Small Intestinal Neuroendocrine Tumour Incidentally Diagnosed Along with Large Mesenteric Lymph Node Metastasis: A Case Report

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ABSTRACT

Small intestinal neuroendocrine tumours (NETs) are rare malignancies that occur in the small intestine. The incidence of small intestinal NETs has increased substantially in recent decades. Similar to that of general NETs, the diagnosis rate of small intestinal NETs is increasing continuously. Small intestinal NETs often metastasize to the lymph nodes, even when the lesions are small. Surgical resection of the primary tumour and associated mesenteric lymph nodes is recommended. We present a case of a NET in the ileum that was incidentally diagnosed along with large mesenteric lymph node metastasis. Abdominal computed tomography for examination of urinary frequency revealed an intra-abdominal mass, measuring 80 mm in diameter. The patient was intraoperatively diagnosed with an ileocaecal mesenteric mass, and ileocaecal resection with lymph node dissection was performed. The resected specimen incidentally showed a NET measuring 14 mm in diameter in the ileum, located 90 cm from the ileocaecal valve. The ileocaecal mesenteric mass was histopathologically diagnosed as lymph node metastasis of the NET. This case confirms the importance of making an immediate intraoperative pathological diagnosis and performing a thorough examination of small intestinal lesions when a large mesenteric tumour is suspected.

Key words: Neuroendocrine tumour, Small intestine, Mesenteric lymph node metastasis

INTRODUCTION

Neuroendocrine tumours (NETs) are uncommon tumours developing from the neuroendocrine cells in the body. Most NETs occur in the gastrointestinal tract1). Small intestinal NETs are rare and slow growing and develop from the enterochromaffin cells found in the crypts of Lieberkühn. Cases of small intestinal NETs are extremely rare in Japan, accounting for only 2.9% of all reported cases of NETs7). Nevertheless, the incidence of small intestinal NETs is increasing continuously, and these tumours are associated with the presence of mesenteric lymph node metastases at diagnosis in 88% of patients30). A 2-cm tumour size is generally considered the cut-off point for the risk of lymph node metastasis in intestinal NETs without other high-risk features; however, metastatic disease has been reported in 12% of tumours in the jejunum and ileum measuring ≤ 1 cm20). The goals of treatment are to resect the primary tumour and associated regional lymph nodes and control NET syndromes, when present30).

CASE PRESENTATION

A 79-year-old male patient was referred to our hospital for the evaluation of urinary frequency. He had a history of acute myocardial infarction but no history of previous abdominal surgery or trauma. His abdomen was soft, with a palpable mass in the right hypogastric region. The patient’s haemoglobin concentration was slightly low (10.9 g/dl), but his white blood cell count, platelet count, and C-reactive protein level were within normal limits. Tumour marker levels were also within normal ranges, (carcinoembryonic antigen, 2.2 ng/ml and cancer antigen 19-9, 15.4 U/ml). The level of soluble interleukin-2 receptor was moderately high at 959 U/ml. Dynamic computed tomography (CT) showed a lobular, heterogeneous intra-abdominal mass measuring 80 × 70 × 60 mm in diameter (Figure 1). The mass was enhanced in the arterial phase. Upper gastrointestinal endoscopy and colonoscopy showed no evidence of tumour. Although fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) revealed accumulation of FDG in the tumour (maximum standardized uptake value,
2.8), we could not find the primary lesion (Figure 2).

As a preoperative diagnosis, we suspected stromal tumour, leiomyoma, lymphoma, or NET; exploratory laparotomy was performed to confirm the diagnosis. Laparotomy revealed a movable tumour measuring 80 mm in diameter located within the ileocaecal mesentery. Combined ileocaecal resection, including the terminal ileum 130 cm from the ileocaecal valve, was mandatory to remove the tumour. The resected specimen showed a mesenteric tumour and incidentally showed a sharply demarcated mass with a central depression measuring 14 mm in diameter, in the ileum located 90 cm from the ileocaecal valve (Figure 3).

Histological analysis of the resected specimen and immunochemical analysis confirmed the diagnosis of G1 NET in the ileum (positive for chromogranin A and synaptophysin; absence of necrosis; mitotic count of 3/10 high-power fields; Ki-67 labelling index < 1%). The analysis also confirmed the large mesenteric lymph node as a NET metastasis (Figure 4A–D).

The increased urinary frequency, which had been the patient’s preoperative complaint, was immediately improved after the surgery, and there has been no relapse thus far.

**DISCUSSION**

Gastrointestinal neuroendocrine neoplasms (GI-NENs), originating from amine precursor uptake and decarboxylation cells in the digestive tract, have the ability to undergo multiple differentiations and secrete various active hormones, leading to significant differences in biological behaviours and prognoses. The World Health Organization’s Classification of Tumours in the Digestive System revised the denomination and classification for GI-NENs, dividing them into NET, neuroendocrine carcinoma, mixed adenoneuroendocrine carcinoma, hyperplasia, and pre-neoplasm. The
The majority of NETs are found within the gastrointestinal tract (55%) and bronchopulmonary system (30%)\(^{11}\). The differences in incidence rates by race are striking\(^{21}\). For NETs in the jejunum and ileum, the reported incidence rates among Caucasian, African American, and Asian/Pacific Islander patient groups are 0.71, 0.88, and 0.09 per 100,000, respectively\(^{21}\). Cases of small intestinal NETs are extremely rare in Japan, accounting for only 2.9% of all reported cases of NETs\(^{7}\).

