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Case Report

Poorly Differentiated Neuroendocrine Carcinoma of Unknown Primary with Metastasis to the Testis: A Case Report

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Keywords
Neuroendocrine carcinoma · Neuroendocrine tumors · Testis · Unknown primary neoplasms

Abstract
Neuroendocrine neoplasms are rare epithelial neoplasms with neuroendocrine differentiation. Few cases of primary testicular poorly differentiated neuroendocrine carcinomas (PD-NECs) have been reported, and secondary testicular neoplasms are rare. A 61-year-old man with a chief complaint of left testicular swelling was referred to our hospital. An orchiectomy was performed in order to determine the pathological diagnosis. Pathological examination showed diffuse sheets of highly atypical cells that were positive for neuroendocrine markers and a Ki-67 proliferation index of 80%. The patient was diagnosed with poorly differentiated small-cell NEC. Contrast-enhanced computed tomography revealed multiple metastases to the pancreas, adrenal glands, and lymph nodes. Esophagogastroduodenoscopy showed multiple gastric metastases, and biopsy revealed the same histological findings as observed for the testicular tumor. Contrast-enhanced magnetic resonance imaging of the head also revealed multiple brain metastases. The confirmed diagnosis was PD-NEC of unknown primary with metastases to the testis, stomach, pancreas, adrenal glands, brain, and lymph nodes. We started the first-line chemotherapy with etoposide and cisplatin. Stereotactic radiotherapy for the brain metastases was administered between the first and second cycles. After five cycles, a partial response was observed; however, disease progression was observed after seven cycles with recurrence of the brain metastases and enlargement of all tumors. To our knowledge, this is the first report of an unknown primary PD-NEC with metastasis to the testis.

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Introduction

Neuroendocrine neoplasms (NENs) are rare epithelial neoplasms with morphological and immunohistochemical features of neuroendocrine differentiation [1, 2]. The annual age adjusted incidence of NENs is 6.98 per 100,000 [1]. The WHO Classification of Digestive System Tumours published in 2019 classified NENs as well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (PD-NECs). NETs are well differentiated and graded as low grade, intermediate grade, and high grade, depending on the mitotic rate and the Ki-67 proliferation index. In contrast, PD-NECs are poorly differentiated and high-grade, with a mitotic rate of >20 mitoses/2 mm^2 and a Ki-67 proliferation index of >20%. Moreover, they are classified as neuroendocrine carcinoma small- or large-cell types [2]. PD-NECs were not distinguished from NETs clearly before the revision of the WHO classification in 2019. Thus, NETs were often reported as PD-NECs in many papers and vice versa.

While cases of primary testicular NETs have been reported, primary testicular PD-NECs have rarely been observed [3]. Secondary testicular neoplasms are also rare [4]. Here, we report a rare case of an unknown primary PD-NEC with metastasis to the testis, which was diagnosed with orchiectomy.

Case Report/Case Presentation

A 61-year-old man with a chief complaint of left testicular swelling was referred to our hospital in 2020. He had hypertension, for which he had taken calcium channel blockers and angiotensin II receptor blockers, and no previous skin cancer history. The patient had no family history. Physical examination revealed swelling of the left testis. Ultrasonography of the left testis showed lower luminant mass which was heterogeneous in echo texture and had blood flow inside. Contrast-enhanced computed tomography revealed multiple pancreatic tumors with dilation of the main pancreatic duct, bilateral adrenal tumors, right axillary lymph node enlargement, and multiple abdominal lymph nodes enlargement (shown in Fig. 1). No significant lesion was observed in the lung field. The levels of human chorionic gonadotropin and β-human chorionic gonadotropin were normal. A primary testicular tumor with metastases to the pancreas, adrenal glands, and lymph nodes was suspected. An orchiectomy was performed in order to determine the pathological diagnosis. Macroscopically, the resected left testis measured 46 × 40 × 32 mm. The cut surface showed a white solid tumor with bleeding and necrosis (shown in Fig. 2a). Pathological examination showed diffuse sheets of highly atypical cells with scant

