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Haemangioma of the Parathyroid Gland. Does it Really Exist?

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Abstract We are reporting a case of a capillary haemangioma-like proliferation arising within a parathyroid gland adenoma, associated with primary hyperparathyroidism. The vessel proliferation bearing a close resemblance to a capillary haemangioma consisted of tightly packed capillaries, endothelial buds and occasional small caliber muscle-containing vessels. The observation expands the spectrum of tumour-associated vascular proliferations by adding an exuberant haemangioma-like pattern to its extreme end. These are a heterogeneous group of lesions reportedly induced by aberrant production of angiogenic factors. We investigated expression of VEGF, pKDR, FGF2, HIF1α and HIF2α and only VEGF gave a strong positive reaction in the adenoma cells entrapped in the vascular meshwork. Although this does not constitute a proof that aberrant VEGF production was a causative agent, unexpected supportive evidence for its pathogenic role emerged from a failure to detect chromogranin A. Chromogranin A is a precursor of several regulatory proteins, including vasostatin I, a multilevel suppressor of VEGF. The production of vasostatin I may have been reduced in a chromogranin A-negative adenoma which could lead to a loss of its opposing effect on VEGF–regulated processes. The only two other published cases of haemangioma of the parathyroid gland were reported in patients diagnosed with primary parathyroid hyperplasia with hyperparathyroidism, a pathophysiologic condition similar to our case. Therefore we raise the question whether these tumours could also represent a reactive phenomenon.

Keywords Parathyroid gland · Chromogranin A · Haemangioma · VEGF · Tumour-associated vascular proliferations

Introduction

Parathyroid glands are usually surgically removed in cases of parathyroid hyperplasia or endocrine cell neoplasia. Other diagnoses such as developmental anomalies and pseudo-tumours are extremely rare [1, 2]. Mesenchymal tumours of the parathyroid gland are neither recognized by reputable surgical pathology textbooks [1, 2] nor by WHO classification of endocrine tumours [3].

Herein we are presenting a unique parathyroid tumour composed of two distinct components—a typical parathyroid adenoma and a capillary haemangioma-like proliferation.

Materials and Methods

An excision biopsy of the parathyroid gland was routinely processed after 24 h fixation in 10% buffered formalin, embedded in paraffin, sectioned at 4 μm and stained with hematoxylin-eosin. Primary antibodies used for immunohistochemical investigations were as follows (clone, dilution, source): pancytokeratins (AE1/AE3,1:50, DAKO), Chromogranin A (polyclonal, 1:1,000, DAKO, Cambridge,

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UK), Synaptophysin (27G12, 1:20, Novocastra, Newcastle, UK), CD31 (JC70A, 1:20, DAKO) and smooth muscle actin (1A4, 1:500, DAKO).

The immunoreactions detecting angiogenic factors were carried out in the Nuffield Department of Clinical Laboratory Sciences, Oxford, UK - VEGF (VG1, 5 μg/ml, DAKO), pKDR (PKDR34a NDCLS, 2 μg/ml, produced in house), FGF2 (polyclonal, 1:200, Santa Cruz, U.S.A.), HIF1α (54, 1:100, BD Transduction Laboratories, U.S.A.), HIF2α (EP190b, 5 μg/ml, DAKO). Antibodies VG1, HIF1α and HIF2α required high temperature antigen retrieval in pH 9.0 Tris /EDTA buffer prior to application.

Products of the immunohistochemical reactions were detected by the DAKO visualization systems ultraView or Envision, respectively, with diaminobenzidine as a chromogen.

Case Report

A 53-year-old male with a clinical history of hypertension, diabetes mellitus type 2, decreased phosphate level for 8 years and borderline calcium level for 3 years underwent a screening examination, which revealed hypercalcemia and also an increased level of parathyroid hormone. This prompted an ultrasound examination, which showed a hypervascular extrathyroid nodule at the lower left pole of the thyroid measuring 20×16×10 mm, assessed as a parathyroid adenoma. The tumour was surgically removed without prior FNA procedure. The removal resulted in the immediate return of calcium and parathyroid hormone to normal limits. The patient remains well and free of laboratory and clinical symptoms of hyperparathyroidism three months after surgery.

