la appropria limitazione di una serie di scelte terapeutiche, quali ad esempio le “target therapies”, e possono avere impatto anche nel punto di vista dei costi generali della sanità. Chi predispone i budget dei singoli reparti dovrebbe quindi avere una visione generale, valutando se l’aumento di spesa di un’unità, quale appunto l’Anatomia patologica, non comporti dei risparmi forse anche maggiore in altre strutture, in quanto induce scelte terapeutiche più appropriate. A solo titolo di esempio basta ricordare come nel carcinoma mammario la corretta valutazione dello stato recettoriale estrogen-progestinico e di Her-2 può indirizzare le scelte terapeutiche non solo per quanto riguarda la somministrazione o meno di Herceptin, ma anche per quanto riguarda varie terapie ormonali, quali tamoxifen vs. inibitori delle aromatasi, che hanno costi nettamente diversi fra loro.

In conclusione è importante che i budget annuali non siano solo valutati con l’occhio degli “esperti in economia” (gli amministrativi) ma anche con l’occhio dei veri “esperti in diagnosi” (i patologi) con una visione globale della spesa in sanità. In tutto ciò si deve mantenere la capacità di decidere quello che si deve o non si deve fare, considerando accuratamente quali siano le vere priorità a fronte di risorse non illimitate.

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Papilloma dei plessi corioidei: analisi citogenetica di un caso e revisione della letteratura

Choroid plexus tumours: cytogenetic analysis of a single case and literature review

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Parole chiave
Plessi corioidei • Papilloma • Analisi citogenetica • Ipotriploidi • Età pediatrica

Riassunto
I tumori dei plessi corioidei sono neoplasie papillari intraventricolari distinte in papillomi, papillomi atipici e carcinomi. Si osservano soprattutto in età pediatrica e possono provocare l’insorgenza di idrocefalo e aumento della pressione intracranica. Scopo del presente lavoro è studiare l’assetto cromosomico, tramite analisi citogenetica classica, di un papilloma dei plessi corioidei insorto in una donna adulta. Il tumore presenta mosaismo. Confrontando i risultati ottenuti con i dati riportati in letteratura, non si osservano differenze significative nelle alterazioni cromosomiche riportate in papillomi dell’età adulta rispetto a quelli dell’età pediatrica, o tra papillomi tipici e atipici né sembra emergere una correlazione con la prognosi e la tendenza a recidivare.

Summary
Choroid plexus tumours are intraventricular papillary lesions that are observed in typical papillomas, atypical papillomas and carcinomas. They usually occur in childhood, and can result in hydrocephalus and increased intracranial pressure. The present paper describes a case of choroid plexus papilloma in an adult woman; cytogenetic analysis of the lesion is also presented, which demonstrated the presence of tumour mosaicism. Compared to the chromosomal aberrations observed in previous cases, those in the present tumour do not show significant differences between papillomas harboured in adults and paediatric patients. Moreover, there was no apparent correlation between genetic alternations in typical and atypical papillomas and prognosis or recurrence.

Introduzione
I tumori dei plessi corioidei sono neoplasie papillari intraventricolari che originano dall’epitelio dei plessi corioidei. Queste neoplasie vengono distinte in papillomi tipici (PPC, Papilloma dei Plessi Corioidei) (WHO grado I), papillomi atipici (WHO grado II) e carcinomi (CPC, Carcinoma dei Plessi Corioidei) (WHO grado III). Si tratta di tumori rari, che costituiscono lo 0,4-0,6% di tutte le neoplasie intracerebrali, ma tale percentuale sale al 2-4% se si prende in considerazione l’età pediatrica e fino al 10-70% nel 1° anno di vita. I PPC sono cinque volte più frequenti dei CPC. Queste neoplasie possono creare un’obstruzione meccanica all’eliminazione del liquor, inducendo l’insorgenza di idrocefalo e l’aumento della pressione intracranica. I PPC vengono trattati mediante chirurgia con sopravvivenza a 5 anni del 100% 1. I CPC sono caratterizzati, invece, da una crescita molto più rapida ed hanno una prognosi generalmente infausta (sopravvivenza a 5 anni del 26-40%) 1.

Sono già stati effettuati vari studi di citogenetica su questi tumori, che hanno messo in evidenza una iperdiploidia con acquisizione di vari cromosomi o duplicazione del braccio corto del cromosoma 9 3-6. Tuttavia la maggior parte dei dati citogenetici riguardanti i tumori dei plessi corioidei è limitata ai pazienti in età pediatrica. Nel presente lavoro, al contrario, vengono riportati i risultati dell’analisi citogenetica effettuata su un PPC insorto in una donna adulta.
**Storia clinica**

Una donna di 31 anni si è presentata con forti emicranie ed instabilità nella marcia. È stata effettuata una riso-nanza magnetica che ha mostrato una lesione a margini espansivi, con presa di contrasto all’interno del IV ven-tricolo. La neoplasia è stata rimossa chirurgicamente in maniera radicale. A 18 mesi dall’intervento, la paziente è libera da malattia e non presenta segni clinici né radiologici riconducibili a ripresa di malattia.

**Materiali e metodi**

**Istologia ed immunoistochemica**

Il campione chirurgico, pervenuto a fresco nel nostro laboratorio, è stato suddiviso in 2 parti: una parte è stata fissata in formalina e inclusa in paraffina per gli esami istologici ed immunoistochimici di routine. Sono state effettuate colorazioni con ematossilina-eosina e indagine immunoistochimica con anticorpo anti-ki67 (Dako; monoclonale: Clone MIB-1; diluizione 1:700) eseguita con immunocoloratore automatizzato Ventana.

**Colture cellulari e analisi citogenetica**

La parte rimanente del prelievo a fresco, macroscopica-mente riferibile a tessuto tumorale, è stata utilizzata per l’indagine citogenetica (eseguita seguendo il protocollo in uso nel nostro laboratorio)\(^7\) e brevemente riassunta di seguito: il campione è stato sottoposto a digestione enzimatica con Collagenasi 400 U/ml (Worthington Biochemical Inc) a 37 °C per 16-18 ore, come descritto da Limon et al.\(^8\). La sospensione cellulare così ottenuta è stata seminata (1 fiasca e due vetri) in terreno di coltura DMEM-F 12 (GIBCO, Milano) addizionato con 10% di FBS (Foetal Bovine Serum, Hy-Clone Laboratories, Celbio, Milano), 0,1% di antibiotici (Penicillina-Streptomicina 500 U/ml GIBCO, Milano) e 0,2% di antimitico (Fungizone, GIBCO, Milano).

La popolazione cellulare, così ottenuta, dopo 9 giorni in coltura, è stata incubata per una notte con Colcemid (0,03 µg/ml, GIBCO, Milano). In seguito, le cellule sono state sottoposte ad un trattamento con soluzione ipotonica (0,8% Sodio Citrato) a 37 °C per 35 minuti e fissate in 4 passaggi successivi, da 20 minuti ciascuno, con Fissativo di Carnoy (Metanolo-Acido Acetico Glaciale in rapporto 3:1).

La coltura cellulare in esame, prima di essere sottoposta ai trattamenti finalizzati all’indagine citogenetica, è stata osservata al microscopio ottico e non sono state individuate figure cellulari morfologicamente riferibili a fibroblasti.

I cromosomi sono stati bandeggiati (Bandeggio G) con HCl e Wright Stain\(^7\).

Il cariotipo è stato, infine, descritto seguendo le Linee Guida dell’ISCN (ISCN 1995 Guidelines for cancer, Mitelman)\(^9\).

**Risultati**

All’esame istologico, la lesione risultava costituita da strutture papillari composte da un asse fibrovasco-lare rivestito da un singolo strato di cellule epiteliali cuboidali e colonnari con nuclei monomorfi e roton-deggianti (Fig. 1a). Non erano presenti aree di necrosi né invasione del tessuto cerebrale. Meno del 2% delle cellule neoplastiche era positivo con anticorpo anti-ki67 (Fig. 1b).

L’indagine citogenetica ha messo in evidenza la pre-senza contemporanea di 2 popolazioni cellulari: una popolazione ad assetto cromosomico normale (46,XX) (riconducibile alla eventuale presenza di cellule normali frammiste alle cellule tumorali) e un clone ipotriploide, presente in entrambi i vetri studiati, descritto in accordo con le linee guida dell’ISCN\(^9\): 58, XXX, -1, -2, -3, -5, -8, -14, -15, -17, -19, -21, -22 (Fig. 2).
Discussione

Gran parte dei dati disponibili in letteratura, riguardanti la citogenetica delle neoplasie dei plessi corioidei, è stata ottenuta in pazienti di età pediatrica. Ciò non sorprende se si considera che tali neoplasie sono piuttosto rare (0,4-0,6% di tutte le neoplasie intracerebrali) nella popolazione adulta. 1 Il caso riportato nel presente lavoro, pur essendo dal punto di vista istologico un esempio classico di PPC, è stato ritenuto meritevole di valutazione citogenetica in quanto insorto in un soggetto adulto.

