Primary Presacral Neuroendocrine Tumor Presenting as Multiple Liver Metastasis: A Case Report

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Patient: Female, 63-year-old
Final Diagnosis: Neuroendocrine tumor
Symptoms: None
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology
Objective: Rare disease
Background: Various neoplasms, including neuroendocrine neoplasms (NENs), can arise from the presacral space. Most presacral lesions are detected due to symptoms arising from tumor growth. However, diagnosing small, asymptomatic presacral tumors is challenging because of their unique location.

Case Report: A 63-year-old woman with chronic hepatitis C underwent follow-up after achieving a sustained virological response. Abdominal ultrasonography revealed multiple new hyperechoic masses in the liver. Physical and laboratory examinations, including tumor marker analysis, yielded unremarkable results. Computed tomography (CT) and magnetic resonance imaging (MRI) indicated metastatic liver tumors but failed to identify the primary site of these lesions. The hepatic mass was biopsied, leading to a diagnosis of grade 2 neuroendocrine tumor.
111In-pentetreotide somatostatin receptor scintigraphy revealed significant radiotracer accumulation in multiple hepatic masses, several bones, and a small presacral space lesion. Pathological examination of the presacral lesion confirmed a grade 2 neuroendocrine tumor, similar to the hepatic mass. Review of a CT scan performed 4 years earlier indicated a small cyst-like lesion in the presacral space suspected of being a developmental cyst; however, the presence of cystic components was not confirmed pathologically. The patient was diagnosed with a primary presacral neuroendocrine tumor, which might have originated from a developmental cyst, with multiple liver metastases. Chemotherapy with everolimus was initiated, and the clinical course has been uneventful.

Conclusions: We report a rare neuroendocrine tumor arising from the presacral space with multiple liver metastases. The presacral space should be examined when a NEN with an unknown primary site is found.

Keywords: Neuroendocrine Tumors • Neoplasm Metastasis • Biopsy, Fine-Needle

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Background

The presacral space, located between the rectum, sacrum, peritoneal reflection, and levator ani, is known to be a potential site for the development of various tumors [1,2]. Presacral tumors are uncommon, with an incidence of approximately 1 in 50,000 among hospitalized patients [3].

Neuroendocrine neoplasms (NEN) are renowned for arising from various organs, but approximately 90% occur in the gastrointestinal tract, respiratory system, and pancreas [4]. The development of NENs in the presacral space is extremely rare, with only a few case reports available in the literature. Previous studies have suggested that typical clinical features of presacral NENs include well-differentiated neuroendocrine tumors (NETs), proliferation without metastasis, and the emergence of certain symptoms associated with tumor enlargement [5].

Herein, we report a rare case of a primary presacral NET diagnosed after multiple liver metastases.

Case Report

A 63-year-old woman was referred to our department for a low platelet count. She had been undergoing regular follow-ups with only blood testing for chronic hepatitis C. The patient was asymptomatic at presentation. Laboratory tests and liver biopsy revealed chronic hepatitis C genotype 1b with hepatitis C virus-RNA of 6.3 log IU/mL and portal fibrosis with a few septae. Treatment with ledipasvir and sofosbuvir achieved a sustained virological response. Thereafter, she underwent annual follow-ups with blood tests and abdominal ultrasonography.

Four years later, abdominal ultrasonography revealed hyper-echoic hepatic masses in S6 and S7 measuring 11 mm, 8 mm, and 7 mm, which had never been observed before. MRI revealed several oval masses that appeared hyperintense on T2-weighted imaging and had restricted diffusion on diffusion-weighted imaging (Figure 1). Multiple liver metastases were suspected based on these findings. Contrast-enhanced computed tomography (CE-CT) was performed to determine the primary site of these lesions; however, it revealed only pale low-density masses in the liver (Figure 2) but not the primary tumor. Moreover, physical and laboratory examinations, including tumor markers such as alpha-fetoprotein (2.06 ng/mL; normal

