Atypical Fibroxanthoma with Osteoclast-like Giant Cells

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Atypical fibroxanthoma has a wide spectrum of histological appearances. A variant recently described is atypical fibroxanthoma with osteoclast-like giant cells. One case of this rare tumour is described. The tumour arose on the forehead of an 87-year-old woman in the form of a subepidermal nodule. The lesion was incompletely excised and recurred 6 months later without showing any characteristics of aggression. Six months after the second operation the patient was well and showed no signs of tumour recurrence. Immunohistological findings showed a “fibrohistiocytic” profile and were similar to those observed in other lesions rich in osteoclast-like giant cells. Flow cytometry revealed the diploid nature of the primary and the recurrent tumour. Atypical fibroxanthoma with osteoclast-like giant cells is a new variant of atypical fibroxanthoma that must be recognized by pathologists, since it can be confused with other benign and malignant tumours with a high proportion of multinucleate osteoclast-like giant cells. Key words: giant cell tumour; macrophage polykaryon; immunohistochemistry; flow cytometry.

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Atypical fibroxanthoma (AFX) is a solitary, nodular ulcerative, exophytic, dermal neoplasm with the histological features of pleomorphic malignant fibrous histiocytoma (PMFH) that occurs most commonly in the actinically-damaged skin of elderly people. Despite its malignant histological appearance, this tumour usually behaves in a benign fashion and complete excision is generally curative. AFX can recur; however, recurrences are not aggressive and almost all patients are cured by re-excision (1).

Wilson et al. (2) described a case which, containing numerous osteoclast-like cells, resembled malignant giant cell tumour of soft tissues (MGCTST), but in a more superficial location.

We here report a new case of AFX containing numerous osteoclast-like cells, with recurrence, and an immunohistochemical and DNA-flow cytometric analysis.

CASE REPORT

An 87-year-old woman presented with a 1-month history of a subepidermal nodular tumour on her forehead. The lesion was 0.8 cm in diameter and showed erosion in the centre. She had no other cutaneous lesions, and no history of previous trauma, and otherwise appeared healthy. The lesion was excised but subsequent pathological examination revealed that it reached the deep resection border. Six months later the tumour recurred as a firm yellowish well-demarcated subepidermal nodule 1.1 cm in diameter. This was excised with tumour-free surgical borders. Six months after the second operation the patient was well and showed no signs of tumour recurrence.

MATERIAL AND METHODS

The surgical excision specimens were fixed in 10% buffered formalin. Routinely processed paraffin sections were stained with haematoxylin and eosin and Perls’ Prussian blue method. Immunohistochemical staining were performed by the alkaline phosphatase anti-alkaline phosphatase (APAAP) method (3), using the APAAP soluble complex (Biomedical Corp., Foster City, CA).

Commercially available antibodies to the following antigens were used: vimentin (monoclonal, dilution 1:20, Biomeda, bovine S-100 protein (polyclonal, dilution 1:500, Dako), Gastrotrup, Denmark), HMB45 (monoclonal, prediluted, Biomeda), desmin (monoclonal, dilution 1:20, Dako), α-1-antitrypsin (polyclonal, dilution 1:500, Dako), α-1-antitrypsin (polyclonal, dilution 1:500, Dako), CD68 human macrophage (monoclonal, dilution 1:25, Dako), lysozyme (polyclonal, dilution 1:200, Dako), HCG (polyclonal, dilution 1:50, Dako), myoglobin (polyclonal, dilution 1:200, Dako), keratin cocktail ck3/22, wide range (monoclonal, prediluted, Biomeda), cytokeratin squamous and non-squamous pool (monoclonal, prediluted, Immunon, Pittsburgh, PA) and AE-1 (monoclonal, dilution 1:50, Dako).

The DNA content of the primary and recurrent tumours was determined by flow cytometry. A nuclear suspension from selected paraffin-embedded tissue blocks of the tumours was prepared using the method described by Hedley et al. (4), with certain modifications (5). A detailed description of this method has been reported previously (5). Ten thousand cells were analyzed with a Becton Dickinson FACS analyzer. The DNA index, G0+G1, S and G2+M phase fractions (PFs), and coefficient of variation (CV) for the G0+G1 peak were calculated using software supplied by Becton Dickinson (FACSSuite model). Inflammatory and stromal cells from the same specimens served as a control.

Pathological examination

The sections stained with haematoxylin and eosin showed a dermal neoplasm which, on primary excision, was covered with a partly eroded epidermis (Fig. 1) and extended downwards to the dermal margin of the surgical resection. The recurrent neoplasm showed a free area subepidermally with expansive growth borders and extended to the subcutaneous cell tissue but did not invade the frontal muscle. Both tumours were composed of numerous multinucleate osteoclast-like giant cells (Fig. 2), uniformly distributed within a second component consisting of mononuclear cells with polygonal, occasionally vacuolated cytoplasm and vesicular nuclei, which were slightly irregular, and occasionally bizarre with prominent acidophilic nuclei. Tumour growth was diffuse with no compartmentalization into nodules. The mitotic index was 6.3 mitoses per 1,000 cells (4 mitoses/hpf) in the primary tumour and 7.6 per 1,000 cells (5 mitoses/hpf) in the recurrent tumour. Mitoses were normal in configuration. The osteoclast-like giant cells showed no pleomorphism or mitosis. Also present were a small number of dispersed lymphoid cells, diffusely distributed hemosiderin pigment within the mononuclear cells or occurring freely in the stroma, and dispersed clusters of extravasated red blood cells, but necrosis was not observed. Solar elastosis was present in the dermis adjacent to the tumour.