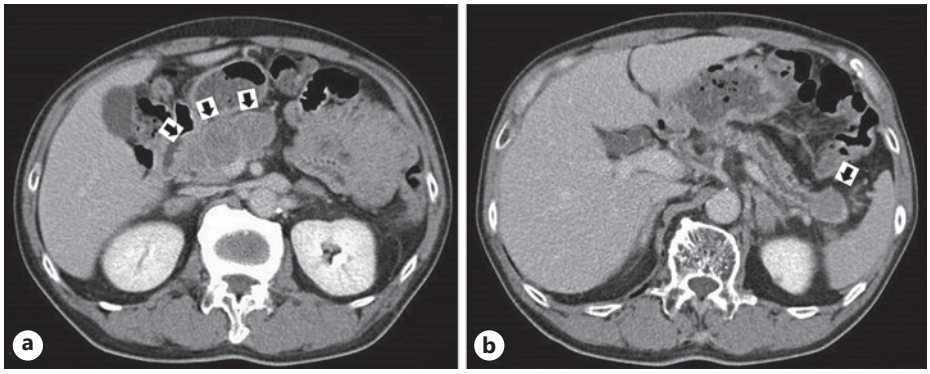

Fig. 1. Multiple tumors (arrow) of the head, body (**a**), and tail (**b**) of the pancreas on contrast-enhanced CT. CT, computed tomography.

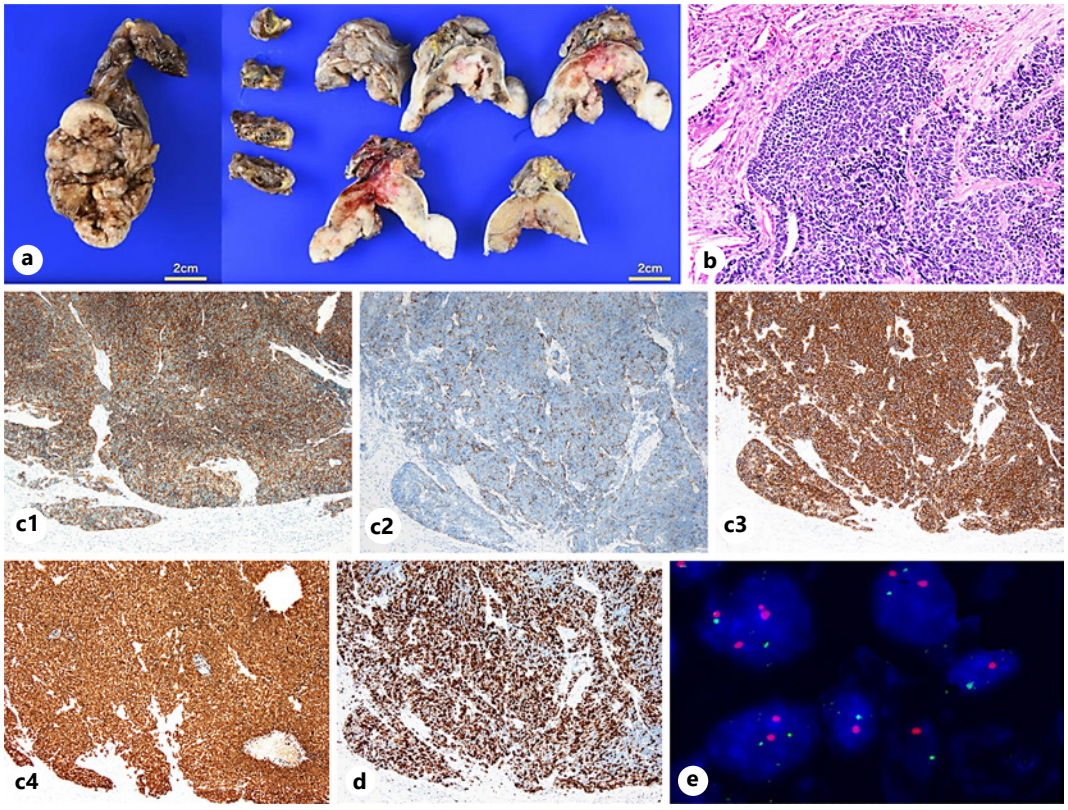

Fig. 2. Pathological specimen of the left testis. **a** The resected left testis, measuring 46 × 40 × 32 mm, with the cut surface of the white solid tumor with bleeding and necrosis. **b** Histological findings with H&E staining show diffuse sheets of highly atypical cells with scant cytoplasm and irregularly fusiform nuclei with granular chromatin. Several mitoses are visible. **c** Immunohistochemistry shows labeling for synaptophysin (**c**1), chromogranin A (**c**2), CD56 (**c**3), and TTF1 (**c**4). **d** A Ki-67 proliferation index with MIB-1 stain of 80%. **e** An isochromosome of the short arm of chromosome 12 (i12p) is not apparent by FISH (green signal). The i12p/CEP12 ratio was 104/92 (<1.5). TTF1, thyroid transcription factor-1. H&E, hematoxylin and eosin.