Figure 1. MRI demonstrating hyperintense hepatic masses on T2-weighted sequences (A, C) and restricted diffusion on diffusion-weighted sequences (B, D). MRI – magnetic resonance imaging.
range: 0-7.0 ng/mL), protein induced by vitamin K absence-II (19 mAU/mL; normal range: 11.4-34.0 mAU/mL), carcinoembryonic antigen (3.1 ng/mL; normal range: 0-5.0 ng/mL), carbohydrate antigen 19-9 (26.6 IU/mL; normal range: 0-37 U/mL), squamous cell carcinoma antigen (0.9 ng/mL; normal range: 0-2.5 ng/mL), carbohydrate antigen 125 (7.1 IU/mL; normal range: 0-35.0 U/mL), neuron-specific enolase (27.1 ng/mL; normal range: 0-16.3 ng/mL), and soluble interleukin-2 receptor (222 IU/mL; normal range: 157-474 U/mL), yielded unremarkable findings. Positron emission tomography-CT (PET-CT) did not indicate abnormal 18-fluorodeoxyglucose uptake in the hepatic masses and other lesions. Esophagogastroduodenoscopy and total colonoscopy also did not reveal tumors that could cause liver metastases. Since these imaging studies could not aid in the diagnosis of the liver masses, ultrasonography-guided liver tumor biopsy was performed with a 21-gauge needle for the 15-mm large growing hepatic tumor in S7.

Pathological examination revealed the outgrowth of atypical tumor cells with trabecular and partly tubular structures and hemorrhagic changes (Figure 3). Silver staining showed that the tumor cells were divided into alveolar compartments by thick septal fibrosis. Tumor cells tested positive for CD56, synaptophysin, CK7, and CK20, and negative for chromogranin A, glypican 3, and hepatocyte paraffin 1. The Ki-67 percentage score was 12%, and poorly differentiated cells, such as those observed in neuroendocrine carcinoma (NEC), were not noted. Therefore, these pathological findings confirmed the presence of a NET grade 2 (G2).

Given that multiple NETs originating from the liver are extremely rare, it was speculated that the primary site could be elsewhere. CE-CT performed 4 years earlier had shown a small cyst-like lesion in the presacral space, suspected of being a developmental cyst (Figure 4). Since PET-CT did not detect these hepatic NETs, somatostatin receptor scintigraphy with 111-In-pentetreotide was performed, which revealed significant radiotracer accumulation in the presacral space, several bones, and hepatic masses (Figure 5). The recent CE-CT review revealed a contrast-enhanced solid mass in the presacral space (Figure 6). Additionally, colonoscopy clarified no tumor in the rectum, supporting the fact that the mass in the presacral space did not originate from the gastrointestinal tract. These findings pointed toward the possibility that a NET derived from a developmental cyst in the presacral space was the primary site. CT-guided fine-needle aspiration was performed for the presacral mass, revealing that tumor cells were positive for CD56 and synaptophysin and negative for chromogranin A, similar to the NET in the liver, and that the Ki-67 percentage score was 4.5% (Figure 7). Biopsy of the presacral mass did not provide evidence to suggest a developmental cyst. A diagnosis of primary NET G2 in the presacral space with multiple hepatic and bone metastases was made according to the current and previous imaging findings. Chemotherapy with everolimus was initiated, and the patient’s clinical course has been uneventful.

