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Epithelioid haemangioendothelioma of the bone tissue

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Summary. An epithelioid haemangioendothelioma arising in a 43-year-old Japanese woman is presented. The patient first complained of severe back pain and neurogenic disturbances due to compression fracture of the spinal bone. Radiographically the tumour masses showed osteolytic lesions without reactive new bone formation. Similar lesions were noted in other bones. Biopsy and surgical specimens showed the features of epithelioid haemangioendothelioma. A lymphocyte associated antigen, HLA-DR which has been regarded as a B lymphocyte marker was detected in the tumour cells. The importance of this finding was emphasized with respect to the identification or classification of vascular tumours.

Key words: Bone tumour – Epithelioid haemangioendothelioma – HLA-DR antigen

Introduction

The epithelioid haemangioendothelioma (EH) is an uncommon vascular tumour in which individual tumour cells present in an apparently epithelial arrangement or growth pattern and produce large intracytoplasmic vacuoles compatible with a primitive vascular lumen. Originally this tumour had been referred to as "histiocytoid haemangioma of benign nature" (Rosai et al. 1979). Weiss and Enzinger have reviewed 41 cases arising in the soft tissue retrospectively and summarized the follow-up information (Weiss and Enzinger 1982). They have suggested a malignant potentiality and proposed the currently used nomenclature "epithelioid haemangioendothelioma". Because of its rare occurrence and resemblance to an epithelial tumour, the tumour may be misdiagnosed as a metastatic carcinoma or other neoplasm. To establish the differential diagnosis for EH, further clinicopathological data are needed.

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The elucidation of the histogenesis of EH is also an important subject. Recent advances in immunological technique have made it possible to define the histogenesis of several tumour lines. Well characterized surface antigens, if present, could be a useful tool for the differential diagnosis and histogenetic study of EH. In this report we describe the first case of primary EH arising in the bone that expressed HLA-DR antigen, a known marker of B lymphocytes. In addition to the clinicopathological characteristics of the lesion, resemblance of endothelial cell tumours and lymphocytes will be discussed.

Case report

The patient, a 43-year-old Japanese woman, had been well until October 1982 when she experienced back pain. She visited the Tsurumai Hospital on November 7 because of severe back pain. There was a compression fracture of third thoracic vertebra and the was admitted to the Chiba-Rosai Hospital on November 18. Her past history was unremarkable except for acute appendicitis at the age of 23. The family history was non-contributory.

Laboratory findings were as follows. The haemoglobin level was 10.8 g/dl; leukocyte count, 6800/mm^3; and platelet count, 33.2×10^4/mm^3. The serum glutamic-oxalacetic transaminase level was 14 U/L; alkaline phosphatase, 11.6 U/L; total bilirubin, 0.7 mg/dl; urea nitrogen, 13 mg/dl; and total protein, 6.4 g/dl. Serum level of calcium 4.3 mg/dl and other serum electrolytes were unremarkable.

Radiographically, lytic lesions were shown in the third thoracic vertebra, 1st and 2nd right ribs, right clavicle, and pelvic bone (Fig. 1). No reactive bone formation was observed. The lungs had no abnormal findings in X-ray films. A biopsy was performed on the right clavicle on December 8, which was reported as epithelioid haemangioendothelioma. On December 16, segmental sensory disturbance extending from the Th4 to its lower level, paralysis of both lower extremities, and dysuria appeared. Compression of spinal cord at the level of Th3 was observed by myelography. Laminectomy and tumour excision were performed on December 22. The patient received corticosteroid followed by local irradiation. All neurogenic disturbances disappeared 1 month after operation.

Materials and methods

Light microscopy. The surgical material was fixed in buffered formalin (pH 7.4) and embedded in paraffin. The following stains were used for 4 μm sections: haematoxylin and eosin (H &E), Weigert's elastic fiber stain, periodic acid-Schiff (PAS), Masson's trichrome, and silver impregnation for reticulin fiber.

Electron microscopy. A small portion of the surgical material was dissected in pieces and fixed in 3% glutaraldehyde, and postifxed in 1% osmium tetroxide, each for 90 min. The tissue blocks were embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and lead citrate and observed with a Hitachi 12 electron microscope.

Immunofluorescence study. Direct immunofluorescence study was performed on the biopsied materials. Fresh and unfixed specimens were placed into embedding medium (OCT, Miles Laboratories, Napervill, Ill). These were snape-frozen on liquid nitrogen and stored at $-60°$ C prior to sectioning. Frozen tissue sections were stained with FITC-conjugated anti-HLA-DR monoclonal antibodies (Becton Dickinson Inc.).

Immunohistochemical analysis for Factor VIII. To identify the Factor VIII related antigen, paraffin-embedded tissue sections were stained by using an immunoperoxidase staining kit (Ortho Diagnostic Systems Inc., NJ, USA) according to the procedure described in the manufacture's technical information sheet.