I PPC sono caratterizzati dalla presenza di cloni cellulari iperdiploidi o ipotriploidi con particolare coinvolgimento dei cromosomi 2, 9, 12, 15, 17 e 18. 2-6 Vari studi, condotti in pazienti pediatrici, hanno dimostrato come condizioni di aneuploidia si osservino anche in papillomi tipici 4,5. Tuttavia Bhattacharjee et al. hanno analizzato 4 casi di PPC dai papillomi atipici, risulta difficile un confronto con gli altri dati riportati in letteratura e con quelli emersi nel presente lavoro.

I risultati degli studi presenti in letteratura e quelli del caso qui riportato sono stati sintetizzati nella Tabella I. L’analisi citogenetica effettuata sul caso oggetto del presente studio ha mostrato un quadro cromosomico triploide con perdita, e conseguente disomia, di una copia dei cromosomi 1, 2, 3, 5, 8, 14, 15, 17, 19, 21 e 22. Confrontando i risultati ottenuti con i dati pubblicati sulla citogenetica delle neoplasie dei plessi corioidei (Tab. I), non si osservano differenze significative nelle alterazioni cromosomiche riportate nei papillomi dell’età adulta rispetto a quelli dell’età pediatrica, o tra i papillomi tipici e quelli atipici né sembra emergere una correlazione con la prognosi e la tendenza a recidivare.

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<th>Studio</th>
<th>Numero casi analizzati, istotipo e metodica</th>
<th>Monosomie</th>
<th>Disomie</th>
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<td>8 tramite ibridazione in situ</td>
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<td>Roland B, 1996</td>
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<td>Presente studio</td>
<td>1 caso di papilloma atipico</td>
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Bibliografia

Case report

Breast metastases from undifferentiated nasopharyngeal carcinoma

Metastasi alla mammella da un carcinoma nasofaringeo indifferenziato

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Key words
Breast metastasis • Undifferentiated nasopharyngeal carcinoma • In-situ hybridization

Parole chiave
Metastasi alla mammella • Carcinoma nasofaringeo indifferenziato • Ibridizzazione in situ

Summary
The most common primary tumours metastasising to the breast include melanoma, lymphoma, lung cancer and ovarian cancer, while metastases from head and neck cancer are rare. Metastases from undifferentiated nasopharyngeal carcinoma cancers are extremely rare, and only 3 well-documented cases have been reported in the English literature. We report a fourth case of breast metastases from nasopharyngeal carcinoma confirmed by in situ hybridization, focusing on clinical data as well as radiologic and pathologic features.

Riassunto
I più comuni tumori primitivi che metastatizzano alla mammella includono il melanoma, il linfoma, il cancro del polmone e il cancro dell’ovaio, mentre metastasi del cancro della testa e del collo sono rare. Metastasi del carcinoma nasofaringeo indifferenziato sono estremamente rare, ed esistono solo tre casi ben documentati nella letteratura inglese. Noi riportiamo un quarto caso di metastasi alla mammella da un carcinoma nasofaringeo confermato dall’ibridizzazione in situ, con particolare attenzione ai dati clinici così come alle caratteristiche radiologiche e patologiche.

Introduction
Although breast cancer is the most common malignancy among females, metastases to the breast are rare representing only about 0.4-2% of all breast malignancies. Not including contralateral mammary tumours, the most common sources of primary tumour metastasising to the breast are, in decreasing order of frequency, melanoma, lymphoma, lung and ovarian cancer.

Metastases from head and neck cancer are rare, and those from undifferentiated nasopharyngeal carcinoma (UNPC) are extremely rare. In fact, only 3 well-documented cases have been reported in the English literature. These included 2 Chinese women, reported in 1991 and another in 2004 that was among 15 cases of extramammary breast metastases.

We report herein a fourth case of breast metastases from UNPC, emphasizing on the clinical, radiologic and pathologic features.

Case history
A 25 year-old woman presented in April 1999 with a 4-month-history of left upper neck swelling. Physical examination revealed a growth in the nasopharynx and bilateral enlargement of the jugular-carotid lymph nodes. Computed tomography of the skull and the nasopharynx disclosed tumour infiltration of the roof and lateral walls. Biopsy from the growth in the nasopharynx confirmed the diagnosis of anaplastic carcinoma at stage T4N3M0. The patient was treated with adriamycin (125 mg/day) and platinum (140 mg/day). Only three courses of chemotherapy were given to the patient before she was lost to follow-up.

In October 2002, she presented with progression of disease showing an enlargement of the lymph node in the left supraclavicular fossa. Physical examination revealed a bilateral breast tumour and a left axillary lymphadenopathy. In the right breast, the mass was firm and measured 8 cm in diameter at the upper quadrants.
Breast metastases from undifferentiated nasopharyngeal carcinoma

In the left breast, the nodule was firm and measured 5 cm in diameter at the upper outer quadrant. Mammography showed well-defined masses with no obvious malignancy in both breasts. Only excision biopsy of the right breast nodule was performed without lymph node biopsy. Histological analysis demonstrated a malignant proliferation growing in a nested and trabecular pattern, arranged in large ill-defined nodules infiltrating amongst residual breast ducts and lobules (Fig. 1). Neoplastic cells exhibited a syncytial appearance with indistinct cell borders. Nuclei were large and vesicular displaying one prominent nucleolus and many mitotic figures (Fig. 2). A dense mononuclear infiltrate separating the epithelial component and intermingling in between epithelial cells was composed of small lymphocytes and plasma cells. Many lymphatic emboli were present. Ductal carcinoma in situ was absent and there were no necrotic foci.

Immunostaining for oestrogen and progesterone receptors were negative. In situ hybridization showed that the neoplastic cells were strongly and diffusely labelled by an EBV-encoded RNA probe (Dako, Denmark, alkaline phosphatase/anti-alkaline phosphatase technique) (Fig. 3).

At moment of diagnosis, the disease was found to be progressive with the presence of multiple metastases in the liver and bone. Palliative care was therefore planned.

Discussion

UNPC is a clinical immunohistological entity that is often diagnosed in Tunisia with an incidence of about 2.5 per 100,000. The disease is more frequent among males (2.4:1) occurring mostly between the age range of 50-60 years; in females it occurs earlier at a mean age of 43.4 years. It is characterised by a tendency to spread diffusely with distant failures occurring in one-third of the cases. Breast metastases from UNPC are rare and usually occur as part of disseminated disease, which leads to suspect of the metastatic nature of the breast tumour on clinical grounds alone. It has been reported, however, that a metastatic breast lesion can be either the first evidence of recurrence or the first manifestation of a clinically occult malignancy. In such cases, accurate diagnosis of metastatic disease of the breast can prevent unnecessary mastectomy and ensure appropriate chemoradiotherapy.

Clinically, breast metastasis usually presents as a rapidly growing and painless firm masse. Although mammary metastases are often superficial, skin involvement and nipple discharge are usually absent. As in our case report, clinically positive axillary lymph nodes may be present.

Upon mammography, it is not easy to distinguish primary mammary carcinoma from metastatic tumours as the spectrum of findings in metastatic nodules can be quite diverse; based on literature review, the aspect
ranges from a single well-circumscribed lesion to poorly marginated masses, with or without cutaneous involvement. However, architectural distortion, speculation as well as microcalcification are uncommon, except for metastatic ovarian carcinoma which is commonly associated with psammoma bodies. Another typical feature is the absence of a significant difference between the tumour size on mammographic and clinical examination, which is probably due to the lack of a desmoplastic stromal response.\(^2\)\(^3\)\(^4\)

Morphologically, metastatic carcinoma shows histological features that can facilitate diagnosis. These include multinodular architecture, frequency of lymphatic emboli and a lack of an intraductal carcinoma or lobular neoplasia component. Furthermore, the finding of more than two grossly evident tumours should lead to the consideration of a metastatic tumour, especially if the histologic pattern is unusual.\(^2\)\(^3\)\(^7\) Nevertheless, metastatic and primary tumours may have some similarities, as in our case, which mimics some histologic types of primary carcinoma including lymphoepithelioma-like carcinoma, medullary carcinoma or a variety of infiltrating ductal or lobular carcinoma with inflammatory stroma. Lymphoepithelioma-like carcinoma of the breast displays multinodular growth, poorly differentiated nuclear grade and dense lymphoid stroma. However, in situ hybridization has never shown association with EBV infection.\(^8\) Differential diagnosis with medullary carcinoma can be difficult as metastatic carcinoma can be well demarcated. The presence of multiple satellite foci associated with lymphatic emboli permits the elimination of medullary carcinoma.\(^7\)

Finally some ductal carcinomas can have a syncytial growth pattern and a prominent lymphoid cell infiltration. The presence of an intraductal carcinoma at the periphery of the tumour, as well as the epithelium of the lobules, will lead to appropriate diagnosis.\(^7\)

**Conclusion**

In the presence of undifferentiated mammary carcinoma with prominent lymphoid stroma, especially if the tumour is bilateral and despite the fact that breast metastases of UNPC are rarely reported in the literature, the high frequency of nasopharyngeal carcinoma in Tunisia renders this a potential neoplastic entity that should be considered by both the surgeon and pathologist.

