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Coincident liposarcoma, carcinoid and gastrointestinal stromal tumor complicating type 1 neurofibromatosis: Case report and literature review

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ABSTRACT

Neurofibromatosis type 1 (NF1) is associated with increased risk of multiple neoplasms. We present a case of a female patient with NF1 who presented with a rectal low-grade neuroendocrine (carcinoid) tumor. Computed tomography imaging found a well-differentiated liposarcoma and a well-circumscribed gastro-intestinal stromal tumor (GIST). Although GIST and carcinoid tumors are frequently found in NF1 patients, liposarcoma complicating NF1 is quite rare and this is the first reported case of well-differentiated liposarcoma in NF1. In summary, we report a case of coincident abdominal carcinoid tumor, GIST and well-differentiated liposarcoma, which illustrates the variability of neoplasms in NF1 patients.

1. Introduction

Neurofibromatosis type 1 (NF1) is a common genetic disease, with an estimated incidence of 1 in 2500–3000 live births.[1] It is inherited as an autosomal dominant disorder with variable penetrance, and is caused by a wide array of mutations in the neurofibromatosis (NF1) gene on chromosome 17. Although neurofibromas are the hallmark of the disease, NF1 patients are at increased risk for the development of neural, mesenchymal and neuroendocrine tumors, among others[2,3] (see also[4] for a review). The clinical severity of NF1 is variable and indicates that phenotypic expression is determined through modifier genes.[5–7] Multiple malignant mesenchymal tumors, or sarcomas, have been reported in NF1, of which malignant peripheral nerve sheath tumor (MPNST) is by far the most common.[8] Liposarcoma (LPS) arising in NF1 patients is very rare.[9–15] It is most often pleomorphic, dedifferentiated or myxoid type. In fact, a case of well-differentiated liposarcoma in NF1 has, to our knowledge, never been reported.

Here, we report an unusual case of a patient with a clinical history of NF1 and three coincident abdominal tumors: a low-grade neuroendocrine tumor of the rectum, a gastrointestinal stromal tumor (GIST) of the small bowel serosa, and a

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well-differentiated liposarcoma of the small bowel mesentery. This unusual case highlights the spectrum of mesenchymal tumors in NF1, and the first case of well-differentiated liposarcoma.

2. Case presentation

A 55-year-old female with NF1 presented with mild rectal bleeding and a history of a prior rectal 'polyp.' The patient had a long-standing diagnosis of NF1, and disease manifestations including numerous cutaneous neurofibromas and mild cognitive deficits. Four years previously, the patient had a 2.5 cm bleeding rectal polyp. This was removed by transanal excision and diagnosed as a low-grade neuroendocrine tumor (performed at an outside hospital with pathology unavailable for review). Margin status of the original excision was not reported. Sigmoidoscopy at this time showed mucosal nodularity at the prior excision site. The patient then underwent sigmoidoscopy directed biopsy.

The biopsy specimen consisted of small fragments of rectal mucosa and submucosa. H&E staining of the biopsy showed small foci of round neoplastic cells arranged in an insular pattern, involving the submucosa (Fig. 1A). Tumor cells showed moderate amounts of finely granular cytoplasm, and characteristic 'salt and pepper' chromatin. Tumor cells exhibited no significant nuclear pleomorphism, no mitoses and no necrosis. Immunohistochemical analysis confirmed the neuroendocrine differentiation of neoplastic cells, with positivity for Synaptophysin and Chromogranin (Fig. 1B). Ki67 labeling index was low, estimated as less than 1% of tumor cells (Fig. 1C). A diagnosis of recurrent, well-differentiated, low-grade neuroendocrine tumor was rendered.

