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Pathology of disappearing bone disease: a case report with immunohistochemical study

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Summary. *A case of disappearing bone disease of the proximal femur is reported with histopathological and immunohistochemical studies. There was a densely packed cellular tissue, positive to endothelial antibodies, in areas of massive bone destruction. A more differentiated vascular tissue was present where trabecular cancellous or cortical bone was preserved with only focal zones of accelerated bone remodelling. The self-limited course correlates well with two phases of evolution of the histopathological lesions with neoplastic-like proliferation of endothelial cells corresponding to the rapid and massive bone destruction, and a later differentiation of the cells in mature vascular structures, but still with accelerated bone resorption which is partly compensated by appositional activity.*

Résumé. *Nous décrivons un cas d'ostéolyse massive idiopathique localisée à l'extremitè proximale du fémur ainsi qu'une étude histopathologique et immunohistochimique. Là où il y a une plus grande destruction osseuse on observe un tissu avec des cellules en amas, ayant une réaction positive aux anticorps endotheliaux. Par contre il y a une plus grande différenciation vasculaire la où l'os spongieux et cortical ètait preservé avec seulement des petites zones ayant un remodelage osseux accéléré. L'évolution autolimitante de cette pathologie est mise en corrélation avec deux phases évolutives des lésions histopathologiques. En premier la proliferation des cellules endotheliales néoplasiques correspond à une énorme et rapide destruction de l'os, ensuite une differentiation successive des cellules en structures vasculaires matures, tandis que la resorption osseuse, est compensèe partiellement par une néoapposition.*

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Introduction

Several reviews of disappearing bone disease have been published [1, 5, 7, 8, 9, 13, 14, 16]. The bone lesions consist of thin walled vessels, like capillaries, filled with blood cells in the marrow spaces and in cortical bone [7]. The mechanism leading to massive osteolysis and the replacement of bone by vascular connective tissue is uncertain, particularly since few osteoclasts have been reported in the bone [2, 6, 10, 12].

Case report

A farmer, aged 55, had pain in the right hip for 6 months; radiographs showed a lytic area in the subtrochanteric region (Fig. 1 a). He refused operation, but 3 days later sustained a pathological fracture (Fig. 1 b). His general condition was good and laboratory investigations, including the alkaline phosphatase, were normal.

The fracture was treated with a dynamic hip screw plate, the lytic area being curetted and filled with acrylic cement. The histology showed bone haemangioma without malignant change.

One month later, he had acute pain; radiographs showed displacement of the cement mass, and extension of the lesion proximally and distally (Fig. 1 c). Bone destruction was rapid and 14 days later, there was further lysis (Fig. 1 d) which would not be expected in an haemangioma.

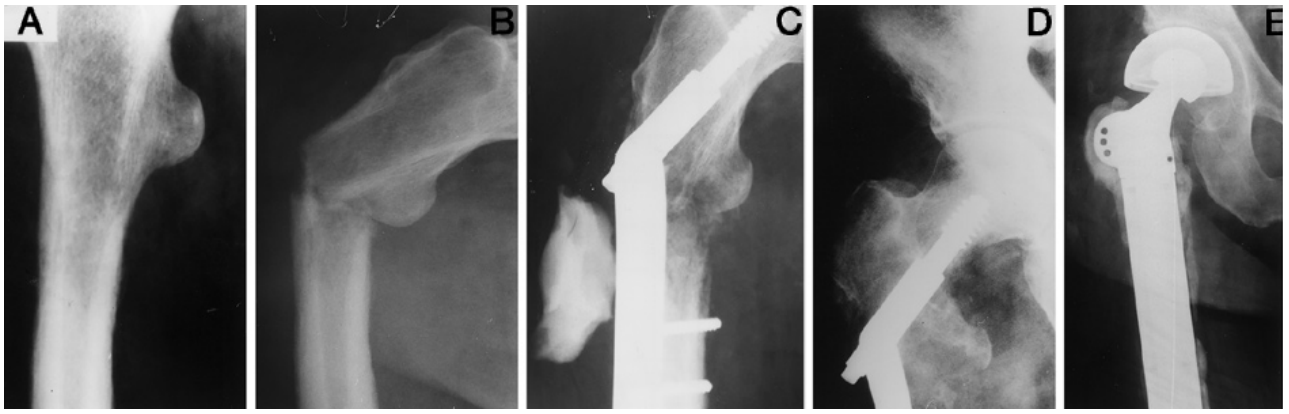


Fig. 1. a Radiograph showing a subtrochanteric lytic area with poorly defined edges. Pain had been present for 6 months. **b** Pathological fracture through the lytic area. **c** One month after operation, the device has failed and the cement is displaced. **d** Proximal and distal extension of the lesion during 2 weeks. **e** Four years after excision of the proximal femur and replacement with a prosthesis. An incomplete cortex has formed around the stem