cytoplasm and irregularly fusiform nuclei with granular chromatin. Mitoses and apoptosis were observed remarkably (shown in Fig. 2b). In immunohistochemistry, these atypical cells were positive for synaptophysin (shown in Fig. 2c1), chromogranin A (shown in Fig. 2c2), CD56 (shown in Fig. 2c3), and thyroid transcription factor-1 (shown in Fig. 2c4), and the Ki-67 proliferation index was 80% (shown in Fig. 2d). The seminiferous tubules around the tumor were negative for SALL4 and Oct3/4 which indicate the presence of germ cell neoplasia in situ immunohistochemically. These atypical cells did not show isochromosomes of the short arm of chromosome 12 (i12p) in fluorescence in situ hybridization (FISH) (shown in Fig. 2e). According to the WHO Classification of Digestive System Tumours in 2019, we diagnosed the tumor as poorly differentiated small-cell NEC [2].

The levels of serum tumor markers were elevated with CEA of 28.7 ng/mL, NSE of 43.9 ng/mL, and ProGRP of 257 pg/mL. Esophagogastroduodenoscopy showed multiple gastric metastases resembling a submucosal tumor in the gastric body (Fig. 3a). The biopsy revealed the same histological findings as those for the testicular tumor. No abnormalities were found in colonoscopy. Contrast-enhanced magnetic resonance imaging of the head revealed multiple brain metastases (Fig. 3b). The confirmed diagnosis was PD-NEC of unknown primary, with metastases to the testis, stomach, pancreas, adrenal glands, brain, and lymph nodes.

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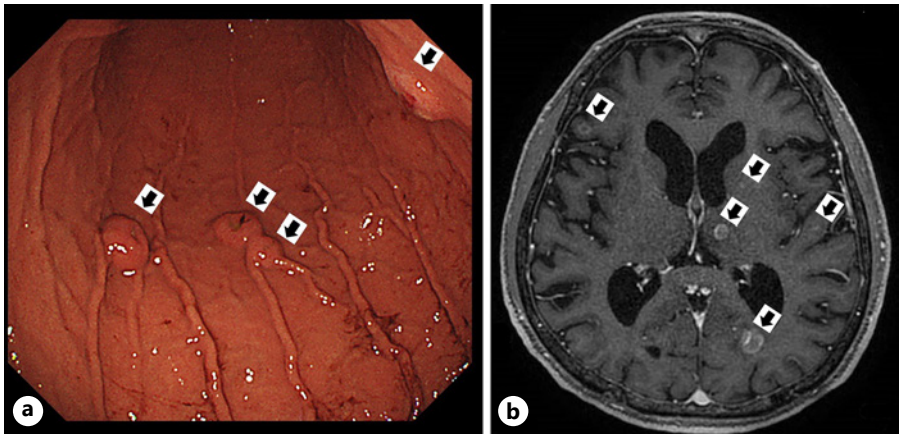

Fig. 3. Multiple metastases. **a** EGDS shows multiple gastric metastases (arrow) resembling submucosal tumors in the gastric body. **b** Contrast-enhanced MRI of the head shows multiple brain metastases (arrow). EGDS, esophagogastroduodenoscopy; MRI, magnetic resonance imaging.

