The Coexistence of Somatostatinoma and Gastrointestinal Stromal Tumor in the Duodenum of a Patient with Von Recklinghausen’s Disease

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Abstract

We herein describe a case of somatostatinoma coexisting with a gastrointestinal stromal tumor (GIST) in the duodenum of an 81-year-old woman with Von Recklinghausen’s disease (VRD) and common bile duct stone who presented with diarrhea of three months in duration. Gastroduodenoscopy revealed an ulcer on the second part of the duodenum. A 2.1-cm enhancing tumor was observed to extend from the ulcer on an abdominal computed tomography scan. Subtotal stomach-preserving pancreaticoduodenectomy revealed a somatostatinoma on the papilla of the vater and duodenal GIST. There have been only eight reports on VRD associated with ampullary somatostatinoma and GIST. An awareness of this possibility in patients with gastrointestinal lesions is necessary for proper treatment and patient management.

Key words: somatostatinoma, gastrointestinal stromal tumor, von Recklinghausen’s disease

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Introduction

Von Recklinghausen’s disease (VRD), also known as neurofibromatosis type 1 (NF1), is an autosomal dominant disorder with variable penetrance, that occurs in approximately 1 per 3,000 births. The gene for VRD has been identified on chromosome 17. Approximately 50% of VRD cases present as de novo mutations (1). Patients with VRD are also known to have a higher rate of malignant tumors during their lifetime (2). The most common tumors that complicate VRD are neurofibromas and endocrine tumors in the papilla of the vater (2). On the other hand, somatostatin-producing endocrine tumors of the duodenum are very rare neoplasms of the gastrointestinal tract. We herein present a case of a somatostatinoma coexisting with a gastrointestinal stromal tumor (GIST) in the duodenum of a patient with VRD.

Case Report

An 81-year-old woman with VRD and a common bile duct stone was admitted to our hospital due to diarrhea of three months in duration. Twenty years previously, she had been diagnosed with VRD based on the finding of a café-au-lait spot and multiple subcutaneous neurofibromas. The patient had no family history of VRD. The usual tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9), as well as routine laboratory tests were within the normal ranges. The patient’s plasma gastrin and insulin levels were slightly elevated at 510 pg/mL and 22 μU/mL, respectively. Atrophic gastritis and the administration of a proton pump inhibitor (PPI) increased her plasma gastrin titer, and a postprandial blood test affected her insulin titer. Her common bile duct stone was treated by endoscopic lithotripsy. Gastroduodenoscopy revealed an ulcer in the duodenum (Fig. 1). An abdominal computed tomography scan showed a 2.1-cm enhancing tumor extending from the ulcer. Subtotal stomach-preserving pancreaticoduodenectomy revealed a somatostatinoma on the papilla of the vater and duodenal GIST. There have been only eight reports on VRD associated with ampullary somatostatinoma and GIST. An awareness of this possibility in patients with gastrointestinal lesions is necessary for proper treatment and patient management.
(CT) scan also showed a 2.1-cm enhancing tumor, extending from the second part of the duodenum (Fig. 2), and three hepatic metastases (S4, 6, and 7). A histological examination of a duodenal ulcer biopsy specimen showed the proliferation of spindle-shaped cells that were revealed to be positive for somatostatin, synaptophysin, and chromogranin A by immunohistochemical examination. However, the specimen was negative for insulin, glucagon, and gastrin. These findings were consistent with a diagnosis of somatostatinoma.

The patient subsequently underwent subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) with extensive lymphadenectomy and multiple hepatic wedge resections (Fig. 3). Grossly, the duodenal tumor was solid and measured 2.0×1.5 cm. On histological examination, the tumor cells were found to be positive for both somatostatin and chromogranin by immunohistochemical staining, which was consistent with a diagnosis of somatostatinoma (Fig. 4); the examination of the resected hepatic tissues likewise confirmed the presence of metastases. Incidentally, the resected submucosal surface of the duodenal mass grossly demonstrated a white solid tumor, the histological examination of which showed the proliferation of spindle-shaped cells, predominantly in the muscle layer (Fig. 5A and B). The tumor cells were positive for cluster of differentiation (CD34 and c-kit) (Fig. 5C and D), and were diagnosed as GIST.

The immediate postoperative course was uneventful. However, 49 days after operation, the patient died from aspiration pneumonia.

Discussion

Multiple neurofibromatosis or VRD was first described in 1882 by von Recklinghausen (3). It is a relatively common autosomal dominant hereditary disorder with variable expression, which occurs in approximately 1 out of 3,000-4,000 live births, with a high rate of de novo mutations. Specifically, VRD occurs due to a mutation of the NF1 gene, a tumor suppressor gene involved in growth regulation, on chromosome 17. This gene encodes a GTPase activating protein which can regulate the activity of the p21 product of the ras oncogene, and which seems to play an important role in controlling cellular proliferation and differentiation in a wide range of tissues. Different gene mutations are involved in the development of the various clinical manifestations of VRD, including malignant tumors (4). The involvement of the gastrointestinal tract has been reported in 25% of VRD patients (1). The association between VRD and tumors of neurogenic and neuroendocrine origin, such as meningioma, glioma, and pheochromocytoma, is well known. On the other hand, the association of VRD with duodenal neuroendocrine tumors, particularly somatostatin-producing endocrine tumors, though uncommon, has become more widely recognized as a distinct neuroendocrine syndrome during the two last decades (5). Patients with VRD have a tendency to develop periamputillary tumors, most commonly somatostatin-producing endocrine neoplasms. The prevalence of pheochromocytoma is also relatively high (approximately 1%) in patients with VRD in comparison to the general population (6). Gastrointestinal endocrine tumors are increasingly being recognized in clinical practice. These tumors may either be functioning or non-functioning, depending on hormonal activity; these types are identical with regard to their development and histology but differ in relation to their clinical course and outcome (5).