Kulke et al. stated that 75% of small intestinal NETs occur in the distal ileum, within 60 cm of the ileocaecal valve\(^{8}\). Patients are commonly diagnosed during an operation conducted for some other reason. The discovery of these tumours often occurs as a result of surgical exploration for chronic blood loss, intestinal obstruction, or during the course of metastatic disease evaluation. Regardless of how they are found, the discovery of a primary NET should engender a diligent search for other tumours because they are often small and numerous\(^{25}\).

Small intestinal NETs are associated with the presence of mesenteric lymph node metastases at diagnosis in 88% of patients\(^{13}\). Tumour size has the greatest effect on the frequency of metastatic disease during the operation. The relationship between tumour size and the occurrence of metastases was investigated in a series by Moertel et al., which showed a metastatic rate of 2% for tumours with diameter < 1 cm, 50% for tumours 1–2 cm in diameter, and 80% for tumours with diameter > 2 cm\(^{123}\).

The incidence of NETs is increasing, which is thought to be largely associated with the introduction of more sensitive diagnostic tools. However, lesions < 2 cm can be difficult to detect, especially within the alimentary canal, where they may not cause any symptoms, such as obstruction. This makes localization of small bowel NET and diagnosis challenging in clinical practice. These tumours cannot be found using upper gastrointestinal endoscopy or colonoscopy; one study reported a diagnostic yield of only 45% in the identification of primary small intestinal NETs using video capsule endoscopy\(^{48}\).

The sensitivity in detecting multiple NETs with these imaging methods remains low. Locally advanced disease with typical mesenteric involvement can be identified using abdominal CT scans as an ill-defined mass at the root of the mesentery, with characteristic radiating of dense soft tissue strands, forming thickened neurovascular bundles\(^{10}\). Recently, integrated FDG-PET/CT has been demonstrated to be an effective tool for differentiating malignant from benign lesions\(^{22}\). Although NETs, especially in the typical form, have a low metabolic activity that reduces the sensitivity of FDG-PET/CT in diagnosing these neoplasms\(^{8}\), only tumours with high proliferative activity and low differentiation may show increased accumulation of FDG\(^{17}\). Differential diagnosis of a large mesenteric lymph node should include gastrointestinal stromal tumour, malignant lymphoma, granuloma, malignant peritoneal mesothelioma (MPM), and mesenteric fibromatosis. A granuloma has no contrast effect on CT scan. Several reports of CT findings of MPM exist, including diffuse omental masses, mesenteric nodules, or parietal peritoneal thickening, with or without ascites\(^{15}\). It is difficult to make a differential diagnosis for these neoplasms because there are no specific imaging features. Definitive diagnosis is made by histopathology.

Goals of treatment are to resect the primary tumour and associated regional lymph nodes and to manage NET syndromes, when present\(^{3}\). Surgical removal of the tumour is curative in localized disease, although finding a small primary lesion is challenging. The goal of surgery in midgut NETs is complete, curative, en bloc resection of the primary tumour and extensive mesenteric lymph node dissection. Currently, no studies have provided a gold standard in the lymphadenectomy procedure required for small intestinal NETs. Hellman et al. suggested that resection of the primary tumour and mesenteric lymph node metastasis improves survival\(^{8}\). Landry et al. reported that regional mesenteric lymphadenectomy, with resection of at least seven lymph nodes, is associated with improved survival\(^{8}\). The American Joint Committee on Cancer in 2010 revealed that the prognosis of small intestinal NETs is poor, with a 5-year survival rate of approximately 60% in the United States. However, with regard to prognosis, patients with R0 resection in small intestinal malignancy have significantly high survival rates\(^{1,15}\).

In this case, the entire primary lesion and lymph node metastasis in the mesentery were fortunately resected, and the prognosis is likely good. Although abdominal contrast-enhanced CT revealed only the intra-abdominal tumour and the primary lesion was not detected before and during surgery, it was incidentally detected on the cut surface. It was difficult in the present case to diagnose the primary lesion, so it might have been better to perform an immediate intraoperative pathological diagnosis of the mesenteric tumour, to detect the primary tumour during the surgery.

Figure 4 Histopathological findings. (A) The mass comprised neuroendocrine tumour cells invading the muscular layer of the intestinal proper (haematoxylin and eosin, original magnification ×100). (B) The mesenteric lymph node also comprised neuroendocrine tumour cells. (C) Immunoreactivity for chromogranin A in tumour cells. (D) Immunohistochemistry showing a mitotic count of 3/10 high-power fields, suggesting Ki-67 labelling index of < 1%.
Various studies have shown that, in many respects, somatostatin receptor-based PET/CT is clearly superior to the standard cross-sectional imaging with CT or magnetic resonance imaging in the detection of G1 and G2 NETs, a finding that has influenced therapeutic strategies. The diagnostic sensitivity of octreoscan ranges between 80% and 90%; this technology can also be used as a follow-up tool. Pasquer et al. reported that 61% of multiple tumours were missed during preoperative procedures. Therefore, surgeons should explore and palpate the entire small bowel to detect all possible small intestinal NETs, given the possibility that they may exist as small or multiple lesions.

CONCLUSION

Small intestinal NETs are rare in Japan. NETs sometimes metastasise to a lymph node that is larger than the primary lesion, even though the NET may be too small to diagnose. In case of a large mesenteric mass, an intraoperative pathological diagnosis and thorough examination for small intestinal lesions before and during surgery should be performed.

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