**References**

Case report

Small cell malignant melanoma: an unusual morphologic variant

Melanoma a piccole cellule: una variante morfologica rara

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Key words
Malignant melanoma • Small cell morphology

Summary
Small cell melanoma is a recognized rare variant of malignant melanoma. We report a case of a brown, ulcerated papule on the left third finger of an 80-year-old woman. Microscopic examination revealed the presence within the epidermis of diffuse sheets of monomorphic small to medium-sized cells. The nuclei were round or oval, and hyperchromatic with inconspicuous nucleoli. Melanin pigment was either absent or minimal. This case report draws attention to the difficulties encountered in the histological diagnosis of this rare variant of malignant melanoma.

Riassunto
Il melanoma a piccole cellule è una rara variante riconosciuta del melanoma maligno. Riportiamo il caso di una papula ulcerata, marrone, del terzo dito sinistro in una donna di 80 anni. L’esame microscopico rivelava la presenza all’interno dell’epidermide di diffusi tappeti di piccole cellule monomorfiche. I nuclei erano rotondi o ovali; ipercromatici con nucleoli non appassiscenti. Il pigmento di melanina era assente o minimo. Questo caso clinico attira l’attenzione sulle difficoltà incontrate nella diagnosi istopatologica di questa rara variante di melanoma maligno.

Introduction

Malignant melanoma presents a variety of cytomorphological features that may be a source of diagnostic difficulties. Small cell melanoma is a rare and under-diagnosed variant, first described by Reed et al in 1965. Herein, we present the histological features of a novel case report of this rare variant.

Case report

An 80-year-old woman presented with a one-year history of a slow growing, painless ulcerated papule on her left third finger associated with homolateral axillary lymphadenopathy. A skin biopsy was performed, and microscopic examination revealed the presence of sheets and nests of monomorphic small to medium-sized cells within the dermis and epidermis (Fig. 1). Nuclei were hyperchromatic, round, oval or irregular with typical nucleoli. The melanin pigmentation was sparse or absent. This case report draws attention to the difficulties encountered in the histological diagnosis of this rare variant of malignant melanoma.

Corrispondenza
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angulated contours and inconspicuous nucleoli (Fig. 2). Cytoplasm were eosinophilic scanty with numerous mitoses (31 mitoses/10 HPF).

Due to the negativity of lymphoid, melanocytic, endocrine and epithelial markers, a diagnosis of malignant small round cell tumour of uncertain type was made. The patient subsequently underwent amputation of her left third finger.

Upon gross examination, the tumour was circumferential, nodular, largely ulcerated with irregular borders. It occupied the distal part of the palmar side of the finger. Microscopic features were similar to those described above. Cytoplasmic melanin pigment was either absent or minimal. There was no adjacent radial growth phase proliferation in the epidermis. Immunophenotypic stains showed focal areas of strong positivity for HMB45 (Fig. 3) and melan-A. The definitive diagnosis was nodular type malignant melanoma with small cell morphology (Breslow thickness 12 mm). Currently, after 1 year of follow-up, the patient has presented with local recurrence associated with axillary and epitrochlear lymphadenopathy.

Discussion

Malignant melanoma presents a wide spectrum of cytological features. The small cell variant is rare and not widely known. It was first described in the literature by Reed et al in 19651. In that study involving 55 patients with giant congenital naevi, 12 of 17 cases who developed a malignant melanoma were described as lymphoblastic in appearance. In fact, these tumours are composed of monomorphic cells that have a size similar to that of lymphoid cells.

This rare variant has been described both in children and adults with no gender preference. In children, it may arise de novo or in the dermal component of large or giant congenital naevi. In adults, this variant has been described at both mucosal and cutaneous sites such as our case. These lesions are composed of small monomorphic cells with oval or round hyperchromatic nuclei, usually with inconspicuous nucleoli and scanty cytoplasm. This variant of melanoma may cause significant diagnostic difficulty. Indeed, it may mimic either benign naevi when it is small, symmetrical and nested or other high-grade malignancies when it is diffuse, infiltrative and ulcerated, such as our case, with an inconspicuous junctional component.

Distinguishing small cell malignant melanoma from the cellular dermal component of a benign naevus requires careful examination of both architecture and cytological features. Unlike benign naevi, small cell malignant melanoma presents expansible, often asymmetric, and deep dermal involvement without evidence of maturation with depth. Moreover, it presents subtle nuclear atypia with coarse chromatin and, importantly, deep dermal mitoses that are exceedingly rare in benign naevi. In fact, in benign naevi, the naevus cells proliferate in junctional nests and then migrate into the dermis. Our case presented with numerous deep dermal mitoses.

Small cell malignant melanoma can also be confused with other small round cell malignant tumours. Notably, Merkel cell carcinoma and high-grade lymphoma must be considered and eliminated on the basis of immunohistochemical analysis. Other differential diagnoses include metastatic small cell carcinoma of pulmonary or non-pulmonary origin, olfactory neuroblastoma and peripheral primitive neuroectodermal tumours.

Regarding the behaviour of this rare variant of malignant melanoma, Barnhill et al. suggested that the small cell phenotype might be an independent risk factor for poor prognosis. These authors reported 5 cases of childhood small cell malignant melanoma that were localised exclusively to the scalp. These cases were thick (mean Breslow thickness 6.7 mm), and associated with aggressive behaviour. These findings led Kirkham to suggest that small cell melanoma might behave in a similar manner to the other subtypes of melanoma in which tumour thickness is the strongest predictor of disease progression.
In conclusion, it is important to bear in mind that the small cell variant of malignant melanoma is rare and not widely known. It must be considered in the differential diagnosis of benign naevocytic lesions and malignant small cell tumours such as high grade lymphoma. Its behaviour is similar to that of the other variants of malignant melanoma.

References

Amartoma mammario con cellule stromali atipiche: un potenziale allarme diagnostico per il patologo

Mammary hamartoma with atypical stromal cells: a potential diagnostic dilemma

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Parole chiave
Amartoma • Mammella • Cellule stromali atipiche

Key words
Hamartoma • Breast • Atypical stromal cell

Riassunto
L’amartoma mammario è una lesione pseudo-tumorale che generalmente non pone problemi diagnostici per il patologo. Sebbene in diverse patologie mammarie, benigne e maligne, si possano riscontrare cellule stromali atipiche, queste non sono state ancora segnalate nell’amartoma. Riportiamo un caso di amartoma mammario con numerose cellule stromali atipiche, mono- e plurinucleate, nel contesto della componente fibro-adiposa. Questo aspetto inusuale poneva problemi di diagnosi differenziale soprattutto con il lipoma pleomorfo, il liposarcoma ben differenziato, il tumore filloide maligno a differenziazione eterologa lipomatosa. La positività delle cellule stromali atipiche alla vimentina ed al CD34 svelava la loro natura fibroblastica, e pertanto furono interpretate come “varianti morfologiche” dei fibroblasti che normalmente popolano lo stroma mammario.

Summary
Hamartoma of the breast is a pseudotumoural lesion that does not usually pose diagnostic problems for the pathologist. Although atypical stromal cell (ASCs) can be encountered in several benign and malignant breast lesions, their occurrence in hamartoma has not been reported to date. The authors report a case of breast hamartoma containing numerous atypical mono- or multinucleated stromal cells within the fibro-fatty component. This unusual feature raised differential diagnostic problems with pleomorphic lipoma, well-differentiated liposarcoma and malignant phylloid tumour with a lipomatous heterologous component. Immunohistochemistry, showing positivity to vimentin and CD34, revealed that ASCs are fibroblastic in nature, and thus are likely to represent a morphological variant of the fibroblasts of the native mammary stroma.