Pathological Findings

Several tan-brown pieces of parathyroid tissue weighing 1.02 g and measuring 20×18×4 mm in aggregate were submitted for histological examination. This showed solid, fat-free parathyroid tissue endowed with a thin fibrous capsule consistent with a chief cell adenoma, a small fragment of normal fat-containing parathyroid gland and thyroid gland tissue.

Approximately two thirds of the adenoma was replaced by tightly packed capillaries, endothelial buds and occasional small caliber muscle-containing vessels without evidence of endothelial atypia or mitotic activity, bearing close resemblance to a capillary haemangioma. Small sheets and nests of adenoma cells were entrapped in the vascular network. These showed a tendency to transition into smaller cells with hyperchromatic nuclei and a hardly distinguishable rim of cytoplasm (Fig. 1). Their appearances resembled ‘crushed cells’ but some cellular nests differed clearly from more typical adenoma cells in expression of vascular endothelial growth factor (VEGF).

The adenoma cells expressed cytokeratins (Fig. 2) but not chromogranin A or synapthophysin either in the affected or the unaffected parts of the adenoma in repeated reactions with positive internal (normal parathyroid gland) and external controls (pheochomocytoma). The endothelial cells expressed CD31 (Fig. 3) and infrequent small caliber vessels gave in addition a reaction for smooth muscle actin.

Immunohistochemical studies of angiogenic factors showed strong expression of VEGF in the endothelium and in a proportion of adenoma cells, particularly ‘the small cells’, creating a girland-like pattern clearly contrasting with only a weak expression in the typical adenoma chief cells (Fig. 4). However, we could not exclude an artifact due to shrinkage of otherwise weakly VEGF positive cytoplasm.

The pattern was similar to the image of VEGF A expression demonstrated by Garcia et al. [4] who, however, did not comment on the cytology of strongly positive cells. pKDR (phosphorylated VEGF receptor) showed inconsistent and weak nuclear expression in endothelial cells. FGF2, hypoxia-inducible factors 1α and 2α (HIF1α and HIF2α) yielded negative results.

Discussion

In 1996 Merino et al. demonstrated two cases of a mass-forming vascular proliferation in the parathyroid glands both of which were associated with primary hyperparathy-

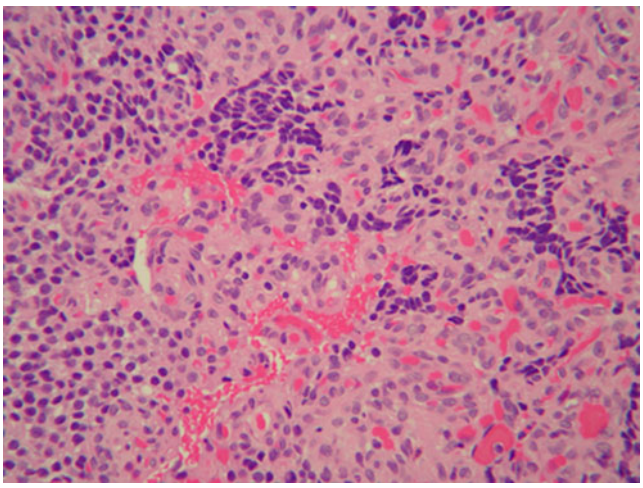

Fig. 1 Capillary haemangioma-like proliferation with entrapped nests of adenoma cells (*left*) with transition into ‘crushed small cells’ (*middle*). Hematoxylin-eosin stain. 200×

