Mixed Endocrine Somatostatinoma of the Ampulla of Vater
Associated with a Neurofibromatosis Type 1:
A Case Report and Review of the Literature

Lydia Deschamps¹, Safi Dokmak², Nathalie Guedj³,
Philippe Ruszniewski⁴, Alain Sauvanet², Anne Couvelard³

¹Department of Pathology, CHU Pierre Zobda-Quitman. Fort-de-France, France.
Departments of ²Surgery, ³Pathology, and ⁴Gastroenterology; Hôpital Beaujon. Clichy, France

ABSTRACT

Context Mixed endocrine tumors are double neoplasms with both glandular and endocrine components; these tumors are rare, especially those arising in the ampulla of Vater. Ampullary somatostatinomas are classically associated with neurofibromatosis type 1. We herein describe the first reported case of a mixed endocrine somatostatinoma of the ampulla of Vater associated with neurofibromatosis type 1; we also present a review of the literature of the 7 mixed endocrine tumors of the ampulla which have been reported so far. Case report A 49-year-old woman presented with atypical abdominal pain. Endoscopic examination revealed a tumor involving the ampulla of Vater and a CT scan identified stenoses of both the distal common bile duct and the main pancreatic duct. A pancreaticoduodenectomy was performed and pathological examination revealed two tumor components, exocrine (high grade adenoma with infiltrative adenocarcinoma) and endocrine (expressing somatostatin hormone) with lymph node metastases originating from both types. The patient was treated with adjuvant chemotherapy and has had no recurrence for 3 years. Discussion In ampullary somatostatinomas, psammoma bodies are pathognomonic and chromogranin A is rarely expressed: these features should alert the pathologist to an association with neurofibromatosis type 1. The management of patients with mixed tumors is challenging. The treatment of choice is surgery, and adjuvant chemotherapy should be adapted to the most aggressive component, i.e. the exocrine one. Conclusion Because of their rarity, the diagnosis of ampullary mixed endocrine tumors is difficult. Our case points out the characteristic features of these neoplasms and their possible association with neurofibromatosis type 1.

INTRODUCTION

Mixed endocrine tumors are rare, especially those arising in the ampulla of Vater. Ampullary somatostatinomas are frequently associated with neurofibromatosis type 1. We report the first case of a mixed endocrine somatostatinoma associated with neurofibromatosis type 1. These tumors raise several difficulties. The first one is to diagnose this rare tumor, composed of both endocrine and glandular components. The second difficulty is the management of this double neoplasm which is often malignant and frequently requires surgical resection with neoadjuvant chemotherapy. Because of their rarity, ampullary mixed endocrine tumors may be misdiagnosed and receive incorrect therapeutic treatment.

CASE REPORT

A 49-year-old woman with neurofibromatosis type 1 presented with atypical abdominal pain. Endoscopic examination revealed a duodenal villous tumor involving the ampulla of Vater. A CT scan showed a 2 cm ampullary tumor with stenoses of both the distal common bile duct and the main pancreatic duct (Figure 1a). Neither lymph node nor distant metastases were found. Endoscopic ultrasound identified an ampullary tumor with some papillary projections in the juxta-ampullary main pancreatic duct and a slight upstream biliary dilatation. Analysis of the biopptic specimens revealed a high grade tubulo-villous adenoma without invasive adenocarcinoma. A pancreaticoduodenectomy was performed, showing an exophytic duodenal tumor invading the ampulla of Vater, measuring 4.5x5.0 centimeters. At the center of this tumor, a well delineated red-brown nodule measuring 12 mm was observed (Figure 1b). Microscopic examination identified two distinct tumor cell populations. The first one corresponded to an exocrine high grade tubulo-villous adenoma largely extending onto the external part of the ampulla and to the duodenal mucosa (Figure 2a). An area of well-
differentiated adenocarcinoma was identified inside the adenoma, measuring 6 mm, infiltrating the duodenal submucosa but sparing the muscularis propria (Figure 2b). The second tumor cell population was of endocrine type. It formed a well-delineated central nodule of 1 cm, sharply demarcated from the exocrine component (Figure 2c). It was composed of cords or acini of well-differentiated endocrine cells combined with psammoma bodies (Figure 2d). Endocrine cells contained regular nuclei, and granular and eosinophilic cytoplasm. Mitotic activity was low (less than 2 mitoses per 10 high-power fields). Immunohistochemical analysis demonstrated positive and diffuse staining of the endocrine component with antibodies directed against the neuroendocrine markers synaptophysin and CD56 and with anti-somatostatin antibody (Figure 2e). Chromogranin A was negative. The proliferation index, evaluated using MIB-1 antibody according to the TNM classification [1] was calculated at 2%. The main pancreatic duct was invaded by the adenomatous high grade component, but the secondary ducts and biliary duct did not display any dysplasia or malignant features. The infiltrating tumors did not extend into the pancreatic parenchyma. Lymph node dissection revealed 6 metastatic nodes: 3 were metastatic from the adenocarcinoma component and 3 from the endocrine carcinoma (Figure 2f).

