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Parathyroid Carcinoma in the Setting of Tertiary Hyperparathyroidism after Renal Transplant

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Parathyroid carcinoma is a rare malignancy, with a prevalence of 0.005 % of all cancers [1]. Previous cases reported in the literature have described a few instances of parathyroid carcinoma in the setting of secondary or tertiary hyperparathyroidism in patients with chronic renal failure on hemodialysis [2–6]. Here, we report on the first case to occur in a patient with tertiary hyperparathyroidism who had undergone renal transplant for polycystic kidney disease.

The patient is a 53-year-old man with a history of autosomal dominant polycystic kidney disease, diagnosed in April 2001. He had progressed to end-stage renal disease by 2007, at which time his lab values reflected secondary hyperparathyroidism, with PTH elevated at 249 pg/mL, calcium normal at 9.1 mg/dL, and phosphate elevated at 6.1 mg/dL. Soon thereafter, the patient's secondary hyperparathyroidism was under good control on Zemplar therapy as demonstrated by his labs, showing that his PTH was elevated at 124, and his calcium and phosphate were normal (10 and 2.9, respectively). His phosphate increased to 5.6 in October 2008, but his hyperparathyroidism remained generally controlled. The clinician suspected that the patient had both primary and secondary hyperparathyroidism. The patient commenced peritoneal dialysis in 2008 and received a renal transplant in September 2011. Since that time, he had had tertiary hyperparathyroidism as defined by elevated PTH (264–324 pg/mL) in the setting of elevated calcium (10.6–11.1 mg/dL), which was refractory to treatment with Sensipar (Cinacalcet), a calcimimetic drug. A nuclear medicine parathyroid scan in April 2013 revealed a 1.9-cm soft tissue nodule inferior and posterior to the lower pole of the left thyroid lobe.

The patient proceeded to surgery in April 2013, at which time the left upper parathyroid was found to be greatly enlarged with its posterior medial side adhered to the recurrent laryngeal nerve along the entire length of the gland, which made the surgeon concerned for invasion. Despite care during the extensive dissection necessary to remove the gland and preserve the nerve, the capsule of the parathyroid gland ruptured; however, grossly, it appeared that the entire gland was removed. The gland weighed 2.5693 g and measured 3.4×2.3×1.0 cm. A frozen section revealed hypercellular parathyroid with absent intracellular lipid. The patient's parathyroid hormone level dropped from 51.6 to 7.8 pmol/L after further removal of the right upper, left lower, and a portion of the right lower parathyroid glands. All three of these glands also showed features consistent with nodular hyperplasia on frozen section.

Permanent section of the left upper parathyroid specimen demonstrates a focus of vascular invasion, as well as fibrous bands (Fig. 1). The focus of vascular invasion is highlighted by immunohistochemical staining for CD31 (Fig. 2). In contrast to most malignancies, the diagnosis of parathyroid carcinoma does not rest on nuclear features. As delineated by Schantz and Castleman [7] in 1973, vascular invasion of tumor cells, as well as the presence of sheets or lobules of tumor

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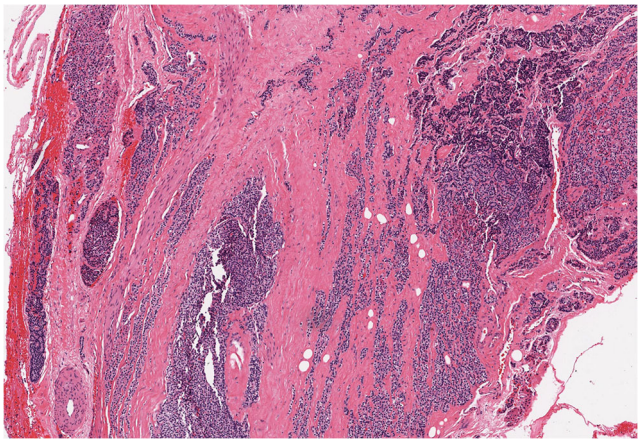

Fig. 1 Permanent section of the left upper parathyroid specimen demonstrates a focus of vascular invasion, as well as fibrous bands

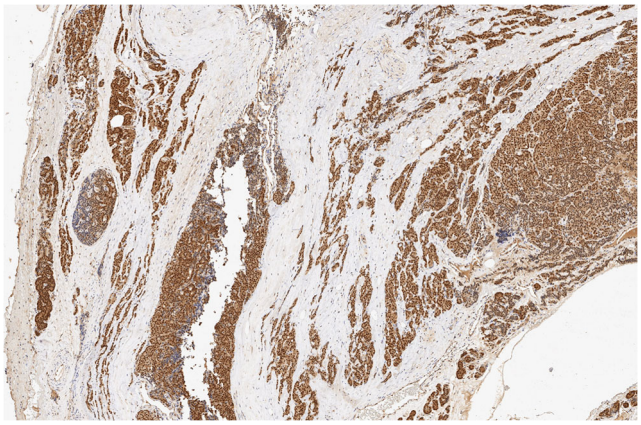

Fig. 3 Parafibromin immunohistochemistry shows that parafibromin expression is largely retained in the tumor, with focal negative areas of staining

cells separated by dense fibrous bands, as seen in the present case, is histological criteria for the diagnosis of parathyroid carcinoma.