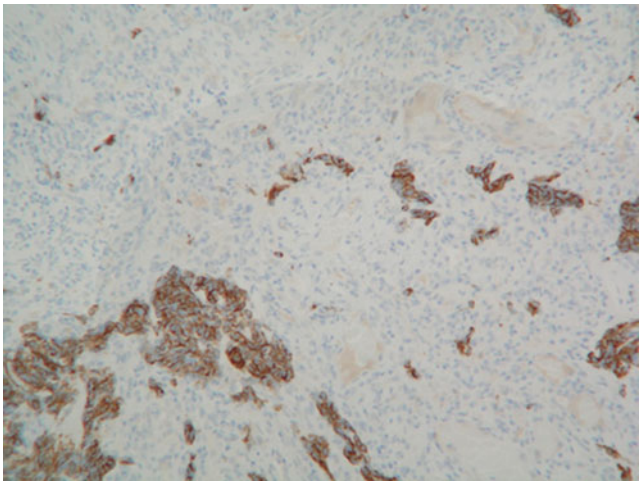

Fig. 2 Immunohistochemical detection of cytokeratins (clone AE1-3) highlighting adenoma cells. 100×

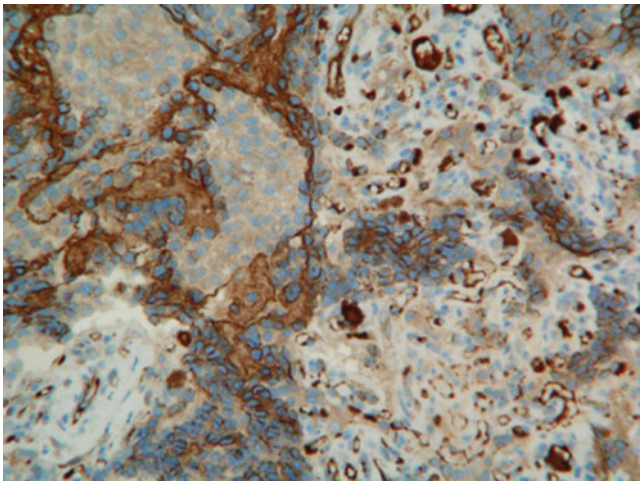

Fig. 4 Strong immunohistochemical expression of VEGF in sheets of adenoma cells (*upper left*) and 'crushed small cells'creating a girland-like pattern (*lower right*) and in the endothelial cells highlighting the vascular lumina. 400×

roidism as a result of primary chief cell hyperplasia [5]. The lesions were designated a capillary haemangioma and a cavernous haemangioma. However, advances in understanding angiogenesis have opened up the way for an alternative interpretation as tumour-related vascular proliferations arising in response to secretion of angiogenic factors.

Examples of tumour-associated vascular proliferations related to both endocrine and non-endocrine tumours are well-documented. In 1995 Gaudin et al. published a series of neuroendocrine and neural tumours remarkable for a prominent vascular proliferation within the neoplastic parenchyma [6]. Two papers published in 1998 and 2001 documented six cases of intracapsular vascular proliferations in the vicinity of penetrating neoplastic buds of encapsulated thyroid gland carcinomas [7, 8]. In reply to the latter, Vodovnik reported a case of vascular proliferation associated with a thyroid gland paraganglioma with a vessel proliferation engulfing neoplastic cells or their nests (Zellballen) [9]. In 2006 Kuhn et al. described five cases of an angioleiomyoma-like proliferation associated with renal cell carcinomas, and discussed another four cases reported previously, including one renal angiomyoadenomatous tumour [10]. The mesenchymal proliferations contained capillaries, muscle-coated vessels and bundles of smooth muscle both at the periphery of the tumours and within the tumours themselves. The authors commented that the vascular proliferations might be related to secretion of angiogenic factors by the neoplastic cells [6, 10] or the mesenchymal cells in response to invasion [9]. However, no special studies were carried out.

