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A NEUROENDOCRINE CAUSE OF ONCOGENIC OSTEOMALACIA

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SUMMARY

All definite cases of oncogenic osteomalacia have, until now, been classified as mesenchymal tumours. We report here a case of oncogenic osteomalacia caused by a spinal tumour. Microscopically, it resembled the mixed connective tissue variant of previously described phosphaturic tumours. Immunohistochemical studies, however, showed the tumour cells to be positive for low molecular weight cytokeratin (CAM 5.2), S100 protein, PGP 9.5, and synaptophysin. Electron microscopy demonstrated neurosecretory granules. The histopathological findings strongly suggest that this is a neuroendocrine tumour.

KEY WORDS—Oncogenic osteomalacia, neuroendocrine, synaptophysin.

INTRODUCTION

Oncogenic osteomalacia (or rickets) can be defined as osteomalacia with hypophosphataemia due to a renal phosphate leak, associated with a tumour, which if totally resected results in cure.[1] Despite normal levels of PTH, 1,25-dihydroxy-vitamin D concentrations are characteristically low, due to decreased 1-alpha-hydroxylation in the proximal nephron.[2–4] So far, over 70 definite cases have been published.[5] Considerable confusion in classifying these tumours has persisted over the years, although a recent review of 17 cases divided them into four morphological types, the commonest of which was a mixed connective tissue tumour with prominent vascular and osteoclast-like giant cell components. The other three types resembled known bone tumours and were labelled as osteoblastoma-like, non-ossifying fibroma-like, and ossifying fibroma-like.[6]

In this paper, we describe a case of oncogenic osteomalacia in association with a spinal tumour of neuroendocrine origin.

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CASE REPORT

Clinical history

A 33-year-old woman was first seen in the rheumatology department in February 1988 giving a 10-month history of low back pain. All blood investigations were reported as 'normal', as were a plain X-ray of her lumbosacral spine, a lumbar myelogram, and a CT scan of her pelvis. She continued to deteriorate and by October 1988 she had generalized bone pains and was limited to walking with crutches. A bone scan showed increased uptake of isotope in the femoral heads and several ribs. A chest X-ray confirmed the presence of rib fractures and one of these was biopsied. This was reported as showing 'hyperosteoidosis' and she was referred to the Metabolic Unit in February 1989 for further investigation. Her serum phosphate was noted to be low at 0·4 mmol/l (normal 0·8–1·45) and in retrospect had been low for 12 months. $TmPO_4/GFR$[7] was also reduced at 0·45 mmol/l (normal 0·8–1·35). Serum calcium, alkaline phosphatase and parathormone levels were all normal. Urine chromatography demonstrated glycinuria. An iliac crest bone biopsy confirmed severe osteomalacia with complete absence of a mineralization front. Treatment was

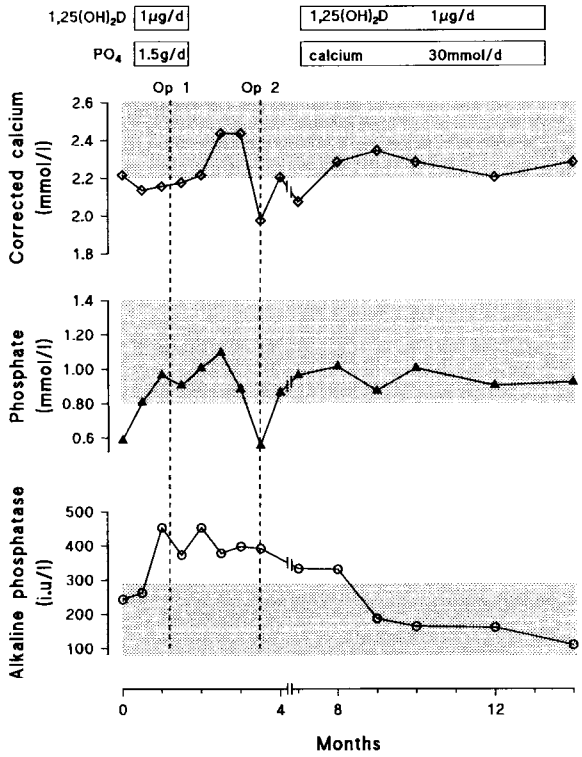


Fig. 1—Summary of serum biochemistry before diagnosis and in response to treatment. The vertical dashed lines represent the two operations for tumour excision. Medical therapy is shown along the top