Somatostatinomas, 70% of which originate in the pancreas, are very rare tumors. The majority of extra-pancreatic tumors originate in the upper gastrointestinal tract and primarily occur in the duodenum or the peri-ampullary region (7). Initially described by Kaneko et al. (8) in 1979, duodenal somatostatin-producing endocrine tumors, which belong to the group of gastrointestinal endocrine tumors, are rare neoplasms which have a prevalence of 1 in 40 million.

In general, pancreatic somatostatinomas tend to be large in size and are often malignant. Many patients with pancreatic somatostatinomas also exhibit manifestations of somato-
Figure 3. Subtotal stomach-preserving pancreaticoduodenectomy in an 81-year-old woman with VRD with a duodenal lesion. (A) Grossly, a 2.0×1.5 cm solid tumor was seen in the second part of the duodenum (black arrow). The vater of the papilla was evident (white arrow). Incidentally, the resected submucosal surface of the duodenal mass revealed a 1.0-mm white solid tumor (black dashed arrow). (B) The cut surface of the solid tumor in the second part of the duodenum revealed a white solid tumor (black arrow). VRD: von Recklinghausen’s disease

Figure 4. A histopathologic examination of the resected duodenal tumor in an 81-year-old woman with VRD. (A) The dense proliferation of small round acinic tumor cells was observed (Hematoxylin and Eosin (H&E) staining, ×200). Immunohistochemical staining (×200) was positive for (B) chromogranin A, (C) somatostatin, and (D) synaptophysin. VRD: Von Recklinghausen’s disease

Statinoma syndrome (9). This entity is often detected incidentally (10), with an average overall post-operative 5-year survival rate of 75%, which ranges from 40-60% in patients with metastases, and which is 100% in patients without metastases. Tumor size is an important prognostic parameter, with the risk for metastasis significantly increasing for tumors over 20 mm in size. In comparison, somatostatinomas arising from the intestine tend to be smaller. When the primary lesion is extra-pancreatic, the prognosis is better, although few patients may present somatostatinoma syndrome (7). The clinical presentation of duodenal somatostatinoma is non-specific and is rarely associated with typical
somatostatin syndrome.

GIST neoplasms, on the other hand, are characterized by CD117-positive mesenchymal spindle, epithelioid, or pleomorphic cells (11) and are often found incidentally during surgery or at autopsy. The incidence of GIST in patients with VRD ranges from 4-25%. GIST is the general terminology for primary non-epithelial tumors of the gastrointestinal tract, which were reported in approximately 3.9-25% of patients with VRD. The unfavorable prognostic factors include a size of >3 cm, cytological pleomorphic atypia, regional and/or portal metastases, and incomplete surgical resection (12).

The coexistence of duodenal somatostatin-producing endocrine tumors and GIST in a patient with VRD is extremely rare. To the best of our knowledge, there have only been eight reported cases in literature. These cases, including the present case, are summarized in Table. The patients’ ages ranged from 36 to 81 years. Two of the patients were male and seven were female. Abdominal pain and diarrhea were the most common symptoms. In 85.7% of patients, the largest diameter of the tumor was 3 cm. Patel et al. reported long term disease free survival with good quality of life in patients who underwent radical resection of both the primary tumor and the liver metastases (13).

Pancreaticoduodenectomy was performed in 66.7% of the reported cases, whereas local resection was performed in the remaining cases (14-21).

The association of non-neurogenic malignancies with VRD has long been considered to be coincidental, however, recent observations reveal a consistent tendency for these malignancies to develop in patients with VRD (16). Although the association of NF-1 with neuroendocrine tumors has been established, it has rarely been described in association with a non-neurogenic malignancy, such as GIST (16). Patients with NF1 may have an increased risk of developing non-neurogenic malignancies because the disease has been shown to arise from a mutation on the NF1 gene on the long arm of chromosome 17. Thus, our case also suggested a possible relationship between VRD and GIST. Most of the cases of GIST associated with VRD were benign or of uncertain biological behavior; reports of malignant tumors are uncommon.

The 16-multidetector computed tomography (MDCT) scanner has enabled the early detection of the malignant hypervascular lesions that are associated GIST. However, different types of neuroendocrine tumors have similar radiological features. Somatostatin-receptor scintigraphy can be used to identify occult primary tumors and to confirm the
clinical stage. In combination with state-of-the-art positron emission tomography (PET)/CT, this examination can also be used to stage the tumor based on the presence of distant metastases (22).

In conclusion, duodenal somatostatin-producing endocrine tumors are rare neoplasms which may be associated with VRD. Clinicians should be aware of this association as part of the differential diagnosis in patients with VRD who present with painless obstructive jaundice or a mass in the duodenum.

The authors state that they have no Conflict of Interest (COI).

References