An interim abdominal CT scan was performed in order to evaluate tumor progression. This contrast enhanced CT scan demonstrated two additional incidental intra-abdominal masses (Fig. 2). No definitive increase in thickness of the rectal wall was identified. The first tumor was a partially enhancing, infiltrative lipomatous mass found within the small bowel mesentery. The mass measured 3.9 cm in greatest dimension and partially encased the superior mesenteric vessels. The second tumor was a well-circumscribed, enhancing 1 cm nodule within the mesentery of the jejunum. The patient underwent a CT-guided biopsy of the lipomatous tumor, which revealed a low-grade lipomatous proliferation with adipocytes of varying size. The histology from the biopsy demonstrated myxoid degeneration containing focally hypercellular aggregates of atypical, hyperchromatic stromal cells and focal floret-like giant cells (Fig. 3A). S100 immunohistochemistry was partially positive (Fig. 3B), while CD117 (CKIT) and DOG1 were negative. Mitoses or atypical mitotic figures were not seen. Cytogenetic analysis found evidence of MDM2 gene amplification, and a pathological diagnosis of well-differentiated liposarcoma was rendered. Given the unusual presentation and rarity of liposarcoma in NF1, plans for an open biopsy, versus possible excision if resectable, were made. Intraoperatively, the tumor was intimately associated with the superior mesenteric vessels, precluding complete resection. Pathologic examination of a 3.5 cm partial resection specimen yielded identical findings, consistent with well-differentiated liposarcoma. No de-differentiated component or adjacent neurofibromatosis tissue was identified.

During surgical exploration of the lipomatous mass, the nodule on the jejunal serosa was identified and completely resected. When assessed histologically, the excisional biopsy demonstrated a relatively bland, circumscribed proliferation of plump spindle cells (Fig. 4A). These cells were arranged in loose intersecting fascicles in a hyalinized stroma. Focal nuclear palisading and scattered areas of epithelioid cells with vesicular nuclei were seen. The cells lacked mitotic activity. Immunohistochemistry for CD117 (Fig. 4B) and DOG1 were diffusely positive (Fig. 4C). CD34 immunostaining was focally positive, and a diagnosis of gastrointestinal stromal tumor (GIST) was made.

Postoperatively, a decision was made in conjunction with the patient and family to undergo clinical and imaging surveillance for her tumors. No additional treatment was recommended for her recurrent neuroendocrine tumor, given its small size, low histologic grade, and low probability of progression. Likewise, no additional treatment was recommended for her GIST, given the benign course of the small GISTs among NF1 patients.[16] Finally, in regards to her well-differentiated LPS, radiotherapy was not recommended as no areas suspicious for de-differentiation were identified on CT. Clinical follow up at 2 months showed no evidence of disease progression.

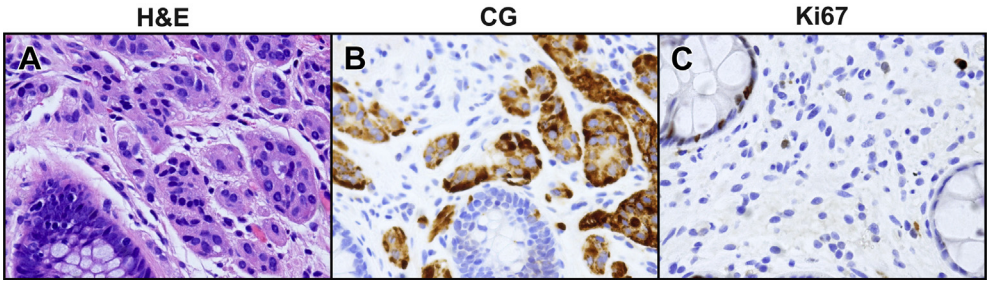

Fig. 1 – Histological appearance of rectal low-grade neuroendocrine tumor. (A) Hematoxylin and Eosin (H&E) microscopic appearance of the rectal mass demonstrates nests of neoplastic cells in the submucosa. (B) Immunohistochemical staining for neuroendocrine markers Synaptophysin (not shown) and Chromogranin (CG). (C) Immunohistochemical staining found a low Ki67 labeling index, indicating a well-differentiated tumor. Histology images were taken at 400×.