started with 1 mcg of $1,25(OH)_2D$ and phosphate supplements (64·4 mmol phosphorus daily). Two weeks later, she presented with weakness of her legs and on examination had signs of spinal cord compression at the T3/4 level. An MRI scan showed an extradural lobulated tumour compressing the spinal cord. A subtotal removal of the tumour was performed: within 2 weeks, the patient was walking and the serum phosphorus was normal (Fig. 1). One month later, the patient relapsed with features of paraparesis and a CT myelogram showed a large tumour recurrence. Fortunately, a good clinical response was seen following extensive tumour excision and a course of radiotherapy (Fig. 1). In view of the severe osteomalacia, she was treated for 8 months with 1 mcg of $1,25(OH)_2D$ and 40 mmol calcium supplements daily. Complete healing of the osteomalacia was documented histologically. Twelve months post-operatively, the patient remains well and is able to walk unassisted. Serum phosphate, calcium, alkaline phosphatase and TmP/GFR remain normal despite withdrawal of $1,25(OH)_2D$ and calcium supplements.

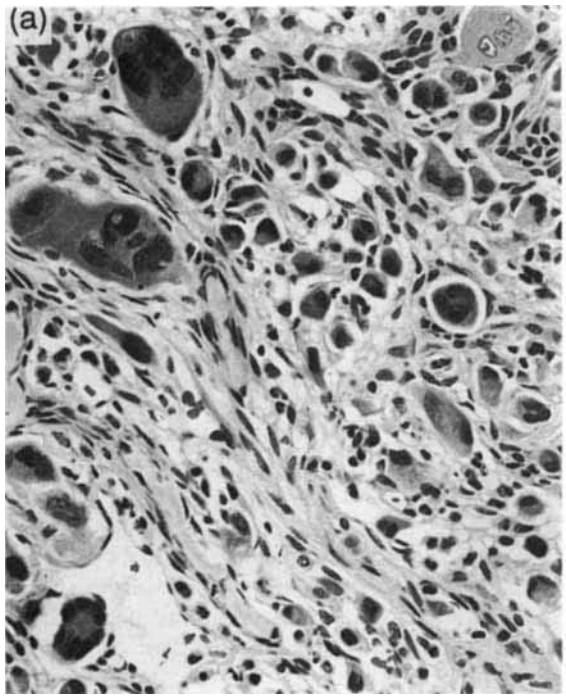
Histopathology

Macroscopically, the tumour presented as a lobulated brownish mass approximately 5 cm in diameter compressing the spinal cord and invading adjacent vertebral bodies and ribs.

Microscopically, the tumour was composed of sheets of multinucleated giant cells as well as mononuclear cells having similar cytoplasmic and nuclear cytological features. These cells were characterized by granular eosinophilic cytoplasm; the nuclei were rounded or oval with a finely granular chromatin pattern and some contained a single nucleolus. No mitoses were seen. A small population of spindle cells was admixed with the other tumour cells. The vasculature of the tumour was prominent with numerous thin-walled vessels. (Figs 2a and 2b). Two vessels contained tumour cells within their lumina and there were small areas of necrosis in some tumour fragments.

The histological diagnosis of a mesenchymal tumour of bone was initially considered. Immunohistochemical studies were performed, however, which showed the tumour cells to be positive for cytokeratin, both in the mononuclear cells and in a proportion of the multinucleate cells as shown in Fig. 3 (CAM 5.2, low molecular weight). A proportion of cells were positively stained by antisera to S100 protein (Fig. 4). and PGP 9.5 (a marker of neuroendocrine phenotype; Fig. 5). Focal positivity for synaptophysin, a neuroendocrine marker specific for neuroendocrine granules, was also demonstrated (Fig. 6). The tumour cells were negative for desmin and alpha-1-antitrypsin.

These results suggested a neuroendocrine tumour origin. Electron microscopy was performed on the tumour tissue, but due to initial formalin fixation, the results achieved were not optimal. Two main populations of cells could be identified. The first was an osteoclast-type cell with a ruffled border bearing microvilli, containing large quantities of rough endoplasmic reticulum and prominent lysosomes. The second type was of similar size but without microvilli on the surface and with prominent intermediate filament bundles and small numbers of 170 nm neurosecretory granules in the cytoplasm (Fig. 7). It is this second population of cells within the tumour which is responsible for the positive immunohistochemistry, with epithelial and neural markers, indicating a neuroepithelial lineage.