Discussion

The presacral space lies between the rectum, sacrum, peritoneal reflection, and levator ani. It is formed prenatally by the adhesions of various tissues, such as the hindgut, proctodeum, and neural tube, thus constituting an area for development of various tumors [2]. Presacral tumors are extremely
rare, with a reported incidence of 1 in 40,000 to 60,000 among inpatients [3]. Jackman et al classified presacral tumors into 5 categories (congenital, inflammatory, neurogenic, osteogenic, and others) [6], of which congenital tumors are the most common [7]. Congenital presacral tumors can range from cystic to solid lesions [8]; the former comprises 3 types of tumors: developmental cyst derived from dysplasia in the germ-layer formation stage, duplication of the intestinal tract, and anterior sacral meningocele. Developmental cysts are the most common congenital lesions in the presacral space. They appear as a well-defined, thin-walled, and unifocal or multifocal low-density area without contrast enhancement on CT [9]. In our case, CT performed 4 years earlier revealed that the appearance of the presacral cyst-like lesion was consistent with that of a developmental cyst. Moreover, all imaging studies, including esophagogastroduodenoscopy and total colonoscopy, showed no abnormalities except for the lesion at the presacrum. Eventually, a final diagnosis of primary presacral NET with multiple metastases was made based on these findings. The presacral NET might have originated from a developmental cyst, although the significant limitation was the lack of histological confirmation of the developmental cysts. Obtaining and verifying the presence of cystic components may require an excision biopsy instead of a needle biopsy.

Figure 3. Pathological examination of the hepatic mass revealed the outgrowth of atypical tumor cells with trabecular and partly tubular structures. The tumor cells were positive for synaptophysin and negative for chromogranin A. The Ki-67-positive cell ratio was 12%. The upper left shows HE, the upper right shows synaptophysin, the lower left shows chromogranin A, and the lower right shows Ki-67. Scale bars, 100 μm. HE – hematoxylin-eosin staining.

Figure 4. CT performed 4 years earlier showed a 12.7×13.4-mm cystic lesion in the presacral space. CT – computed tomography.
Most patients with malignant presacral tumors present with symptoms such as sacrococcygeal/perianal pain and bowel or urinary dysfunction [5]. Cases involving patients with a history of imperforate anus have also been reported [10]. The tumors are typically discovered by imaging studies [5]. Approximately half of these presacral tumors are larger than 50 mm at diagnosis, and the tumor size is closely linked to the patient's problem, thus serving as a trigger for their identification [1].

However, small presacral tumors are difficult to diagnose because of their unique location and lack of symptoms. In our case, the primary NET was small and asymptomatic at the time of metastasis to the liver, which contributed to the difficulty in identifying the primary site of the NET.

NENs are defined as epithelial neoplasms with predominant neuroendocrine differentiation that can arise from most organs [11,12]. Previous epidemiological studies showed that NENs occur predominantly in the gastrointestinal tract (53.2%), respiratory system (27.3%), and pancreas (7.3%), followed by considerably less frequent locations such as the ovaries (<1%), breasts (<1%), and urinary system (<1%) [4]. Primary NENs in the presacral space are extremely rare and have been described in only a few case reports [5,13-15]. Additionally, only 3 cases presented with liver metastases at the time of diagnosis [16-18]. Most lesions from among the 17 cases with available histological information were well-differentiated NENs: NET grade 1 in 11 (64.7%) cases, including 1 with liver metastasis; NET G2 in 6 (35.3%) cases, including 2 with liver metastasis; NET grade 3 in 0 (0%) cases; and NEC in 0 (0%) cases [5,14,15]. These earlier reports suggest that typical clinical characteristics of primary presacral NENs are as follows:


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well-differentiated NETs, proliferation without metastasis, and eventual emergence of some symptoms associated with tumor enlargement [5]. However, as in the current case with NET G2, the lesion remains small and asymptomatic and metastasizes in a few cases. Therefore, presacral NEN must be included in the differential diagnosis when a NEN with an unknown primary site is found.

Conclusions

We reported an extremely rare case of a small and asymptomatic NET in the presacral space, which might have originated from a developmental cyst, with multiple liver metastases.

Figure 7. Pathological examination of the presacral tumor revealing tumor cells with a 4.5% Ki-67-positive cell ratio, which were positive for synaptophysin and negative for chromogranin A, similar to the NET in the liver. The upper left shows HE, the upper right shows synaptophysin, the lower left shows chromogranin A, and the lower right shows Ki-67. Scale bars, 100 μm (low-power field) and 20 μm (high-power field). NET – neuroendocrine tumor, HE – hematoxylin-eosin staining.

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Declaration of Figures’ Authenticity

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