Due to lymph node metastases from the adenocarcinoma component, chemotherapy with 5-fluorouracil and oxaliplatine was given to the patient; oxaliplatine was stopped after two courses because of liver cytolysis and abdominal ascites without tumor cells. The four following courses were administered without complications. The patient is alive with no signs of recurrence 3 years after the surgery.

**DISCUSSION**

Mixed endocrine tumors are tumors composed of at least two distinct tumor populations, one of which is endocrine. Three main types of endocrine mixed tumors are recognized [2, 3]. Collision tumors are formed by two independent tumor populations. Composite tumors are made up of two tumor populations deriving from a common precursor. Amphicrine tumors are made up of a unique cell population presenting a double differentiation. Composite tumors are the most frequent types of mixed endocrine tumors [2, 3]. The recent WHO classification recommends restricting the term “composite endocrine tumor” to those containing at least 30% of obviously tumoral endocrine cells; some authors recommend using higher thresholds (50%) in order to avoid overdiagnosis [4, 5]. The endocrine component is usually well differentiated, easily recognized on standard histology and confirmed with immunohistochemistry by detection of specific endocrine markers (chromogranin A and synaptophysin). When the endocrine component is poorly differentiated, it is more difficult to identify without specific immunohistochemistry.

Mixed endocrine tumors have rarely been described in the ampulla of Vater. We reviewed seven cases in the English literature [6, 7, 8, 9, 10, 11, 12] (Table 1). These tumors affected women rather than men (six women versus one man). The median age was 63 years (range: 45-78 years). Tumor size varied from 0.6 to 3 cm. Two patients had lymph node metastasis, including one having both endocrine and exocrine infiltration in the same lymph node; the other patient presented an endocrine lymph node metastasis. Two other patients had widespread metastases (liver, lung and vertebrae with both endocrine and glandular components) and died from their disease. Among the endocrine contingents, 3 were well differentiated and 3 were poorly differentiated (differentiation was not noted in one patient). Only one patient had an endocrine component expressing somatostatin, without clinical functional syndrome and without neurofibromatosis [6]. The exocrine component formed glands or tubules...
with goblet cells and was well-, moderately- and poorly-differentiated in 2, 3 and 2 patients, respectively [12]. In 5 out of 7 cases, the two components were intermixed, in line with the diagnosis of mixed tumors of a composite type. All seven tumors spared the pancreas.

Our case could be considered a collision tumor with two well-differentiated and well-delineated components. In addition, the adenocarcinoma component was associated with a large duodenal high-grade adenoma. The endocrine component contained psammoma bodies and calcifications, a figure which favors the diagnosis of somatostatinoma, the second most frequent duodenal endocrine tumor [13]. The diagnosis was confirmed by the strong and diffuse positivity of somatostatin at immunohistochemistry; somatostatinomas rarely express chromogranin A, as was observed in our case [14]. Many “somatostatin-producing” tumors are not associated with a functional somatostatinoma syndrome and should not be reported as “somatostatinomas” [4, 13, 14, 15]. In our observation, we did not find symptoms due to excessive hormone production and the somatostatinoma was diagnosed incidentally at postsurgical histological examination. However, in some cases, the so-called somatostatinoma syndrome may be present but difficult to recognize as a functional tumor before resection because the clinical syndrome, which associates recent diabetes mellitus and steatorrhea, may be difficult to diagnose. Among the previously reported ampullary somatostatinomas, we did not find any mixed tumors and, to our knowledge, our case is the first reported mixed somatostatinoma associated with a neurofibromatosis type 1 [16, 17, 18, 19, 20]. Ampullary somatostatinomas are classically associated with neurofibromatosis type 1 [14, 18, 20, 21]. Neurofibromatosis type 1 is an autosomally-inherited disease, with an incidence of about 1 per

Table 1. Main clinico-pathological characteristics of the seven reported patients with mixed endocrine tumors of the ampulla of Vater