Parafibromin is a putative tumor suppressor protein with predominant nuclear localization, involved in transcriptional regulation and histone modification, whose expression is lost in 66–100 % of parathyroid carcinomas [8–11]. In this case, parafibromin immunohistochemistry shows that parafibromin expression is largely retained in the tumor; however, focal areas were devoid of staining (Fig. 3).

Approximately 2 months after parathyroidectomy, the patient's PTH is elevated at 156 pg/mL, suggesting that the remaining portion of parathyroid may have increased its function or that an implant of parathyroid carcinoma deep to the recurrent laryngeal nerve or a metastasis is present.

It has been suggested that hyperplasia may progress to carcinoma [4]; however, this hypothesis is supported only by the association of carcinoma with preceding hyperplasia, without causative evidence. Most cases of parathyroid hyperplasia in secondary or tertiary hyperparathyroidism are monoclonal neoplasms, as shown by X-inactivation analysis [12, 13], and oncogenes or tumor suppressor genes may play a role in the pathogenesis of clonal hyperparathyroidism [14]. The monoclonal neoplasms, in particular, show nodular hyperplasia, in contrast to polyclonal diffuse hyperplasia. The case reported in this paper is consistent with the hypothesis of the progression of hyperplasia to carcinoma. The patient had a history of secondary hyperparathyroidism prior to his transplant. At surgery, nodular hyperplasia was found in the remaining three noncancerous parathyroid glands (Fig. 4).

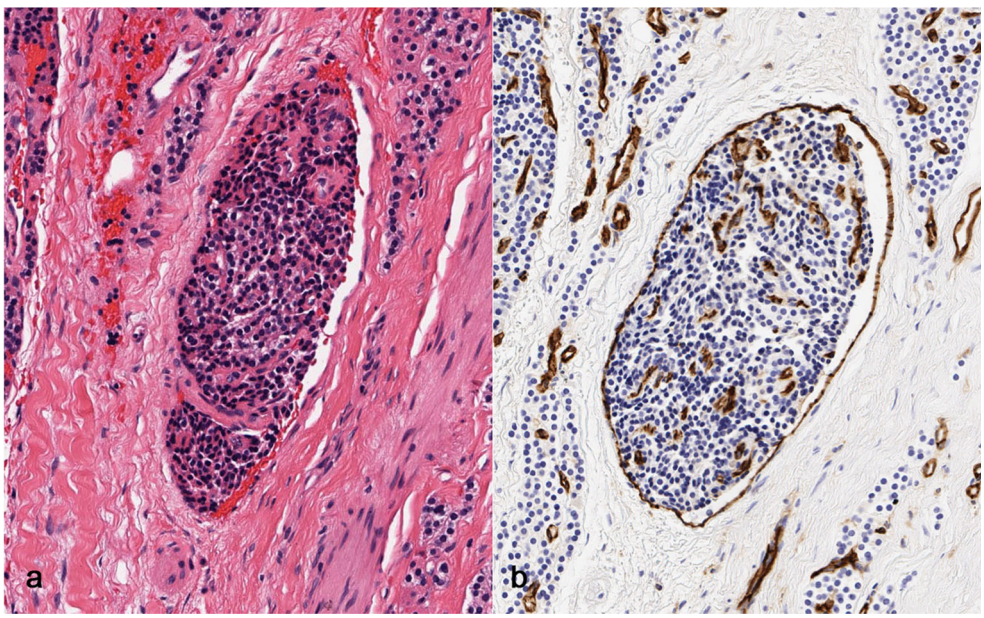

Fig. 2 The focus of vascular invasion is highlighted by immunohistochemical staining for CD31 establishing the diagnosis of parathyroid carcinoma

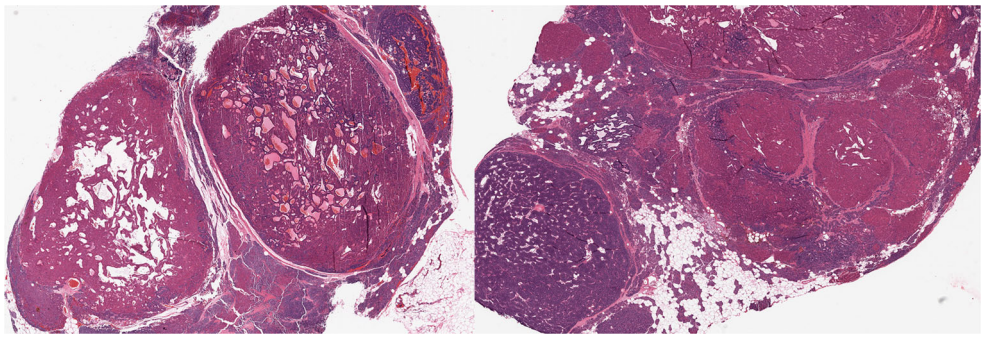

Fig. 4 The remaining three parathyroid glands showed nodular hyperplasia

Retention of parafibromin expression is consistent with a unique pathway of oncogenesis in parathyroid carcinoma in the setting of secondary/tertiary hyperparathyroidism, distinct from that seen with parafibromin loss.

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