Introduzione
L’amartoma mammario (AM) è una lesione simil-tumorale poco frequente, tipica dell’età perimenopausale, spesso asintomatica e localizzata nei piani profondi del parenchima mammario; meno frequentemente può presentarsi come una massa voluminosa che deforma il profilo cutaneo della mammella. Poiché l’AM ricorda istologicamente la mammella normale o la mastopatia fibroso-cistica – essendo usualmente costituito da una variabile commistione di tessuto adiposo e fibroso in cui sono immerge strutture duttulo-lobulari normali – potrebbe non essere riconosciuto dal patologo 1 in quanto si ha l’impressione di osservare “mammella dentro mammella”. Per tale motivo la diagnosi di AM non è esclusivamente istologica, ma clinico-patologica, che il patologo è autorizzato a formulare soltanto quando è di fronte ad una lesione a margini ben circoscritti, spesso svelata da indagini strumentali (ecografia, mammografia) e con i suddetti caratteri morfologici. L’AM, oltre a presentare l’aspetto tipico della mastopatia fibroso-cistica, può contenere focolai di iperplasia stromale pseudoangiomatoso, o aree predominanti di tessuto adiposo (adenolipoma), di tessuto fibroso (fibro-adenolipoma) o, più raramente, di metaplasia leiomiomatoso (amartoma mioide o muscolare) o condromatoso (adeno-condro-lipoma). Lesioni istologicamente simili all’AM sono state riportate in letteratura con il termine di “lesioni epitelio-stromali” o di “tumori benigni fibro-epiteliali” 2. Sebbene cellule stromali atipiche (CSA) siano state riportate in tessuti normali, iperplastici e neoplastici (benigni e maligni) della mammella 3-4, a nostra conoscenza, non sono state descritte nell’AM. Riportiamo un caso di AM con numerose cellule stromali atipiche mono- e multinucleate che, per la loro commistione con la componente fibro-adiposa della lesione, possono
rappresentare un potenziale allarme diagnostico per il patologo.

**Caso clinico**

Il caso clinico giunto alla nostra osservazione riguardava una donna di 50 anni che, per aver notato un’alterazione del profilo della mammella destra, fu sottoposta a visita clinica e ad esami radiologici. Clinicamente si apprezzava una massa sottocutanea di cm 6 di diametro massimo, a margini netti, e di consistenza teso-elastica. Sia l’ultrasonografia che la mammografia confermarono la presenza di una neoformazione di circa 6 cm di diametro massimo, a margini ben circoscritti, in corrispondenza del quadrante infero-esterno della mammella destra. Dopo aver effettuato un agoaspirato, che evidenziò rari lobuli adiposi e cellule duttali tipiche, la massa fu asportata chirurgicamente. Macroscopicamente si osservò una neoformazione nodulare di 6 cm di diametro massimo, a contorni ben circoscritti e a superficie esterna liscia. Al taglio si osservava un aspetto complessivamente sovrapponibile alla mastopatia fibroso-cistica, essendo presenti aree biancastre di consistenza fibrosa, commiste ad aree giallastre di tessuto adiposo (Fig. 1). L’esame istologico evidenziò una lesione simil-tumorale, non-capsulata, a margini espansivi, costituita prevalentemente da tessuto fibroso denso (Fig. 2A), ed in minor quota da tessuto...
adiposo maturo, in cui si riconoscevano rare strutture duttali ed unità duttulo-lobulari normali (Fig. 2A). Focalmente erano rappresentati i classici aspetti della mastopatia fibroso-cistica. Un aspetto morfologico del tutto inaspettato fu la presenza di numerose cellule stromali atipiche, mono- o multinucleate, nel contesto della componente fibro-adiposa (Fig. 2B). Queste cellule presentavano forma fusata o poligonale, con uno o più nuclei con atopia di grado lieve-moderato, raramente severo, e con rari e piccoli nucleoli. Talora erano presenti anche cellule giganti plurinucleate tipo floret-like (Fig. 2C), simili a quelle riscontrabili nello stroma di mammelle normali 3, di fibroadenomi, di tumori filloidi e di altre patologie mammarie, quali l’adenomioipiteleiomà, l’adenosi sclerosante, il papilloma intraduttuale, il carcinoma invasivo 34. Per stabilire la natura delle cellule atipiche e di quelle con aspetto tipo floret-like furono eseguite indagini immunohistochimiche con i seguenti anticorpi: vimentina, CD34, β-actina muscolare liscia, desmina, proteina S-100, CD68, pancytcheratina, ÉMA, HMB45. L’esclusiva immunoreattività delle suddette cellule per vimentina e CD34 (Fig. 2D) confermarono la loro natura fibroblastica. La diagnosi conclusiva sulla base dei dati clinico-patologici fu di “amartoma mammario con cellule stromali atipiche”. Dopo un follow-up di circa 5 anni, la paziente è in buone condizioni di salute, senza evidenza di malattia.

Discussione

Con il termine di “amartoma” si intende in generale una lesione simil-tumorale costituita da tessuti specializzati maturi, normalmente presenti nella sede di insorgenza, commistisi però in modo disordinato. L’AM è una lesione inusuale che viene diagnosticata in circa lo 0,2% degli esami mammografici 1 e rappresenta circa il 4% della patologia mammaria benigna 6. Pur interessando un’ampia fascia d’età (30-80 anni) è più comunemente osservata tra i 20-40 anni, la paziente è in buone condizioni di salute, senza evidenza di malattie sistemiche o patologie mammarie correlate. L’AM è definito come una lesione non neoplastica, caratterizzata da un accumulo di tessuto connettivale, specializzato, che può assumere aspetti di tipo adiposo o fibroso. L’AM può presentare diverse caratteristiche morfologiche, tra cui una componente adiposa, fibrosa, o mista, e può essere associato a altre lesioni mammarie, come tumori filloidi e fibroadenomi. La presenza di cellule giganti plurinucleate tipo floret-like nel tessuto di AM potrebbe essere un indicatore di una possibile trasformazione tumorigena.

Il termine di “amartoma” si intende in generale una lesione non neoplastica dell’AM. Dell’AM si basava essenzialmente sulla presenza di lipoblasti. Poiché è stata riportata la possibilità che nel contesto di un AM possa originare un tumore filloide maligno con componente lipomatosa 10, il nostro caso potrebbe essere poten-
zialmente misdiagnosticato come tale. Tuttavia mancano le seguenti caratteristiche macro- e microscopiche del tumore filloide maligno: i) l’aspetto infiltrativo, anche se parziale, dei margini; ii) la diffusa ipercellularità stromale; iii) il marcato pleomorfismo nucleare; iv) elevato indice mitotico; v) la marcata condensazione delle cellule stromali atipiche in sede sottoepiteliale; vi) l’eventuale presenza di aree necrotico-emorragiche.

In conclusione, è ipotizzabile che le cellule stromali atipiche e le cellule giganti del tipo floret-like nel presente caso di AM rappresentino soltanto una variante morfológica dei fibroblasti che normalmente popolano lo stroma mammario, probabilmente in risposta a stimoli di natura sconosciuta, così come già osservato in altri tessuti quali la vesica, laervice, la vulva, la vagina, il naso, il testicolo, la laringe 3-4. Sebbene la diagnosi di AM non ponga particolari problemi diagnostici, la presenza di CSA in questa lesione, pur non avendo alcuna rilevanza prognostica, potrebbe allarmare il patologo. La conoscenza di questa rara possibilità aiuta ad interpretare correttamente un’entità clinicopatologica benigna che potrebbe essere misdiagnosticata come maligna.

Bibliografia


Angiomiofibroblastoma vulvare. Relazione su un caso, con revisione della letteratura. Una rara ma distinta entità

Angiomyofibroblastoma of the vulva: a rare but distinct entity. Case report and literature review

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Parole chiave • Key words
Angiomyofibroblastoma • Vulva • Angiomyxoma aggressive

Riassunto

L’angiomiofibroblastoma è un tumore vulvare benigno dei tessuti molli, caratterizzato da un’alternanza di aree ipo-ipercellulari di cellule stromali con aspetti fusati, frammiiste e disposte attorno a piccoli vasi sanguigni.
Si pone l’attenzione sul riconoscimento di tale entità, che manifesta un comportamento biologico benigno rispetto ad altre lesioni mesenchimali, caratteristiche di questa sede, con comportamento biologico più aggressivo.

Summary

Angiomyofibroblastoma is a benign vulvar tumour involving soft tissue that is characterized by alternating hypocellular and hypercellular areas of spindle stromal cells, admixed and aggregated around blood vessels.
It is important to recognize this entity as it shows benign behaviour with respect to other mesenchymal tumours of the vagina, which have a more aggressive behaviour.

Introduzione

L’angiomiofibroblastoma è un tumore vulvare benigno dei tessuti molli, caratterizzato da una alternanza di aree ipo-ipercellulari, di cellule stromali con aspetti fusati frammiiste e disposte attorno a piccoli vasi sanguigni (Figg. 1, 2).
Questi elementi cellulari sono all’indagine immmunoi-
stochimica positivi per vimentina, desmina e recettori ormonali (ER, PR); solitamente negativi per actina e citocheratine.