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Tumor size (cm)</th>
<th>Lymph nodes metastasis</th>
<th>Distant metastasis</th>
<th>Hormone expression</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. [6]</td>
<td>1989</td>
<td>Female</td>
<td>64</td>
<td>1.5</td>
<td>No</td>
<td>No</td>
<td>Somatostatin</td>
<td>Alive (3 months)</td>
</tr>
<tr>
<td>Burke, Lee [7]</td>
<td>1990</td>
<td>Female</td>
<td>45</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td>Serotonin</td>
<td>Alive (N/A)</td>
</tr>
<tr>
<td>Shah et al. [8]</td>
<td>1990</td>
<td>Female</td>
<td>67</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Dead</td>
</tr>
<tr>
<td>Misonou et al. [9]</td>
<td>1990</td>
<td>Female</td>
<td>47</td>
<td>3</td>
<td>Yes, endocrine</td>
<td>No</td>
<td>Serotonin</td>
<td>Suspected recurrence (9 months)</td>
</tr>
<tr>
<td>Williams et al. [10]</td>
<td>1997</td>
<td>Female</td>
<td>58</td>
<td>1.2</td>
<td>Yes, endocrine and exocrine</td>
<td>No</td>
<td>Serotonin, gastrin</td>
<td>N/A</td>
</tr>
<tr>
<td>Alex et al. [11]</td>
<td>1998</td>
<td>Female</td>
<td>63</td>
<td>1.5</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Alive (24 months)</td>
</tr>
<tr>
<td>Moncur et al. [12]</td>
<td>2002</td>
<td>Male</td>
<td>78</td>
<td>2.3</td>
<td>No</td>
<td>Yes*</td>
<td>N/A</td>
<td>Dead (2 months)</td>
</tr>
</tbody>
</table>

* In this case, the exocrine component was of the acinar type and distant metastases of both the endocrine and the exocrine components were noted in the liver, lung and vertebras

N/A: not available
3,000 births, equally involving males and females. The disease is secondary to mutations in neurofibromatosis type 1 tumor suppressor gene (NFL), encoding the cytoplasmic protein neurofibromin. In neurofibromatosis type 1, some malignancies occur at an increased incidence compared to the general population and an association is recognized with gliomas, ependymomas, malignant peripheral nerve sheath tumors, pheochromocytomas, myeloid leukemia, nephroblastomas, gastrointestinal stromal tumors and endocrine tumors [22]. Digestive endocrine tumors occur in about 1% of neurofibromatosis type 1 patients. They typically arise in the ampullary region of the duodenum [23]. Their exact pathogenic mechanism of development in neurofibromatosis type 1 is not fully understood. In gastrointestinal stromal tumors associated with neurofibromatosis type 1, the loss of heterozygosity of NFL has been evidenced [24, 25]. Interestingly, there are 2 reported cases of a combination of gastrointestinal stromal tumors and somatostatinomas in patients with neurofibromatosis type 1, suggesting the existence of a common pathway in the development of both diseases [26, 27]. There have been only 2 reports of ampullary adenocarcinomas in neurofibromatosis type 1 [28, 29]. Prognosis may be difficult in mixed tumors. Adenocarcinomas of the ampulla with an intestinal phenotype have a significantly better long-term prognosis than adenocarcinomas located in the head of the pancreas [10]. However, ampullary endocrine tumors have a poorer prognosis than small bowel endocrine tumors and tumor size is a prognostic factor; when greater than 2 cm, the risk of metastasis increases significantly [10, 16, 21, 30].

Our patient had an aggressive tumor with 6 metastatic lymph nodes (of both exocrine and endocrine types). The conventional treatment for both ampullary endocrine and exocrine tumors is surgery; local excision may be indicated for small non-infiltrative lesions. A more radical treatment, i.e. pancreaticoduodenectomy, is appropriate for larger tumors with good long-term survival especially for patients with endocrine peripancreatic metastatic disease [18, 19, 20]. Our patient received adjuvant chemotheraphy for the exocrine tumor since this component was considered to be the most aggressive one and since adjuvant chemotherapy is not recommended for resected endocrine tumors.

CONCLUSION
We report the first ampullary mixed endocrine tumor with somatostatin expression in a neurofibromatosis type 1 patient. Somatostatin expression and the presence of psammoma bodies in ampullary endocrine tumors must alert the pathologist to the possible association with neurofibromatosis type 1 disease. The management of patients with mixed endocrine tumors is challenging but an early diagnosis allows curative surgical treatment.

Conflict of interest The authors have no potential conflicts of interest

References