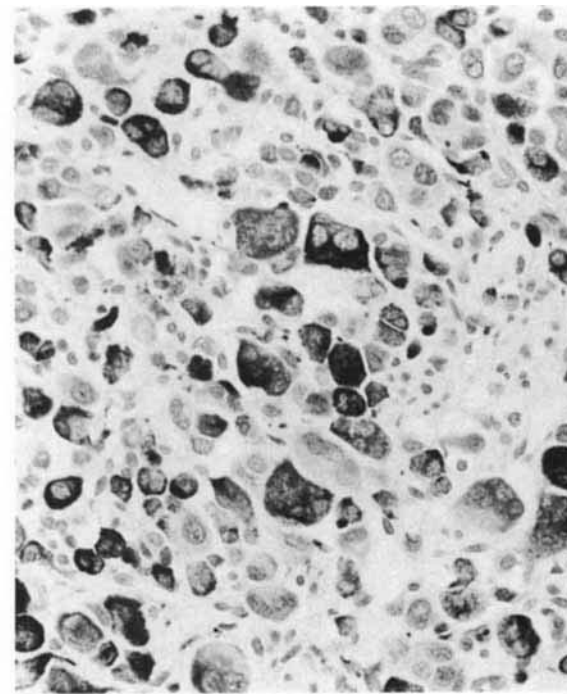


Fig. 3—Strong cytoplasmic immunoreactivity of both mononuclear and multinucleate cells with cytokeratin (CAM 5.2)

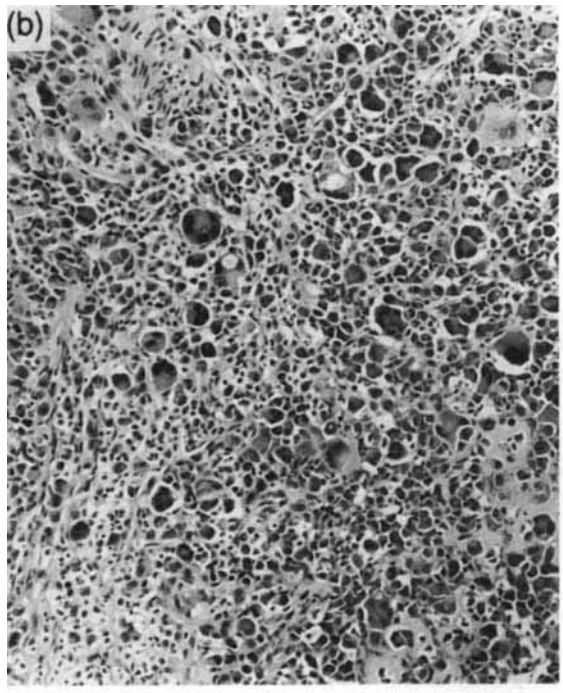


Fig. 2—(a) Tumour showing spindle cells as well as multinucleate giant cells. (b) At lower magnification, areas composed of sheets of mononuclear cells were prominent

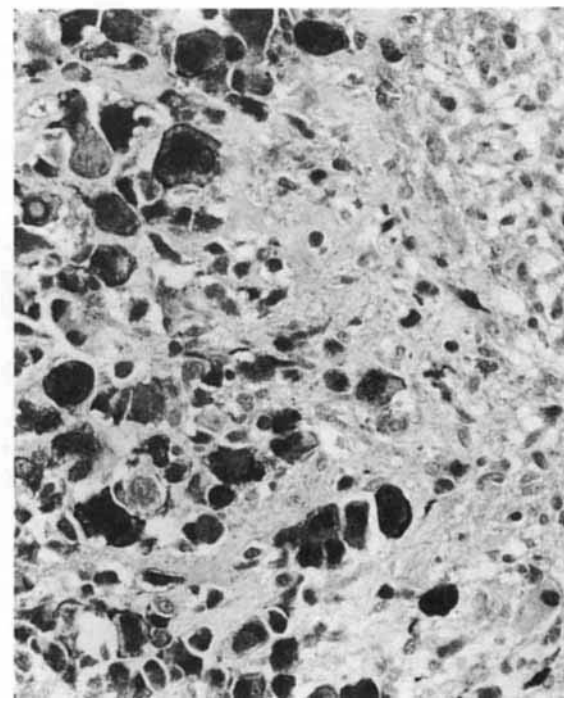


Fig. 4—S100-positive cells in the tumour (anti-S100 protein)

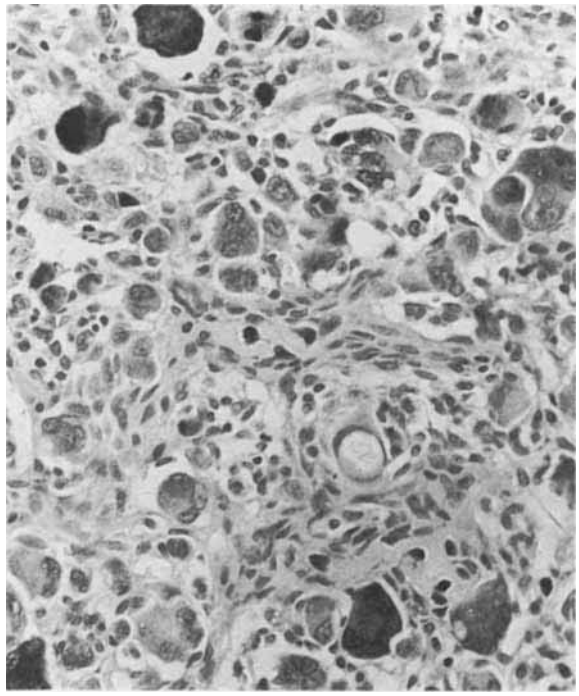


Fig. 5—Strong immunoreactivity of some cells for PGP 9.5 (anti-PGP 9.5)