Table 1. Immunohistochemical markers

Antigen	Source	Working dilution	Cell marked
F VIII	Biomeda (Foster City[b])	prediluted	Endothelia
CD3 1	Dako (Denmark)	1:20	Endothelia
ULEX[a]	Vector Lab (Burlingam[b])	1:200	Endothelia
KP1	Dako (Denmark)	1:50	Monocyte/ macrophage
CD3	Dako (Denmark)	1:20	T-lymphocyte
UCHL1	Biotest (Germany)	1:100	T-lymphocyte
L26	Dako (Denmark)	1:50	B lymphocyte
4KB5	Dako (Denmark)	1:50	B lymphocyte

[a] Lectin
[b] USA

Investigations showed no primary neoplasm in the extraskeletal organs, his general condition remained good and laboratory tests were normal. Because of the clinical course the proximal femur was resected and replaced with a prosthesis.

After 4 years, he was free of symptoms and radiographs showed no sign of recurrence of the lesion.

Histopathology

The resected femur was split in the frontal plane after removal of the plate and screws, decalcified in a solution of hydrochloric and acetic acid, and embedded in paraffin. Sections were stained with haematoxylin-eosin and studied immunohistochemically with the avidin-biotin-peroxidase complex technique [11]. The following markers were used: for endothelium factor VIII, CD3 1, Ulex; for histiocytes, KP1; for T-lymphocytes, CD3, UCHL1, and for B-lymphocytes, L26, 4KB5 (Table 1).

Two main histopathological appearances were seen:
(1) a densely packed cellular tissue was present in zones of the specimen where there was massive bone destruction (MOZ = massive osteolytic zones); this was confirmed by remnants of the original lamellar bone of the cortex, presenting a moth-eaten surface completely surrounded by pathological tissue (Fig. 2 a). The latter was characterised by cells with large nuclei and scanty cytoplasm, as well as capillary-like lumens. (2) zones where cancellous trabeculae or cortical bone were preserved (BSZ = bone structured zones) which presented with medullary spaces or large lacunae of the cortex occupied by vascular tissue formed by flattened or focally plump endothelial cells. These merged with a network of anastomosing thin-walled capillaries with irregular and often cystic spaces, and venous structures (Fig. 2 b, c). Lymphoid aggregates and

Table 2. Distribution of cellular immunoreactivity in relation to zones in the specimen and cell morphology

		Markers							
		F VIII	CD3 1	ULEX	CD3	UCHL1	L26	4KB5	KP1
MOZ	Densely-packed vascular tissue	+	+	+	–	–	–	–	–
	Lymphoid infiltrate	–	–	–	+	+	–	–	–
	Osteoclasts	–	–	–	–	–	–	–	+
BSZ	Differentiated vascular tissue	+	+	+	–	–	–	–	–
	Lymphoid infiltrate	–	–	–	+	+	–	–	–
	Osteoclasts	–	–	–	–	–	–	–	+