The tumour cells failed to stain with immunohistochemical stains for keratins, S-100 protein, HMB45, HCG, myoglobin and desmin. Occasional mononuclear tumour cells were focally positive for α-1-antitrypsin, α-1-antitrypsin and CD68. These cells were positive for vimentin. The osteoclast-like giant cells stained positively for CD68. The mononuclear lymphoid cells in the stroma were positive for lysozyme.

The findings of the DNA analysis are summarized in Table 1 and Fig.
3. Primary and recurrent tumours were diploid, with an S PF > 10 in both lesions.

DISCUSSION
Different types of predominant cells may be found in AFXs, e.g. spindle-cells (7), pleomorphic giant cells (1) and osteoclast-like giant cells (2), as well as osteoid (8) and chondroid (2) production.

Osteoclasts are specialized multinucleate cells responsible for bone reabsorption which have been considered to form part of the mononuclear phagocyte system. They are formed by fusion of mononuclear precursor cells which are derived from pluripotent haemopoietic stem cells. Both osteoclasts and macrophage polykaryons are multinucleate cells which closely resemble each other morphologically and immunohistochemically. Osteoclasts express a restricted range of macrophage-associated antigens including CD68 (9) and also have a limited

Table I. Ploidy, phase fractions and coefficient of variation (CV)

<table>
<thead>
<tr>
<th>DNA index</th>
<th>Primary tumour 1 (diploid)</th>
<th>Recurrent tumour 1 (diploid)</th>
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<tbody>
<tr>
<td>Cell cycle statistics</td>
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<tr>
<td>- Phase fractions (%) -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G0 + G1</td>
<td>52.2</td>
<td>78.8</td>
</tr>
<tr>
<td>S</td>
<td>20.5</td>
<td>10.9</td>
</tr>
<tr>
<td>G2 + M</td>
<td>27.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Calculation parameters (Pop. 1)</td>
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<td></td>
</tr>
<tr>
<td>G1 CV</td>
<td>6.5</td>
<td>7.8</td>
</tr>
<tr>
<td>G2 + M/G1 ratio</td>
<td>2.02</td>
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phagocytic capacity (10). Direct evidence of bone reabsorption by macrophage polykaryons has recently been presented (11), showing that this is not a unique characteristic of osteoclasts.

Definitive characterization, however, must rely on a functional assessment of hormone responsiveness such as response to calcitonin. Contradictory results as to the origin of these cells have been reported in PMFH. They have been judged osteoclasts (12) and macrophage polykaryons (13). Since no specific marker for osteoclasts has been identified (9), we could not determine in our case whether the giant cells were osteoclasts or osteoclast-like. The bland cytology of these osteoclast-like giant cells and the absence of mitoses raise the suspicion that these cells are reactive rather than neoplastic. Local growth or differentiation factors, produced by the tumour, may stimulate the proliferation and differentiation of circulating precursor cells into osteoclast-like giant cells.

AFX with osteoclast-like giant cells appears very similar to the MGCTSP. Recently two cases of MGCTSP, presenting as ulcerating skin tumours of the arm and foot, have been reported (14). The tumours were relatively small and involved the entire dermis and subcutaneous tissue. Kutchemeshig et al. (15) described two cases of dermatofibroma with osteoclast-like giant cells that pursued a benign course without recurrence.

The immunohistochemical profile of AFX relies on the presence of diffuse staining for vimentin and negative staining for epithelial and melanocytic markers and desmin. Longacre et al. (16) have presented evidence for an immunohistological bimodal pattern in AFX, namely the “fibrohistiocytic” (CD68+, actin+) and the “myofibroblastic” (CD68−, actin+) phenotypes. Our immunohistochemical results are similar to the “fibrohistiocytic” pattern reported by these investigators.

Recurrence in our case was due to incomplete excision in the first operation. However, the recurrent tumour was not aggressive. Analysis of the histogram of the primary tumour (Fig. 3A) might lead us to believe that there is a second peak of a truly tetraploid cell population. Nevertheless, in this case, we consider that the second peak represents a G2+M fraction due to the existence of significant S/PF between the two peaks, 20.5%, a G2+M/4N ratio of 2.02 and the absence of the correspondent aneuploid G2+M population in the 8N position. The high S PF, which is common in aneuploid tumours, is also seen occasionally in some diploid tumours with giant cell patterns (17), without implying more aggressive biological behaviour; it simply represents a high proliferative activity, consistent with the high mitotic index found in both the primary and the recurrent tumour. Worrel et al. (18), in a study of the DNA ploidy of AFX, showed diploid distribution in 13 out of the 14 lesions studied. Their results suggested that AFX could be distinguished from PMFH on the basis of DNA content.

AFX with osteoclast-like giant cells is a histological variant of AFX which must be recognized because of the possibility of confusion with other benign and malignant tumours, characterized by a high number of osteoclast-like giant cells.

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