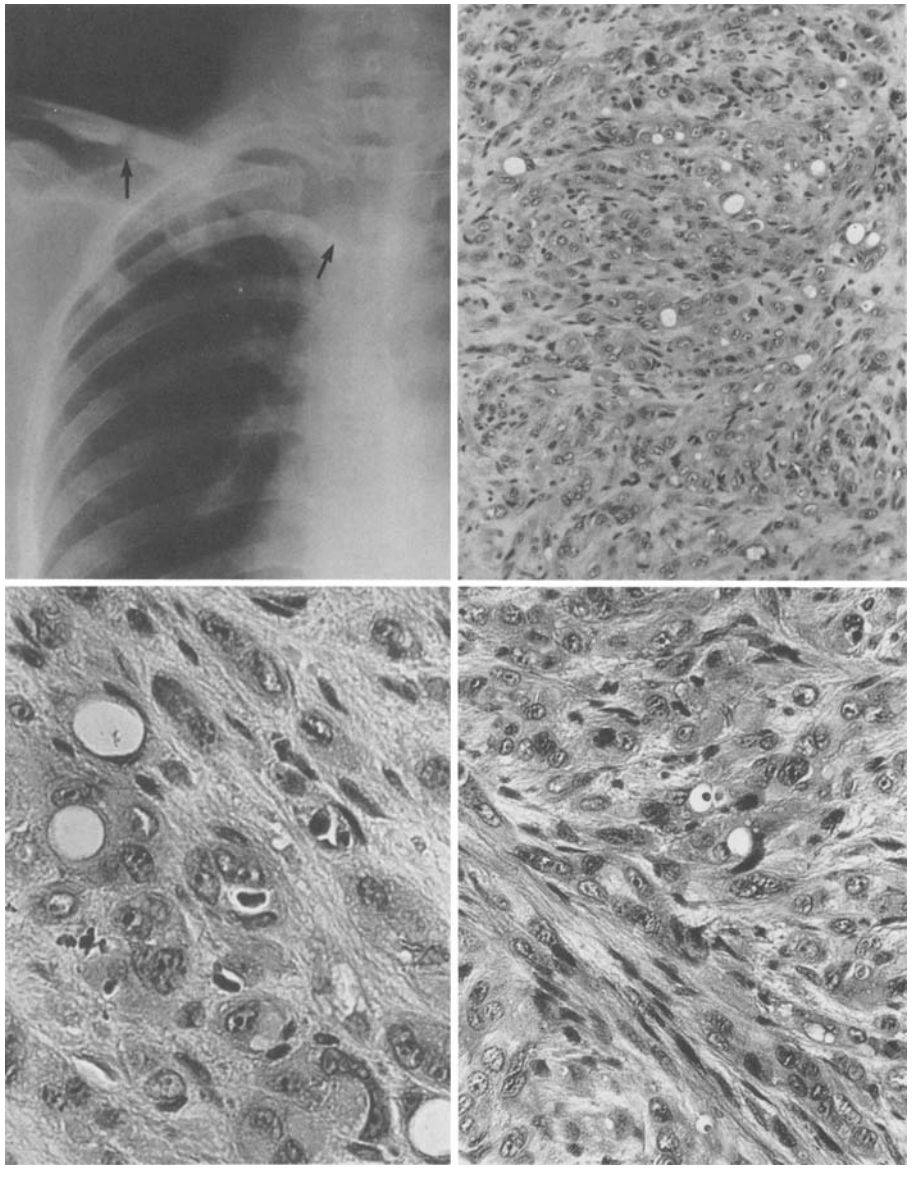

Fig. 1. Radiograph showing destructive change of vertebral (Th3) bone and osteolytic lesion of right clavicular bone (*arrows*)

Fig. 2. A portion of surgically removed tumour mass. Note characteristic epithelioid arrangements of tumour cells with frequent cytoplasmic vacuolization (H & E, ×100)

Fig. 3. A high power view of intracytoplasmic vacuoles (primitive blood vessels). Red blood cells can be seen within some vacuoles (H & E, ×400)

Fig. 4. A tumour cell cluster with a pattern resembling epithelioid leiomyoblastoma (H & E, ×200)