Tali lesioni sono ad andamento biologico benigno, con un rischio di recidiva locale estremamente basso, ma con la possibilità di una trasformazione sarcomatososa (angiomiofibrosarcoma).

Istologicamente la lesione appare ben circoscritta e mostra talora caratteri morfologici di transizione tra l’angiomixoma aggressivo e l’angiofibroma cellulato, tanto da ipotizzare la possibilità che essi possano essere istogeneticamente correlati fra di loro.

**Casino clinico**

Una donna di 44 aa. (I.A.R.), si presentava alla nostra osservazione.

La paziente era in menopausa chemioterapia (U.M. nel l’agosto 2005), in quanto nello stesso anno manifestava una tumefazione in regione mammaria dx che veniva sottoposta a biopsia chirurgica, con il seguente esame istologico: Linfoma non Hodgkin diffuso a grandi cellule B, stadio II EA bulky, delle dimensioni di 14 x 8 cm. Successivamente veniva sottoposta a protocollo chemioterapico con R-ACOD, con anticorpi monoclonali 6 cicli completi x 3 volte al mese.

Giunta alla nostra osservazione nel febbraio 2006 evidenziava sui genitali esterni (margini esterno del grande labbro dip. frame), neoformazione perivascolare di circa 3 cm di diametro, in parte peduncolata; il restante apparato uto-annessiale, non presentava alterazioni di niente di ri-pleo.

Pertanto tale tumefazione veniva sottoposta ad escissione chirurgica ed inviata per esame istologico; la diagnosi formulata era la seguente: Angiomiofibroblastoma vuvare; lesione presente sui margini di eseresi. Successivamente la suddetta veniva testata con indagini immunoistochimiche, la cui componente neoplastica evidenziava positività per ER, localmente per CD-34; negatività per desmina, actina muscolo-liscio, S100 e PR.

**Discussione**

Da una revisione della letteratura a decorrenza dal 1995 sino al 2006, si evince che l’insorgenza di tale lesione ap-

pare nell’età media di vita, cresce lentamente e raggiunge dimensioni che oscillano fra 1,5 cm e 6 cm, ed è localizzata nel sottocute vuvare. Gli angiomiofibroblastomi sono tumori ben demarcati e vascolarizzati, alterando aree iper-ipocellulare, composte da cellule fusate-ovali stromali, frequentemente aggregate ai vasi sanguigni.

Le indagini immunoistochimiche effettuate sulle cellule stromali mostrano positività per vimentina e desmina; negatività per actina muscolo liscio, miosina, S100 e CK. A distanza di 1 vs. 4 anni, dai margini di escissione non viene evidenziata recidiva.

Tali tumori manifestano predilezione anatomica per il perineo femminile, e vengono erroneamente diagnosticati “clinicamente”, quali Cisti dei Bartolini.

Il profilo immunoistochimico in tutti i casi riscontrati, evidenza positività per vimentina ed ER; in taluni vi è positività per desmina e actina muscolo-liscio.

Tutti i pazienti vengono generalmente trattati con escissione locale, limitata all'area tumefatta.

Il follow-up delle pazienti dimostra andamento biologico benigno, senza segni di recidiva.

**Conclusioni**

L’angiomiofibroblastoma è una distinta neoplasia che ha una predilezione nella sua localizzazione nel tratto genitale femminile.

Il riconoscimento di tale entità è importante per porre una diagnosi differenziale con altre neoplasie vulvare angiomixoidi, che hanno un comportamento biologico più aggressivo, come l’angiomixoma aggressivo, in cui è necessario procedere ad un allargamento dei tessuti periferici per prevenire le recidive.

Pertanto la semplice escissione per angiomiofibroblastoma, con atteggiamento conservativo è raccomandata, in quanto recidiva locale o metastasi non sono state riportate in letteratura (per quanto la sua trasformazione sia estremamente rara), tale considerazione è suffrargata dal fatto che in un lavoro del 2006 viene riportato il caso di una donna di 48 anni portatrice di tale neoformazione delle dimensioni di 11 cm di diametro che si era gradualmente ingrandita in un periodo di circa 7 anni.

Per ciò che riguarda la sua possibile istogenesi, si ipotizza che esso possa derivare dalle cellule staminali perivascolari con una capacità di una differenziazione miofibroblastica.

**Bibliografia**

Mesenchymal hamartoma of the chest wall in an infant

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Key words
Mesenchymal hamartoma • Congenital lesion • Chest wall

Summary
Mesenchymal hamartoma of the chest wall is a very rare, benign tumour with distinct clinical, radiological and histopathologic characteristics. The lesion develops during foetal life, and is present at or shortly after birth with an extrapleural mass arising from the rib cage with or without respiratory distress and marked rib deformity. Several imaging techniques have been used for diagnosis, but a definitive diagnosis is established only by histopathological examination. Such lesions are composed of a varying admixture of hyaline cartilage that has features resembling growth plate cartilage, along with fascicles of spindle cells, woven bone and hemorrhagic cysts. Accurate diagnosis of mesenchymal hamartoma is important since many chest wall masses in children are malignant. We report a case of mesenchymal hamartoma of the left posterior chest wall surgically resected in an infant who was found to have a palpable mass at birth. Two years after surgery, the patient is alive and well, with no evidence of recurrence.

Introduction
Mesenchymal hamartoma of the chest wall is an extremely rare congenital lesion of the rib, with an incidence of 0.03% among primary bone tumours. This unusual lesion is notable for its occurrence in early infancy and alarming clinical presentation, which often suggests malignancy. It is not considered as a true neoplasm and is composed of maturing proliferating normal skeletal elements, with no propensity for invasion or metastasis. We report a case of this rare entity that can be easily mistaken for a malignant tumour.

Case report
A 6-month-old infant was found to have a 2-cm posterior and lateral mass of the left side of the chest wall at birth. The mass was progressively increasing in size. On physical examination, a well circumscribed parietal mass was found adhering to the seventh, eighth and ninth costal posterior arch. This mass measured 8 cm and was painless and fixed. A collateral venous circulation was also noted. Imaging findings showed a 6-cm mass originating from the left posterior arch of the eighth, ninth and tenth ribs with costal destructions. This mass contained cystic components of 1.8 cm and peripheral calcifications. Laboratory tests showed normal rates of the β-HCG and α-foetal-protein. Surgical resection was performed and the tumour was totally removed in association to the eighth and ninth ribs and the posterior part of the tenth rib. On gross examination, the ribs were totally destroyed by a well circumscribed mass. The cut surface revealed grey to white solid areas adjacent to cystic cavities filled with blood. Microscopic findings consisted in an encapsulated mass associated with areas of mature hyaline cartilage showing occasional enchondral ossification (Fig. 1). Areas resembling...
Chondroblastoma were also noted in association to areas with fibroblast-like cells. Cystic areas showed typical features of aneurysmal bone cysts (Fig. 2). Based on the histologic findings, the diagnosis of mesenchymal hamartoma was retained. The patient presented no complications after a follow-up period of 2 years.

**Discussion**

Mesenchymal hamartoma of the chest wall in infancy is a very rare lesion, recognized as a pathologic malformation during embryonic development that is tumour-like but non-neoplastic. Since Ber and Stout described this typical lesion in 1962, it was considered to be a chondrosarcoma or an osteochondrosarcoma. Since that first description, many terms have been used to describe the lesion, including benign mesenchymoma, atypical benign chondroblastoma and infantile cartilaginous hamartoma. The currently-accepted name of mesenchymal or chest wall hamartoma, as initially proposed by McLeod and Dahlin in 1979, is now considered the most appropriate. This final denomination was also used by the WHO in the last classification of the tumours of the bones and soft tissue in 2002. Approximately 75 cases have been documented in the literature. Multiple lesions are extremely rare with only 5 cases reported to date, and bilateral localisations are atypical for this lesion. In about 40% of the cases, the mass is apparent at birth; nevertheless, most cases present between 1-12 months. Less frequently, lesions may present in children up to 8 years of age. The lesion has also been diagnosed in utero with CT scans or ultrasound. Only 2 cases have been reported in adults that were aged 21 and 26 years. Mesenchymal hamartoma of the chest wall usually presents as a mass or fullness of the rib cage. Most often, this mass is intrathoracic frequently causing respiratory distress. Some of these tumours are diagnosed clinically at an early stage because of compression phenomena of adjacent structures. Frequently, the palpable tumour mass at the rib area is the only clinical symptom, such as found in our patient. Imaging findings show usually a large, extrapleural, partially calcified soft-tissue mass arising from one or more ribs, with associated destruction and distortion of the adjacent osseous thorax.