Chemotherapy with etoposide (100 mg/m^2) and cisplatin (80 mg/m^2) was administered as the first-line chemotherapy in combination with pegfilgrastim. Stereotactic radiotherapy for the brain metastases was performed between the first and second cycles. After five cycles of chemotherapy, the sum of diameters of the target lesions decreased from 142 mm to 74 mm, and a partial response was achieved according to RECIST guideline version 1.1 [5]. Disease progression was observed after seven cycles of chemotherapy, with a chief complaint of appetite loss and fatigue. Magnetic resonance imaging of the head showed recurrence of the brain metastases, and computed tomography revealed enlargement of all tumors. After the whole-brain irradiation, the second-line chemotherapy with ramucirumab and paclitaxel was performed. After seven cycles, disease progression was observed with the enlargement of all tumors. Although only one cycle of third-line chemotherapy with nivolumab was performed, the chemotherapy was discontinued due to his poor performance status. He died 15 months after the diagnosis while receiving palliative care.

Discussion/Conclusion

NENs arise from enterochromaffin cells, which are distributed in most epithelial organs of the body, including the lungs, digestive tracts, pancreas, thyroid, adrenal glands, and other organs [2]. The most common primary sites of NENs are the respiratory and gastrointestinal tracts. NENs are rarely observed in the testis, which is not an epithelial organ [1]. In immunohistochemistry, NENs are positive for neuroendocrine markers of synaptophysin, chromogranin A, and CD56 [2]. In addition, TTF-1 appears on not only pulmonary NECs but also extrapulmonary NECs; for example, those arising in the digestive and urogenital systems [6].

However, there have been several reports on testicular NENs. NENs arising from the testis are thought to occur in the background of teratomas because testicular NENs have i12p, which is the most common chromosomal abnormality occurring in germ cell tumors [7]. In our case, the testicular tumor did not coexist with teratomas or germ cell neoplasia in situ which represents the precursor lesions for many types of testicular germ cell tumors. In addition, FISH did not detect i12p. Although we cannot completely deny the diagnosis of a primary testicular tumor, these findings suggest that this testicular tumor did not occur in the background of teratomas.

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Although several cases of testicular NENs have been observed, few cases of primary testicular NECs have been reported. One Croatian urologist reported a case of primary testicular large-cell neuroendocrine carcinoma with metastases to the inguinal lymph nodes [8]. In a comparative study of lung and extrapulmonary PD-NEC based on the SEER database including 162,983 cases of PD-NEC, only 9 cases (0.0055%) originated in the male genital tract except for the prostate; however, 4,151 cases (2.8%) were unknown [9]. As for germ cell tumors, most testicular germ cell tumors metastasize to the lung, liver, bone, and brain; furthermore, only one case of testicular germ cell tumor with gastric metastasis has been reported [10, 11]. In our case, since the gastric tumors were multiple and submucosal-like, we diagnosed them as metastatic tumors in the stomach [12]. In addition, the pancreatic tumors were also assessed to be secondary pancreatic tumors because these were multinodular lesions with fusion [13]. Therefore, we concluded that this case was an unknown primary PD-NEC with multiple organ metastases including the testis, rather than a primary testicular PD-NEC.

Metastases to the testis, stomach, and pancreas from solid tumors are rare. A retrospective study of 738 consecutive autopsies of adult men with solid malignant neoplasms reported only 5 cases (0.68%) of secondary testicular neoplasms [4]. In another study of 6,380 autopsied patients with solid malignant neoplasms, 347 cases (5.4%) had metastases to the stomach [14]. Moreover, in another autopsy study of 690 cases of malignant tumors, 103 cases (14.9%) had pancreatic secondary tumors [15]. In contrast, metastases from small-cell lung carcinoma and gastrointestinal NEC have often been found in the liver, bone, lung, and brain [16, 17]. Based on these studies, metastases to the testis, stomach, and pancreas are very rare for solid tumors, including NECs.

In summary, our case was an unknown primary PD-NEC rather than a primary testicular PD-NEC. Furthermore, PD-NECs rarely metastasize to the testis. To our knowledge, this is the first report of an unknown primary PD-NEC with metastasis to the testis diagnosed according to the recent classification of NENs.

Acknowledgment

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Statement of Ethics

Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. Ethical approval was not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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No funding was received.

Author Contributions

Momoko Sano is the lead author. Masaaki Noguchi is a guarantor of integrity of the entire study. Momoko Sano and Masaaki Noguchi carried out literature research and manuscript preparation. Momoko Sano, Masaaki Noguchi, Akiyoshi Kinoshita, Mayo Nakamura, Kazuhiko Koike, and Masayuki Saruta were involved in manuscript editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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