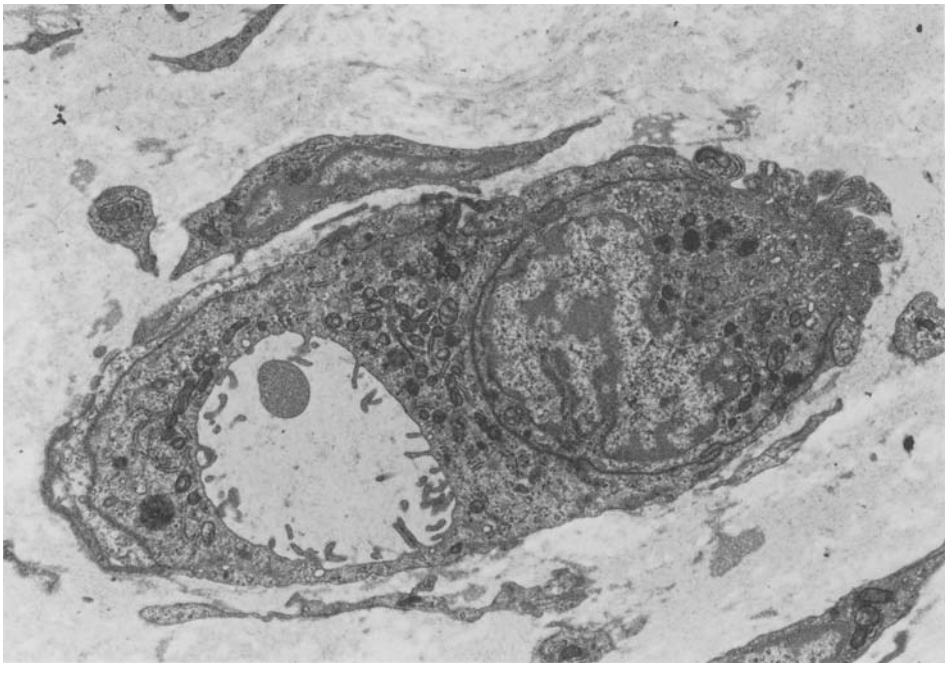

Fig. 5. Electron micrograph showing single cell vasculization (× 12,000)

Results

Histologically, the tumour was composed of spindle and/or oval cells proliferating in the hyaline stromal tissue. The cells were arranged in short cords or produced small cell clusters showing an epithelioid pattern in some areas (Fig. 2). They had an amphophilic or slightly eosinophilic cytoplasm, often with a fibrillar quality. The nucleus, with sparse chromatin, was round or oval and often located peripherally in the cytoplasm. Mitotic figures were only occasionally observed. The tumour cells were sometimes arranged in sheets, thereby resembling a pattern that is seen in epithelioid leiomyoblastoma. An angiocentric location of the tumour (Enzinger and Weiss 1983a) could not be confirmed. Characteristically, scattered tumour cells had a large intracytoplasmic vacuole that sometimes contained a red blood cell, indicating their vasoformative nature (Figs. 3 and 4). In some areas, distinctive vascular channels were formed by several cells. Occasionally, the cell clusters were dispersed in the oedematous stroma, resulting in a myxoid appearance.

Ultrastructurally, the cells usually contained a considerable amount of rough endoplasmic reticulum, mitochondria, vesicles, and dense lysosomal granules with heterogeneous contents. They were connected by junctional complexes and were surrounded by discontinuous basement membranes. It was reconfirmed that a large cystic vacuole occurred in a single cell (Fig. 5). Occasionally, many microvilli could be seen extending from the

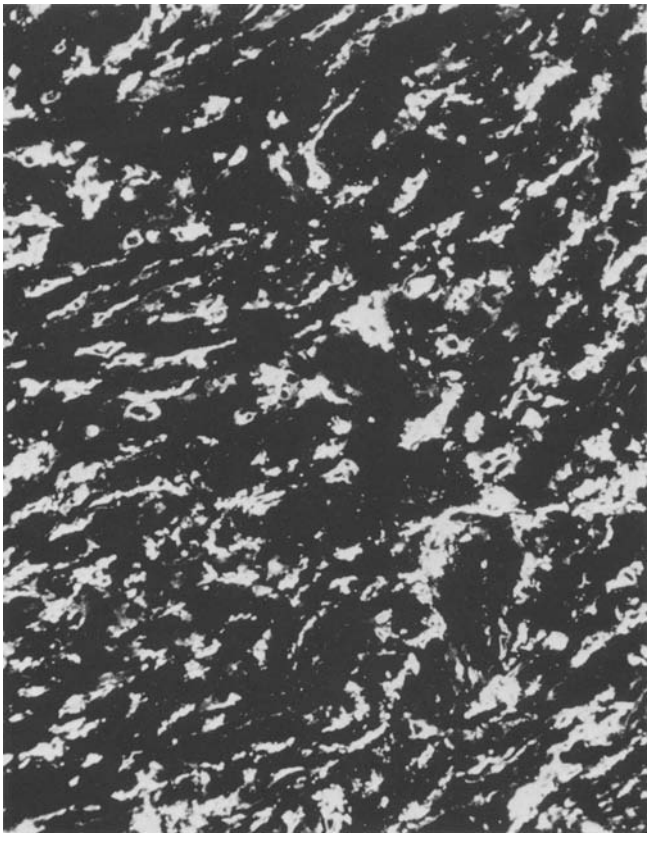

Fig. 6. Direct immunofluorescence demonstrating HLA-DR antigen in tumour cells (× 200)

wall into the lumen. No Weibel-Palade bodies were detected in the tumour cells so far examined. Immunoperoxidase staining for Factor VIII related antigen was strongly positive in tumour cells. The endothelial origin of the cells was demonstrated by the presence of Factor VIII related antigen.