MOZ = massive osteolytic zones
BSZ = bone structured zones

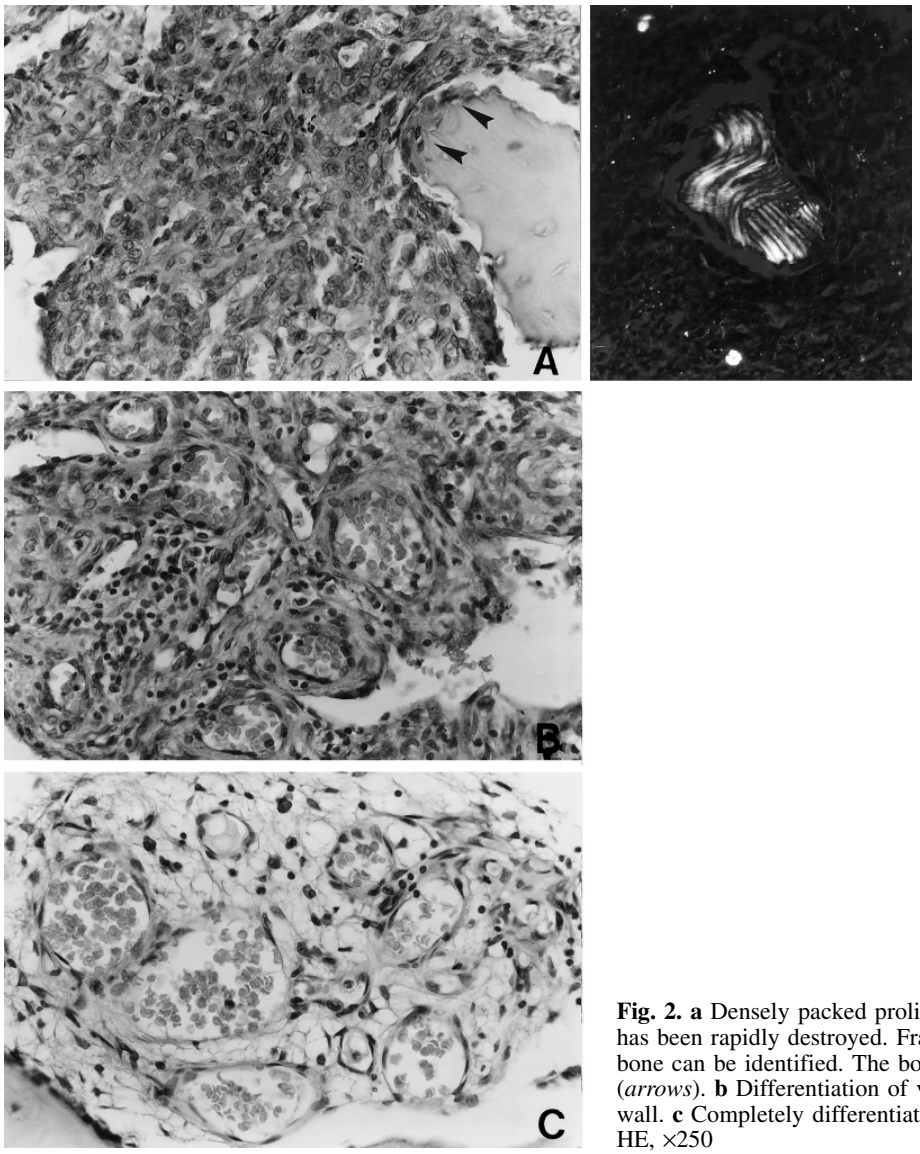


Fig. 2. a Densely packed proliferating cells in an area where bone has been rapidly destroyed. Fragments of original cortical lamellar bone can be identified. The bony surface is attacked by cells (*arrows*). **b** Differentiation of vessels with a multi-layered cellular wall. **c** Completely differentiated thin-walled capillary-like vessels. HE, ×250

perivascular plasma cells infiltrated the stroma (Fig. 2 b). Focal areas of accelerated bone remodelling were present with many osteoclasts lining the trabecular surface and cortical lacunae associated with wide appositional fronts (Fig. 3).

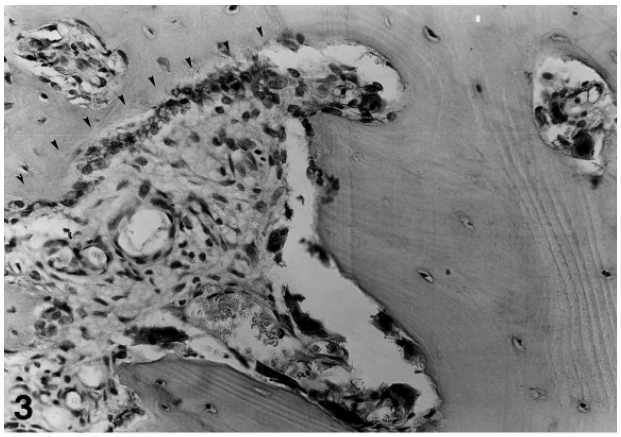
The compact tissue of the MOZ and the more differentiated vascular tissue of BSZ were both positive for the endothelial markers factor VIII, CD31 and Ulex (Fig. 4). Lymphoid aggregates and perivascular infiltrate reacted to markers CD3 and HCHL1 suggesting that T-lymphocytes were prevalent in the lymphoid component.

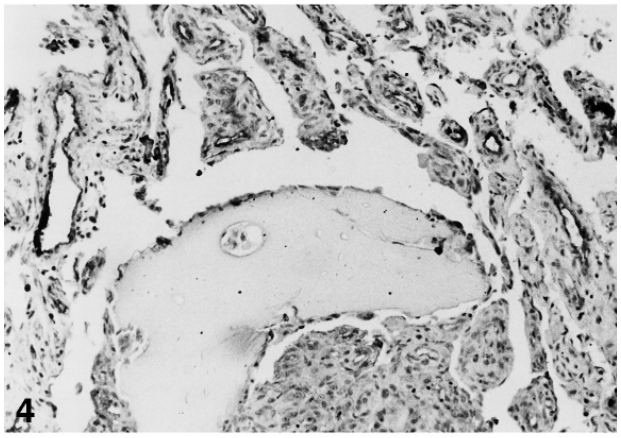
Osteoclasts (Fig. 5) and interstitial monocytes were KP1 positive (Table 2).