The differential diagnoses include neuroblastoma, ganglioneuroma, schwannoma, paraganglioma, Askin’s tumour, lymphangioma, teratoma, other primary bone tumours and undifferentiated malignancies. Generally, correct diagnosis can be obtained by correlating radiological and pathological findings. Gross examination reveals a well-circumscribed, expansive lesions ranging from 3 to 7 cm in maximum dimension. Cut surface reveals variably sized foci of chondroid areas alternating with soft to friable, grey-white regions and cystic cavities filled with blood. Microscopic findings consist in solid areas consisting primarily of mature hyaline cartilage, although areas resembling chondroblastoma may be present. The cartilage often shows enchondral ossification, and areas with fibroblast-like cells are also present. Cystic areas show typical features of aneurysmal bone cyst: blood-filled lakes are bounded by fibrous septae which contain reactive bone and osteoclast-like giant cells. As areas of immature mesenchymal cells are often highly cellular and sometimes show frequent mitoses, it is often misdiagnosed as malignant. The hypercellular proliferative features may be suggestive of malignancy to pathologists unaware of this lesion, and indeed mesenchymal hamartomas have been misdiagnosed as chondrosarcoma, osteosarcoma or osteoblastoma. These diseases, however, are characterised by aggressive or malignant features such as nuclear atypia and hyperchromatism, which are notably absent in mesenchymal hamartoma of the chest wall. Although there have been cases of recurrence after limited surgery, mesenchymal hamartoma in infancy is believed to be essentially benign and the cure generally consists in a wide resection. Scoliosis is the most frequent complication after an extensive rib resection, and prognosis is favourable. Cure has been reported in cases of complete removal of the affected ribs. Lesions that are not removed surgically remain stable, but patients may die of respiratory insufficiency. To our knowledge, there is only one report of malignant transformation. Freeburn and McAloon described the expectant management...
and long-term follow-up of a case of uncomplicated spontaneous resolution and rib remodelling, and recommended a non-surgical approach to the management of asymptomatic patients. In conclusion, this tumour may regress spontaneously and can be easily mistaken as a malignant lesion. Therefore it is necessary to recognize this rare entity before performing surgery to avoid over-treatment. Despite its aggressive appearance and tendency to attain a massive size, the lesion behaves biologically in a benign fashion, with no reports of recurrence or metastasis following complete surgical resection.

References

Granuloma multiforme: first case report in Tunisia

Granuloma multiforme: il primo caso riportato in Tunisia

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Key words
Granuloma multiforme • Dermatosis • Skin

Summary
Granuloma multiforme is a rare granulomatous skin disease, usually reported in sub-Saharan African countries. The exact aetiology of granuloma multiforme is still unknown. We report the case of a patient who presented clinical and histopathological features of granuloma multiforme that can be considered the first described case in Tunisia.

Introduction
Granuloma multiforme (GM) is a rare skin disorder of unknown aetiology, characterised clinically by confluent annular lesions. Histologically, it shows multiple areas of histiocytic granulomas with focal necrobiosis, and many multinucleated giant cells. The disease is generally found in adults over the age of 40, with a predilection for females. It has been reported mostly in sub-Saharan African countries, but rarely from other parts of the world. Recent advances in pathogenesis are discussed. We describe a patient with GM, and on the basis of a literature review clarify the relationship between GM and related diseases. To the best of our knowledge, this is the first case reported in Tunisia.

Case report
A 54-year-old man Tunisian presented with a prominent erythematous elevated plaques on the upper chest, neck, abdomen and lower extremities of one year duration. The lesion initially started as small papular lesions on the upper chest and neck. He had no other systemic complaints. There was no family history of similar skin disease. Physical examination disclosed linear erythematous papules coalescing into plaques on the trunk, extremities and annular, polycyclic infiltrated lesions distributed over the upper chest and neck varying in size from 1-5 cm (Fig. 1). All the lesions had a papular border and a firm consistency. Some of the lesions showed minimal central atrophy. There were no mucosal lesions, no tactile loss and no peripheral nerve thickening. The initial clinical diagnosis was patch stage mycosis fungoides. Routine investigations were normal. A skin biopsy demonstrated a perivascular and interstitial lymphocytic infiltrate admixed with a few plasma cells, seen in superficial and mid dermis. There were scattered epithelioid histiocytes and prominent multinucleated giant cells of the Langhans type, between collagen bundles (Fig. 2). The number of nuclei per giant cell varied from 3 to more than 10. In addition there were foci of collagen degeneration surrounded by granulomatous infiltrates. Solar keratosis was not apparent. Elastic stains using orcein showed a loss of elastic fibres in areas of granulomatous infiltrates, but without elastophagocytosis, histiocyte palisading, or mucin deposition (Fig. 3). The epidermis was of normal thickness and was not infiltrated by lymphocytes. No acid-fast bacilli were detected. Periodic acid-schiff and Giemsa stains were negative for microorganisms. Alcian blue stain did not show mucin deposits in necrobiotic areas. On the basis of clinical presentation and histopathological findings, our case appeared to be a multiforme granuloma (GM).

The patient was treated with disulone (25 mg/day). After two months of therapy, the lesions were no longer

Corrispondenza
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spreading but were still present. The patient subsequently interrupted treatment.

**Discussion**

Granuloma multiforme (GM) is rare granulomatous skin disease characterised histologically by focal necrobiosis and multinucleated giant cells. The clinical presentation varies considerably. In 1964, Leiker et al. coined the term GM to describe a variety of clinical presentations with a granulomatous histology. It has been reported mostly from sub-Saharan African countries, but a few cases have also been reported in India. To the best of our knowledge this is the first case reported from Tunisia. The disease usually affects older adults over the age of 40 with a slight female predilection. GM lesions are localised primarily on sun-exposed areas, including the neck, upper back and face, but are less common in covered areas such as the abdomen, chest and urogenital flexures. In our case, the lesion occurred in both sun-exposed and non-exposed areas (abdomen).

In 1979, Hanke and al. considered the entities previously described as atypical facial necrobiosis lipoidica, actinic granuloma of o’Brien, Miescher’s granuloma of the face and granuloma multiforme of Leiker to be identical. In each of the lesions, elastolysis is often found. It is still unclear whether these disorders correspond to variants of single process or are in fact separate and distinct entities. According to some authors, the term annular elastolytic giant cell granuloma (AEGCG) can be applied to GM. Whilst the relationship between GM and annular granuloma is not clear, on the basis of clinical and histological patterns, the autonomy of GM appears to be established. When the clinical features in our case are combined with the histopathological findings of a dermal elastolysis with many giant cells, seen in superficial and mid-der-
mis, a number of other conditions must be considered (Tab. I). Actinic granuloma is an annular connective tissue disorder affecting sun-exposed areas of skin. The lesion often occurs insidiously on a background of severe solar elastosis. In our case, the lesions were on both sun- and non-sun exposed areas.

Annular granuloma may lack an annular configuration, appearing as widespread papular lesions. The latter are usually present on the chest, inner arms and thighs in contrast to the distribution of lesions in our patient. In addition, annular granuloma affects a younger age group, unlike GM, that is seen in patients over the age of 40, which presents as annular plaques. In addition, diffuse annular granuloma has been described in immunosuppressed patients. In our case, the patient was not immunodeficient.

Annular elastolytic granuloma is a distinct clinical entity that affects older adults. It is localised primarily on sun-exposed areas, but less commonly on covered areas. The dominant features are elastolysis and elastophagocytosis with infiltration by numerous multinucleated giant cells. In our case, elastophagocytosis was not seen. Necrobiosis lipoidica is a chronic granulomatous dermatitis that is associated with diabetes mellitus. Histologically it shows a palisading granuloma surrounding large foci of necrobiosis. The skin lesions of our patient are different.

The exact pathogenesis of GM remains unclear. Some authors suggest that it is related to photodermatosis where UV rays could cause cumulative damage to collagen and induce cellular immune reactions. This is supported by the fact that the lesions are usually confined to sun-exposed areas. However, in our case, the lesions were on both sun and non-sun-exposed skin areas. This lesion may respond to intralesional corticosteroid therapy, but no effective therapy is available at present for this uncommon disorder.

This is the first case reported in Tunisia, so this rare entity is not confined to Sub-Saharan regions of Africa or India, as initially believed, and a special effort should be made to distinguish this lesion from other granulomatous skin diseases. Further studies should be performed to clarify its aetiology.

**References**

Cystic nephroma in the adult: pathological aspects and therapeutic implications

Il nefroma cistico dell’adulto: caratteristiche istopatologici e implicazioni terapeutiche

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Key words
Cystic nephroma • Multiloculus cysts of the kidney • Mixed epithelial and stromal tumor of the kidney • Renal tumor

Summary
Cystic nephroma is a benign renal neoplasm. Since its initial description, there has been much debate regarding its origin. Preoperative diagnosis of Cystic nephroma is difficult to achieve. The differential diagnoses of Cystic nephroma are recently described mixed epithelial and stromal tumours of the kidney and cystic renal cell carcinoma. The Authors report three cases of Cystic nephroma and illustrate the clinical, radiological and histological features of this renal neoplasm.