To determine the mode of existence of HLA-DR antigen, immunofluorescence staining with FITC-anti-HLA-DR was performed. As shown in Fig. 6, most of tumour cells reacted distinctively with anti-HLA-DR monoclonal antibody.

Discussion

Weiss and Enzinger have established the entity of EH and have indicated a malignant potentiality (Weiss and Enzinger 1982). In their review the characteristic histological features are summarized as follows: 1) Proliferation of rounded, eosinophilic endothelial cells with a frequent cytoplasmic vacuolization, 2) a distinctive epithelial appearance, 3) a frequent angiocentric location, namely an intimate relation between the tumour and the venous

system, and 4) a myxohyaline stroma. The most frequent site of occurrence is the soft tissue of the extremity. Dahlin states that over one third of bone haemangioendotheliomas may occur in the long tubular bones (Dahlin 1978). However, it appears that there has been no reported case of primary EH of bone.

Schajowicz and co-workers summarized the clinical course of conventional haemangioendotheliomas. Most patients complained of pain and/or local swelling (Schajowicz et al. 1972). In EH, Weiss and Enzinger also found that the initial symptom is pain and a tender mass (Weiss and Enzinger 1982). In the present case, the initial symptom was back pain and neurogenic disturbance due to spinal cord compression by the tumor then followed. Osteolytic lesion of the spinal bone was observed in X-ray studies and was the largest of all lesions including the others found later. No tumour mass was seen in any other place except for bone. It presumed that the primary site is the spinal bone. Radiographical characteristic of conventional haemangioendotheliomas in bone shows osteolytic zones without any reactive new bone formation (Dahlin 1978) and similar osteolytic masses were shown in the present case.

A review of the follow-up study of 31 cases of EH showed that three developed local recurrences and six metastases (Weiss and Enzinger 1982). It is thus suggested that this unique tumour is a biologically "borderline" neoplasm. Because of its epithelioid appearance, the differential diagnosis from metastatic tumour is particularly important. Critical points for the differentiation may include the demonstration of a primitive vascular lumen formed by a single cell. The present case had these characteristics.

There are several tumours resembling EH other than metastatic carcinomas. For example the myxoid changes in the tumour may mimic some features of chondrosarcoma, myxoid liposarcoma, myxoid malignant schwannoma, or myxoid malignant fibrous histiocytoma. Rosai and coworkers described a group of disorders showing proliferation of endothelial cells and designated as histiocytoid haemangioma (Rosai et al. 1979). This entity encompasses EH. Another disorder to be differentiated is epithelioid leiomyoblastoma, in which the tumour cells show frequent cytoplasmic vacuolization and epithelioid arrangement (Kurman and Norris 1975). The presence of numerous myofilaments in the spindle cells along with the absence of vasoformative nature would be a distinctive clue for the differentiation.

The origin of EH has been assumed to be of endothelial cells because of its vasoformative character, especially the formation of vascular lumen by a single cell. Additionally a definitive marker, Factor VIII was positive in the present case. Recent advances in immunology have indicated a new connection between the vascular endothelium and lymphocytes. Several investigators have demonstrated that there exists a close similarity between endothelial cells and lymphocytes in terms of the cell membrane antigen expressed and their immunological functions (Hirschberg et al. 1980; Burger et al. 1982; Pober and Gimbrone 1982; Stastny and Nunez 1984). From the morphological aspect, it has also been reported that some diffuse histio-

cytic lymphomas resemble proliferating angioendotheliomatosis, and vice versa (Ansell et al. 1982; Enzinger and Weiss 1983b). In view of the facts, it is of considerable interest to examine whether the lymphocyte-associated antigens are expressed on the endothelial tumour cells or not. We therefore attempted to prove this by using monoclonal anti-HLA-DR serum. The identification of HLA-DR antigen on the tumour cells thus made has povided some new insights into the nature of haemangioendotheliomas. The result suggest that the relationship between vascular endothelial cells and lymphocytes should be further examined from the histogenetic aspect. It is also suggested that, as in lymphoma study, the detection of HLA-DR antigen could be supplementary tool for differentiating haemangioendotheliomas from other non-vascular tumours.

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