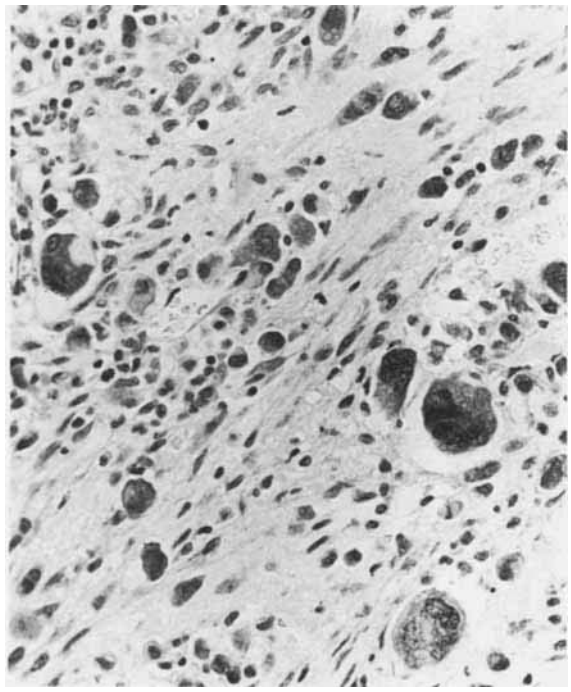


Fig. 6—Faint granular cytoplasmic staining of mononuclear cells for synaptophysin (anti-synaptophysin)

Fig. 7—Electron micrograph of part of cell showing intermediate filaments and neurosecretory granules

DISCUSSION

We believe that this is the first report of a neuroendocrine tumour causing oncogenic osteomalacia. Until now, all definite cases have been characterized as mesenchymal tumours. Other tumour types have been associated with hypophosphataemic osteomalacia, but in all such cases metastases were present so that cause and effect could not be proven.[8,9] This is a genuine case of oncogenic osteomalacia since removal of the tumour has resulted in cure. The patient did receive calcium and $1,25(OH)_2D$ supplements for several months postoperatively to ensure optimum bone healing in the context of severe bone disease. No relapse has occurred since withdrawal of medical treatment and a repeat bone biopsy has confirmed resolution of the osteomalacia.

It is particularly interesting that many of the histological features of this neuroendocrine tumour are shared with those of the mixed connective tissue variant of the phosphaturic mesenchymal tumours described by Weidner *et al.*[6] The three cardinal features of these tumours are primitive-appearing stromal cells, prominent vascularity, and osteoclast-like giant cells. Indeed before immunohistochemistry, our tumour was labelled as being mesenchymal in origin. This case may genuinely represent the first reported neuroendocrine tumour to cause this syndrome. Alternatively, there are other tumours already reported which have not been subjected to modern immunohistochemistry which might have been of neuroendocrine origin. Documented tumours which have been studied with immunohistochemical methods have shown vimentin reactivity of tumour cells.[6,10,11] One tumour was found to be S100-positive.[10] The case reported here is the first to demonstrate cytokeratin immunoreactivity in tumour cells, previous cases never having shown cytokeratin reactivity.[6,10–12] This may be because the cytokeratin antibody that we used

(CAM 5.2) detects a less well-differentiated epithelial type and is found in neuroendocrine tumours.[13] The antibody to high molecular weight cytokeratins used in the cases previously reported to be negative reacts with more terminally differentiated epithelial cells. Stains for neuroendocrine and nerve sheath cells have also been negative,[11] but no tumour, so far reported, has been tested for the presence of synaptophysin, thought to be a glycoprotein specific to neuroendocrine granules[14] and which was strongly positive in this case. The presence of PGP 9.5 immunoreactivity is also supportive, but not diagnostic, of a neuroendocrine phenotype.[15] Of the tumours which have been studied with electron microscopy, no neurosecretory granules have been reported.[5,6,10,12]

In conclusion, the immunohistochemical profile exhibited by this tumour, together with the findings on electron microscopy, is strongly suggestive of a neuroepithelial origin giving rise to a neuroendocrine tumour causing oncogenic osteomalacia. It is now important that other lesions causing the syndrome with the appearance of the previously described mesenchymal tumours are subjected to similar immunohistochemical investigation. As yet, the nature of any putative secreted endocrine factor remains uncertain and was not investigated in this case.

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