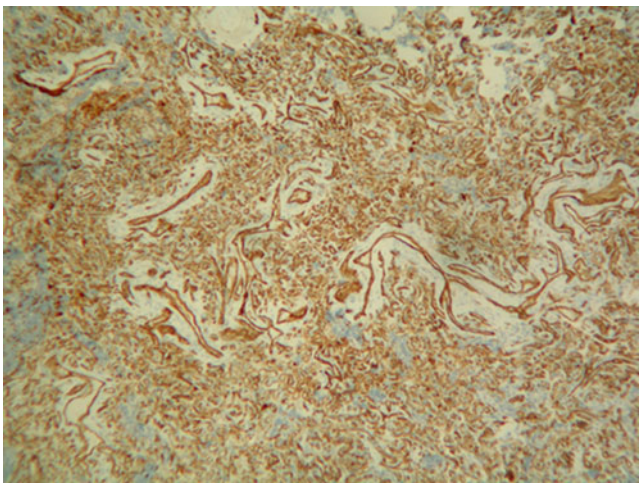

Fig. 3 Immunohistochemical detection of antigen CD31 documenting the vascular nature of the proliferation. 100×

In the parathyroid glands, an increased microvascular density associated with endocrine proliferative lesions such as primary or secondary hyperplasia, adenoma or carcinoma is a recognized phenomenon elicited by a complex interplay between pro- and anti-angiogenic factors [11–15]. It is more than tempting to speculate that in its extreme the vessel proliferation can acquire a haemangioma-like morphology.

In the presented case we had an opportunity to investigate not only VEGF and its activated receptor but also the expression of their up-stream regulators HIF1α and HIF2α. The observed co-expression of VEGF in endothelial cells and a subpopulation of adenoma cells along with expression of pKDR in endothelial cells suggest that in the presented case VEGF might be a driving angiogenic force. Immunohistochemical detection of HIF1α and HIF2α failed to prove that ischemia could be a triggering mechanism. The negative reaction with anti-FGF2 antibody

was unexpected, as FGF2 was a major angiogenic factor in proliferative parathyroid lesions in other studies [4, 13, 15]. Admittedly, the informative value of our investigations is compromised by the facts that there were no external controls available and no comparisons could be made between the expression of angiogenic factors in the adenoma cells entrapped in the vascular meshwork, the chief cells of the unaffected part of the adenoma or normal parathyroid gland tissue mainly due to the disappearance of tissue from the paraffin block during the process of re-cutting.

The lack of chromogranin A expression was surprising. On the other hand, this peculiarity offers an intriguing clue for pathogenic considerations concurrent with the above-mentioned results. Chromogranin A is a precursor of several regulatory proteins, one of which is vasostatin I. This is a multilevel inhibitor of VEGF-mediated effects, endowed with ability to suppress migration of endothelial cells and formation of vessels both in-vitro and in-vivo experiments [16]. Hence, the unopposed VEGF activity may have contributed to the development of the reported lesion.

Unlike chromogranin, synaptophysin is an integral membrane protein present in microvesicles, a compartment different from chromogranin A-containing secretory granules, and its expression is not a constant feature of parathyroid adenomas [17].

Obviously, a question may arise why only a part of the adenoma was affected by the vascular proliferation. This can hardly be answered by the available data but a variable level of endothelial sensitivity and/or VEGF production by adenoma cells is a plausible explanation.

In summary, we are presenting a case of a haemangioma-like proliferation affecting a parathyroid chief cell adenoma. We are proposing that this vasoformative lesion occupies the extreme end in a continuum of tumour-associated vascular proliferations, reportedly resulting from effects of angiogenic factors secreted by neoplastic or stromal cells. Chromogranin A negativity with the possible lack of vasostatin I- mediated inhibitory effects on VEGF may have played a pathogenic role in the presented case.

The only two other published cases of haemangioma of the parathyroid gland were reported in patients diagnosed with primary chief cell hyperplasia with hyperparathyroidism [5], a pathophysiologic condition similar to our case. Therefore we raise the question whether these might also represent a reactive phenomenon.

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