Discussion

The extensive bone destruction in disappearing bone disease is related to the angioma- or lymphangioma-like tissue reported in most studies [2, 6]. In a few cases, vascular proliferation also involved the skin and soft tissues overlying the bony lesion [5, 8, 9, 15]. The mechanism leading to the massive bone resorption is still not explained because increased osteoclastic activity has not been described [6, 10, 12].

Our case shows new histopathological features which have not been previously described. Densely packed cellular tissue was associated with the massive osteolysis. The moth-eaten appearance of the surface of remnants of cortical bone which are scattered in this tissue is peculiar to osteoclastic bone resorption. These features indicate that there must have been an earlier phase of intense osteoclastic activity. The immunohistochemical study confirmed the endothelial nature of this neoplastic-





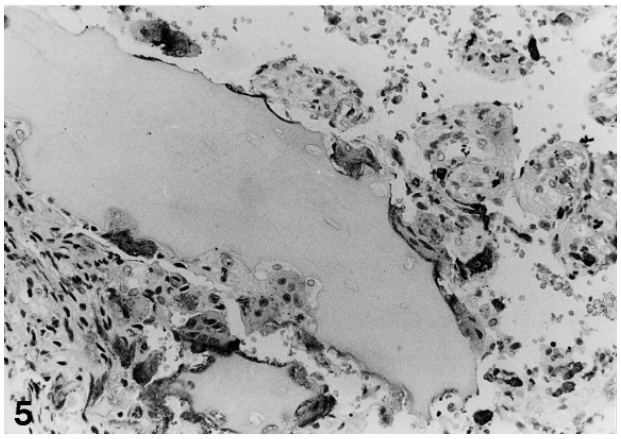


Fig. 3. Area of accelerated bone remodelling with numerous osteoclasts and a front of osteoblastic apposition (*arrows*). The marrow spaces are occupied by incompletely differentiated vascular tissue. HE, ×250

Fig. 4. Vascular channels with a CD31 endothelial layer. ABC-peroxidase, DAB-haematoxylin, ×200

Fig. 5. Resorption of a fragment of cortical bone by numerous KP1-positive osteoclasts. Vascular proliferative tissue surrounds the bone. ABC-peroxidase, DAB-haematoxylin, ×400

like proliferation which showed the same reaction to antibodies factor VIII, CD31 and Ulex as the more differentiated vascular tissue of BSZ. In this tissue, increased remodelling was limited to focal areas, and the number of osteoclasts or rate of resorption is not sufficient to produce the bone loss of the MOZ.

The lymphoid infiltrate of T-lymphocytes seems peculiar to disappearing bone disease and suggests an immunological cell-mediated mechanism of bone destruction. The production of lymphokines by T-lymphocytes could induce recruitment of activated monocyte and macrophage elements, and of osteoclasts. On the contrary, the usual angiomatous lesions of bone are formed by thin-walled vessels without perivascular cellularity and inflammatory infiltration. They typically show a slowly progressive lysis, and not the rapid and massive resorption of disappearing bone disease.

In our case, it was possible to correlate the rapid radiographic progress of the lytic lesion with the histopathological findings. Bone resorption was massive in the areas of solid tissue which had completely replaced the original cortical bone, where the vascular tissue was more differentiated while the process of accelerated bone remodelling was prevalent.

The vascular proliferation does not have malignant characteristics which is in keeping with the self-limiting course of disappearing bone disease [3, 4]. The reported histological findings make it possible to suggest an evolving type of disease, a first phase characterised by neoplastic-like proliferation of endothelial cells corresponding to the massive bone destruction and a second phase with better differentiated vascular structures, where bone resorption is still accelerated but partly compensated by appositional activity.

In several reports, osteoclasts have not been observed on bony surfaces in spite of the radiographic appearance of massive osteolysis [6, 10, 12]. Hypotheses have been advanced to explain the role of mononuclear perivascular cells and hydrolytic enzyme activation as due to hypoxia and low pH stimulated by the slowed blood flow in the capillary-like network [10]. This contrasts with the view that bone resorption is carried out by osteoclasts. If the evolving pattern we have suggested is correct, the latter histological features can be explained because the examination was carried out when the disease was already in a quiescent phase with exhaustion of resorption and bone remodelling becoming normal. In this case only thin-walled well differentiated vessels remain in the medullary and lacunar spaces in the bone. Conse-

quently, it is possible that the disease might be successfully treated with radiotherapy [3] or cytotoxic drugs in the first phase, but no effect could be expected in the second phase.

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