Introduction
Cystic nephroma (CN) is a rare and benign renal tumour¹. Preoperative diagnosis remains difficult despite the progress of imaging procedures. We report three cases of CN and, based on a review of the literature, discuss the diagnostic and therapeutic features of this rare entity.

Case reports

CASE 1
A 64-year-old man with no history of hormone therapy presented with isolated right lumbar pain. Physical examination found a mass in the right flank region. Intravenous urography showed a “mass syndrome” in the lower pole of the right kidney. Ultrasound revealed a renal mass consisting of multiple anechoic cysts separated by thick septa. Three diagnoses were suspected: a multi-vesicular hydatid cyst, necrosed tumour and CN of the kidney. Computed tomography (CT) was not available at that period (1981). Selective renal arteriography showed a slightly vascularised, well-limited, expansive process of the lower pole of the right kidney. Hydatic immunology was negative. The patient underwent right lumbotomy. Perioperative exploration of the right kidney revealed a well-circumscribed lower pole mass formed by 8 non-communicating cysts. Partial nephrectomy was performed. Final histologic examination revealed a flat epithelium of the cyst wall and CN was diagnosed (Tab. I). Ultrasound follow-up showed no recurrence 7 years after surgery.

CASE 2
A 40-year-old woman presented with a 2-year history of left lumbar pain. She had no history of oestrogen therapy. Ultrasound revealed a well-circumscribed multi-cyst formation measuring 17 cm. Intravenous urography revealed a left renal mass syndrome. Hydatic immunology and CT had not been done. The diagnosis of type III hydatid cyst of the kidney was retained. The patient underwent left lumbotomy. Surgical exploration revealed a multi-cystic mass leaving only a thin upper-pole
renal parenchyma. Left nephrectomy was performed. Macroscopic examination of the specimen showed a cystic mass with thin, slightly vascularised septa (Fig. 1). Histologic examination found non-communicating cysts with flat-epithelium-covered walls (Tab. I), thus confirming a diagnosis of CN (Fig. 2).

Case 3
A 24-year-old woman with no history of oestrogen therapy presented with isolated right flank pain. Ultrasound showed a mediorenal multicystic mass of the right kidney with important dilatation of the renal pelvis and calyces. CT found a multicystic formation measuring 12 cm in diameter, which occupied the right renal “loge” and was slightly enhanced upon visualisation with contrast media (Fig. 3). A diagnosis of cystadenocarcinoma was retained and the patient underwent radical right nephrectomy. Histology of the resected specimen confirmed the diagnosis of CN (Tab. I).

Discussion
CN is a rare cystic tumour of the kidney. The histologic origin of this entity has been the subject of controversy since its original description by Edmunds in 1892, and CN has long been considered to have a bimodal age distribution. In 1998, Eble and Bonsib introduced age among diagnostic criteria for CN. Eble classified infantile CN as cystic partially differentiated nephroblastoma given the differences in sex ratio distribution according to age and the anatomo-clinical findings of CN in children and adults.

CN occurs in predominantly in female patients in the sixth decade of life, with a male-female ratio of 1:8. Its

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/Sex</th>
<th>Tumour size (cm)</th>
<th>Hormonal therapy</th>
<th>Histology</th>
<th>Immunohistochemical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64/M</td>
<td>NA</td>
<td>–</td>
<td>Flat epithelium</td>
<td>ER</td>
</tr>
<tr>
<td>2</td>
<td>40/F</td>
<td>17</td>
<td>–</td>
<td>Non-communicating cysts</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>24/F</td>
<td>12</td>
<td>–</td>
<td>Flat epithelium</td>
<td>–</td>
</tr>
</tbody>
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Tab. I. Summary of clinical, morphological and immunohistochemical data in the 3 cases of CN.

NA: not available; ND: not done; ER: oestrogen receptor; PR: progesterone receptor; CK: cytokeratin
aetiopathology remains unclear. Some Authors support that it is a non-familial, benign renal neoplasm, while others suggest that it may be related to a malformation. CN is well circumscribed by a thick fibrous capsule, with an average size of 9 cm. It often originates from the renal polar parenchyma, and may sometimes protrude into the renal pelvis or calyces. The cut surface of the tumour reveals multiple, non-communicating, fluid-filled cysts separated by connective tissue septa. Microscopically, the cysts are covered with a flat or cuboid epithelium with a hobnail appearance. Lining cells have bland nuclear chromatin. Varying degrees of nuclear atypia are noted, and mitoses are not identified. Stroma is usually hypocellular, and may sometimes present as “ovarian-like” stroma.

The main differential diagnoses of CN are cystic renal cell carcinoma, mixed epithelial and stromal tumour (MEST) and hydatid cyst of the kidney, which is more plausible in endemic areas. Histologic differential diagnosis with cystic renal cell carcinoma is usually easy whereas it may be more difficult with MEST. MEST is a benign tumour that was originally reported by Michael in 1998 and was considered as a new entity in the 2004 WHO classification of the renal tumours of the adult. CN and MEST have similar epidemiologic, clinical, morphologic and histologic features. Differentiation between these two entities is based on stroma density, which is abundant in MEST. This notion is highly subjective, and distinguishing these two tumours is, at present, controversial. Two recent series comparing CN and MEST suggest that they represent a spectrum of the same entity. In both lesions, immunohistochemical studies revealed that the epithelial component was diffusely positive for pan-keratin and focally positive for CD10, CK7 and high-molecular-weight keratin; stains for oestrogen and progesterone receptors were negative. In cases 2 and 3 of the present report, the epithelium was positive for CK7 and negative for CK20; oestrogen and progesterone receptors were negative. No immunohistochemical study was performed in patient 1 since it was not available at that period. Further investigations with a larger patient cohort along with molecular biology studies are needed to support this hypothesis.

CN is often discovered incidentally. Symptoms and signs are rarely related to the presence of a mass: lumbar pain, haematuria, renal colic and occasional acute abdominal pain related to spontaneous rupture. Ultrasound usually demonstrates a multicystic anechoic mass with thin echoic septa. This aspect should prompt a diagnosis of multi-vascular hydatid cyst of the kidney in endemic areas. Upon CT, CN manifests as an encapsulated multicystic mass, presenting moderately contrast-enhanced thin septa. On occasion, these septa show higher enhancement after visualisation with contrast media. These CT aspects correspond to types II and III of the Bosniak classification. Hora suggested that these radiologic aspects can give rise to two differential diagnoses of CN: multilocular cystic renal cell carcinoma and MEST of the kidney.

By MRI, the capsule and septa show low signal intensity on T2-weighted MR images. Cysts have variable signal intensity on T1-weighted images (depending on their contents) and a high signal intensity on T2-weighted images. A typical septa enhancement is noticed after intravenous gadolinium administration. However, these aspects are not specific for CN, and MRI still has a limited contribution.

Treatment of CN is surgical. Conservative procedures might be proposed when clinical and radiologic aspects confirm diagnosis. Some Authors propose partial nephrectomy for tumours not exceeding 4 cm in diameter. Some cases of excision of the tumour have been reported with uneventful outcome. Other authors, however, consider that total nephrectomy remains the recommended treatment for CN given the difficulty in obtaining a preoperative diagnosis. CN is a benign tumour with good prognosis. Nevertheless, 4 cases of recurrence, all occurring after conservative surgery, have been reported. The cysts rarely progress to neoplasia. A few cases of sarcomatous, carcinomatous or lymphomatous transformation have been described, but no metastases have been reported.

Conclusion

CN is a rare benign cystic tumour of the adult. Pre-operative diagnosis remains difficult. At present, histologic criteria differentiating CN and MEST are not well-defined. Conservative treatment (nephron-sparing surgery) can be proposed in selected patients.

References

In fond memory of Hans Cottier, Prof. Dr. Med. H.C.

This biography of Hans Cottier is based on almost 30 years of personal memories, reconstructed with help from Hans’ old students Jean Laissue and Thomas Schaffner who succeeded him as Directors of the Institute of Pathology in Bern University, as well as from Dan Slatkin, a collaborator from his days at Brookhaven National Laboratory, and his nephew, Paul Cottier.

Professor Hans Cottier (Hane, to his many friends) was a man of broad culture. Aside from his considerable contributions to science, he had wide-ranging interests from history to art, from music to cinema, and one sometimes felt inadequate in comparison with him. However such feelings rapidly dissipated in his presence due to his gentle manner of relating to people, and his amiable ways of speaking so that one immediately felt relaxed and at ease with him.

