Mixed Periampullary Adenocarcinoma and Somatostatinoma with Small Bowel Gastrointestinal Stromal Tumour in Neurofibromatosis Type 1

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ABSTRACT

Context Gastrointestinal (GI) involvement is present in about one quarter of cases of neurofibromatosis type 1 (NF1). Adenocarcinomas have been reported in several organs. Gastrointestinal stromal tumors are the most common GI lesion seen in NF1. GISTs in combination with ampullary neuroendocrine tumors in NF-1 have been reported rarely. Case Report We present the case of a 44 year old male patient with NF1 and a rare finding of periampullary adenocarcinoma and somatostatinoma associated with small bowel GIST.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited condition, with an incidence of 1 in 3000 births. Diagnosis is usually made clinically, based on first-degree family history and a triad of symptoms: café-au-lait spots, cutaneous neurofibromas and neoplasms of the central or peripheral nervous system [1]. Malignancies are found in 3-15% of patients [2].

Gastrointestinal (GI) involvement is present in about one quarter of cases [3]. This occurs in three principal forms: 1) hyperplasia of the submucosal and myenteric nerve plexuses; 2) gastrointestinal stromal tumors (GISTs); 3) periampullary carcinoid which may be associated with phaeochromocytoma [4, 5]. Glandenocarcinomas have been reported in the oesophagus [6], stomach [7], duodenum [8], small bowel [9], colon [10], gallbladder [11], biliary tract [12] and pancreas [4, 5, 13].

Mixed periampullary adenocarcinoma and somatostatinoma in a patient with NF1 has only been previously reported once [14]. We present the case of a
DISCUSSION

Phaeochromocytomas and paraganglionomas are the most commonly occurring endocrine tumors in NF1 and are seen in 1-2% of patients [15]. Somatostatinomas are the most frequently occurring gastrointestinal neuroendocrine tumor seen in NF1 and they are most often located in the duodenum and account for 48% of all duodenal somatostatinomas [16]. A few cases of insulinoma in association with NF1 have also been reported [15]. Duodenal somatostatinomas tend to be located in the periampullary region [17, 18].

Periampullary tumors in NF1 are usually pure somatostatin-staining as compared with the multihormonal variety seen in non-NF1 patients [19]. Mixed endocrine tumors, composed of at least two distinct tumor populations, have rarely been described in the ampulla of Vater [14].

GISTs are the most common GI tumors seen in NF1 [20] but fewer than 5% of cases are symptomatic [21]. The incidence of GIST in patients with neurofibromatosis varies from 4-25% while the rate of neurofibromatosis in patients with GIST is 6% [22, 23]. GISTs in NF1 tend to be multiple. It has been suggested that the pathogenesis of GIST in NF-1 may be different from that of non-NF1 patients. The c-kit and PDGFRA (platelet-derived growth factor receptor alpha) mutation, which is generally seen in non NF1 GISTs is usually absent in NF1 and somatic inactivation of the wild-type NF1 gene has been found in them [24, 25].

Synchronous tumors, in the ampulla of Vater and GIST of the jejunum, have previously been reported [5]. GISTs in combination with ampullary neuroendocrine tumors in
NF-1 have been reported rarely [26, 27]. Several reported cases of GISTs in combination with somatostatinoma in patients with NF-1 suggest there may be a common pathway in the development of these diseases [28].

Cordier offered the first description of a gastrointestinal tumor comprising both neuroendocrine and exocrine components in 1924 [29]. Subsequently, these tumors have been subdivided into three types. Collision or composite tumors are those in which the two components are distinct and occur adjacent to each other within the same lesion. Combined tumors are those in which individual cells or glands show the phenotype of one or other of the two subtypes but are admixed with each other. The final type are the amphicrine tumors in which single cells display the phenotype of both components, for example where cells contain both cytoplasmic mucin and neuroendocrine granules [30].

These mixed exocrine-neuroendocrine tumors were defined as mixed adenoneuroendocrine carcinomas (MANECs) by the World Health Organization (WHO) in the 2010 classification of tumors of the digestive tract [31]. By definition, MANECs comprise at least 30% each of exocrine and endocrine components. The nomenclature also implies that both components are capable of metastasizing hence the term ‘carcinoma’, however the prospective behaviour of neuroendocrine tumors of the gastrointestinal tract is determined by assessment of a variety of features including site, size, degree of differentiation, Ki-67 index on immunohistochemistry, vascular invasion and whether the tumor is functioning or non-functioning [32, 33].

In the present case, although the tumors were arising in a similar area they appeared histologically quite distinct with the endocrine component localised to the ampulla and the carcinoma component invading through the duodenal wall. This is almost certainly an example of a collision tumor that does not fit the defining criteria of a MANEC as each component has arisen independently and the endocrine component represented less than 30% of the overall tumor. Prognosis is likely to be determined by the more advanced and aggressive adenocarcinoma [31].

The current case highlights the spectrum of associated tumor types which can be seen in association with NF1. Patients with NF1 who present with jaundice and weight loss should be investigated in the usual manner with increased suspicion for duodenal and ampullary tumors.

Conflict of Interest
Authors declare to have no conflict of interest.

REFERENCES