He received his baccalaureate in 1939 and, in 1942, dedicated himself to the study of medicine, finishing in 1948 and becoming a student of Walhard and Zuppinger at the Institute of Pathology and Radiology in Bern. Later when working in Bonn he had decided to become a cardiologist and heart surgeon, but this was not to be. While climbing in the mountains he had an accident in which he suffered a broken skull and permanent hearing damage. Speaking of this later he was remarkably philosophical, almost as though the accident that had changed his life had happened to someone else. Luckily for many of us, this misfortune brought him back to the study of pathology. From 1960 to 1963 he was occupied with radiobiology at Brookhaven National Laboratory on Long Island; this was an intellectually stimulating environment with scientists such as Cronkite, Bond, Stoner and Quastler. His studies there mainly involved cellular kinetics and led him to organise an extremely important immunopathology conference in 1966, the proceedings of which (“Germinal Centers in Immune Responses”) represented a fundamental advance in understanding the role of lymphoid organs in immune response. Another result of his experiences in the USA was the development of collaboration between scientists from Brookhaven and the Institute of Pathology in Bern that continue to this day. I remember that he never spoke of his years in the States without remembering, his eyes twinkling, the habits of his colleagues and his fishing adventures.

Over the next decades (1963-1987) managed the Institute of Pathology in Bern. Under his guidance, the Institute became an outstanding centre for research, teaching and clinical diagnosis, where addressing fundamental questions about diseases engendered by the pathologist’s daily diagnostic routine was pivotal to the research strategies that Hans fostered. He encouraged and carried out joint projects with other Institutions, and helped many colleagues and former students both personally and professionally, many of whom became his friends. For him, friendship was rooted in ethics and was of infinite solidity. He also had an immense capacity for self-sacrifice: his working hours were regularly 12 hours a day, sometimes even staying away from home for days on end. His achievements at this time were commensurate with his effort. Not only did he build up a wealth of some 250 PubMed-cited reports, but in 1970 he began the daunting task of writing a treatise on the origin and development of diseases, the “Pathogenese”.

This two-volume work published in 1980 by Springer Verlag won widespread praise not only from pathologists, but from students and clinicians who also relished his clarity of explanation. His approach to the subject is now mainstream, but at the time he was among the first to integrate knowledge from a variety of biological disciplines (such as biochemistry and immunology) into pathogenic processes. Many important questions that he posed have yet to be properly addressed. His commitment to numerous collaborative projects and larger organizations cannot be forgotten; the Swiss study group of the WHO and the International Commission on Radiological Protection deserve special mention in this regard. His love for his country was also boundless, and he was a dedicated officer in his nation’s reserve army and spent much time on this commitment.

He was not, nor ever wanted to be, a great orator: he often lowered his voice when speaking from the podium, and his tone was humble. He would mock of formalism of any kind – from either individuals or ceremonies. It seemed that for him nothing was sacred, nothing was absolute and nothing was entirely true. In fact the truth for him often lay in doubt, even in scientific matters, but this did not mean that he would accept compromises in the method of seeking truth or the results of his research. His scientific rigour was a model for all of us, especially the youngest, to whom he communicated and affirmed his seriousness almost light-heartedly, through stories that may have been real or may have been inventions. These stories, or witticisms, were breaks rather than interruptions in a life characterised by rules – a life of daily commitment to work. His rules were unbreakable and inflexible, but his sense of humour was always in the background and would strike, albeit benevolently, all of us who were lucky enough to know him. The same holds true for his puns on cholesterol-eating smooth muscle cells, and even scribbled (as if he wanted to draw one of his much-loved caricatures) to illustrate the path of lymphocytes through lymphoid organs and his good-natured blaming of immunohistochemistry, which he would call “imunooistocomica” (immunohistocomical, a pun on the Italian “immunootochimica”). His propensity for joking, irony and irreverence was already evident in his youth, at the “Patria” Boy Scout summer camps and in the “Flamberg” Boy Scouts, when he led his companions to the Swiss national championship, or in his personal recollections on Hitler’s radio broadcasts about the future of
the world under German Aryan control. His cartoons and humour were a way of communicating that brought emphasis and, indeed, in his “Pathogenese” the illustrations were his own.

I first met Hane thanks to the proceedings of the 1966 immunopathology congress, because we were also setting up a work group on lymphoid organs pathology in Siena. This, however, was a few years before Hans introduced the quantification of lymph node changes in the various patterns of immune response in a well-known study published under the aegis of the WHO. I went to meet him in Bern and we began a scientific collaboration, which for a few years concentrated on the thymus and its incredible progressive disappearance with age – what he called, with his usual irreverent sense of humour, thymus tourism (many journeys were made between Bern and Siena with suitcases full of thymuses). We progressed way beyond this, to set up a School of Pathology with Hans Cottier as the only, unsurpassable, teacher and many young doctors from Siena who trained following his inimitable example. Hans’ “Siena Years” really took off when he retired from the Institute of Pathology in Bern. He stayed at the Certosa di Pontignano just outside the city for a few months every year, many years in a row, where we enjoyed unforgettable evenings with him, always marvelling at his way of being master of his art. We were captivated by his questioning of everything and the opposite of everything, but also by his answers, which gained him ever more admiration, until we became accustomed to his genius, even when he taught genetics and molecular biology with inexpressible refinement and competence. His arrival in spring was anticipated with affection, but it was also preceded by the rigorous preparation of issues to bring to his attention as a starting point for a common project. The University of Siena awarded him a laurea honoris causa in medicine, which he accepted with joy, despite his aversion to ceremonies, due to his love for Siena.

We miss Hane sorely, but it is some consolation that though poorer for his absence, we are blessed by being much richer for his legacy.

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Aggiornamenti sulla diagnosi differenziale del mesotelioma

New diagnostic markers for mesothelioma

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Il profilo immunofenotipico del mesotelioma è attualmente ben definito e numerosi marcatori sono disponibili per effettuare diagnosi differenziali su materiale citologico ed istologico. Tra i marcatori più utili ed utilizzati ricordiamo BER-EP4, calretinina, citocheratina 5/6, WT1, podoplanina/D2-40, ed altri. La criticità della diagnosi del mesotelioma continua però a stimolare la ricerca di nuovi marcatori che consentano di incrementare la sensibilità e la specificità in differenti contesti di diagnosi differenziale (mesotelioma e adenocarcinoma del polmone, mesotelioma peritoneale e carcinoma sieroso dell’ovaio, mesotelioma e mesotelio reattivo).

Segnaliamo due marcatori recentemente descritti in letteratura come potenzialmente utili nel contesto della diagnosi differenziale del mesotelioma: mucina 4 e glut-1. La mucina-4 (MUC4) appartiene alla famiglia delle mucine, proteine glicosilate prodotte dalle cellule epiteliali e coinvolte nei meccanismi di difesa tissutale. MUC4 è una proteina di membrana (come MUC1 e MUC3) ed è espressa negli epiteli del sistema respiratorio, ma non nel mesotelioma. La possibilità di utilizzare MUC4 nella diagnosi differenziale tra mesotelioma epitelioide (MUC4 negativo) ed adenocarcinoma del polmone (> 90% MUC4+) è stata proposta da Llinars et al. nel 2004. Più recentemente, MUC4 è stato segnalato come potenzialmente utile nella diagnosi differenziale tra mesotelioma peritoneale e carcinoma sieroso dell’ovaio. In questo studio sono stati confrontati i profili di espressione genica delle due neoplasie, e MUC4 appariva, tra i 54.675 geni analizzati con unsupervised hierarchical clustering tra le molecole più interessanti come marcatori distintivi. È da sottolineare inoltre che recenti dati dimostrano per MUC4 un ruolo biologico rilevante in diversi tipi di carcinoma (pancreas, polmone, mammella, vescica, prostata, ovaio, ecc.) ed è coinvolto nella modulazione della pathway HER2/ErbB2.

La diagnosi differenziale tra mesotelioma maligno ed iperplasia reattiva del mesotelo può presentarsi come critica e diversi marcatori sono stati proposti come utili in questo contesto di diagnosi differenziale (p53, EMA, desmina e pochi altri). Nessuno dei marcatori proposti ha però retto ad una verifica di efficacia. Recentemente la proteina GLUT-1 – membro della famiglia "facilitative glucose transporter" (GLUT) coinvolta a livello cellulare nel trasporto del glucosio contro gradiente – è stata proposta come marcatore utile nel contesto della diagnosi differenziale tra mesotelioma maligno (GLUT-1 positivo nel 100% dei casi) e mesotelio reattivo (0% di casi positivi). Va sottolineato come l’espressione anomala di GLUT-1 non discrimina solamente mesotelio reattivo e mesotelio neoplastico, ma è anche utilizzabile per distinguere su preparati citologici cellule mesoteliali reattive e cellule di adenocarcinoma. Naturalmente le potenzialità applicative di questi due marcatori vanno sottoposte a conferma e validazione in più ampie casistiche.

Bibliografia