Primary small cell neuroendocrine carcinoma of adrenal gland

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Abstract

Neuroendocrine tumors are an extremely rare form of retroperitoneum tumor. A 79-year-old man presented with abdominal pain. Computed tomography and magnetic resonance imaging revealed a 51 × 36 mm mass in the left adrenal gland. Gastrofiberscopy, colonfiberscopy and positron emission tomography were performed and showed no lesions or other malignancies. Endocrine tests were normal. Two months later, the mass had grown to 68 × 52 mm. Suspecting a malignant tumor, we performed laparoscopic adrenalectomy. Histopathological diagnosis revealed the tumor was small cell neuroendocrine carcinoma. No other malignancies were revealed, so we diagnosed primary small cell neuroendocrine carcinoma of adrenal gland. To our knowledge, this is only the third report in English of primary small cell neuroendocrine carcinoma of the adrenal gland and the first report that is confined to the adrenal gland. Adrenal masses are often misdiagnosed as adenoma; however, we need to raise awareness of the potential for malignant adrenal tumors such as the rarer small cell neuroendocrine carcinoma.

Keywords Adrenal gland · Small cell neuroendocrine carcinoma

Introduction

Primary adrenal gland malignancy is a rare disease. Sometimes, functional tumors are diagnosed from clinical symptoms; however, many tumors are non-functional and found incidentally. Neuroendocrine tumors (NETs) often originates in the pancreas and gastrointestinal tract. Adrenal NET is well known as pheochromocytoma, but small cell neuroendocrine carcinoma is extremely rare. We present a case of primary small cell neuroendocrine carcinoma of the adrenal gland that was diagnosed during investigating of abdominal pain.

Case report

A 79-year-old man presented with abdominal pain. His past medical history was diabetes mellitus. Abdominal computed tomography (CT) scan revealed a 51 × 36 mm mass with inhomogeneous enhancement lesion in the left adrenal gland. Magnetic resonance imaging (MRI) revealed the mass with high intensity on T2-weighted images (T2WI) and intermediate intensity on T1-weighted images (T1WI). Whole-body CT, gastrofiberscopy, colonfiberscopy and positron emission tomography and computed tomography (PET-CT) were performed; however, no evidence of other malignancies and metastasis was observed. Endocrine testing, such as the level of plasma renin activity, dehydroepiandrosterone adrenocorticotrophic hormone, cortisol and plasma aldosterone were normal. From these findings we suspected primary carcinoma of the adrenal gland. At that time, the patient had cognitive decline, so we took a wait-and-see approach. Two months later, follow-up CT showed the mass had grown from 51 × 36 mm to 68 × 52 mm (Fig. 1a) and no tumor metastasis was detected. Tumor markers were not examined after tumor progression. Suspecting a risk for development of malignant tumor, we performed laparoscopic adrenalectomy. The total operative time was 201 min. The total blood loss was about

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Fig. 1 **a** Preoperative abdominal CT scan showed 68×52 mm mass in the left adrenal gland. **b** The postoperative 3 months, enhanced abdominal CT scan showed 22 mm mass in the spleen. **c** The postoperative 6 months, enhanced abdominal CT scan showed that the tumor in the spleen grew to 46 mm. **d** The postoperative 6 months, enhanced abdominal CT scan showed that distant metastasis to right adrenal gland was appeared

150 ml. Peritoneal dissemination was not found during the operation. Therefore, the exact reason for abdominal pain was unclear. Cut surface of the resected specimen showed white solid tumor tissue with necrosis tissue (Fig. 2a). Histological examination of the specimen showed no adrenal normal tissue in the section and adipose tissues, vessels and nerve tissues are observed. There were small cell proliferation with high nucleus-to-cytoplasm ratio and irregular necrosis was observed (Fig. 2b). The tumor was invading surrounding tissue with lymphovascular invasion. There was no evidence of tumor tissue at the surgical margin. Immunohistochemically, tumor cells were positive for CD56 and synaptophysin (Fig. 2c, d). Histopathological diagnosis revealed the tumor as small cell neuroendocrine carcinoma. Considering the patient's low level of activity of daily living and performance status, he was not given chemotherapy. The postoperative 3-month CT showed 22 mm tumor mass in the spleen (Fig. 1b). The postoperative 6-month CT revealed the splenic tumor had grown to 46 mm (Fig. 1c), and we diagnosed metastasis. Furthermore, the CT revealed local recurrence around the superior pole of the left kidney under the diaphragm, and distant metastasis to the right adrenal

gland (Fig. 1d), liver and left renal hilar lymph node. Eleven months post-operation, the patient's general condition deteriorated, and he died of cancer.

Discussion

Neuroendocrine neoplasms originate from neuroendocrine cells throughout the body. Neuroendocrine neoplasms are diagnosed by characteristic histologic features and immunoprofiles (using markers such as chromogranin, synaptophysin and CD56). In 2017 the WHO classified tumor activity based on mitotic count and Ki-67 proliferation index into NET G1, NET G2, NET G3 and neuroendocrine carcinoma (NEC). NECs are histologically composed of either small cells or large cells. The most common location of NETs is the gastrointestinal tract, followed by the respiratory tract, with other locations being rare [1]. NETs found in the retroperitoneum are mainly metastatic tumors [2]. Primary NETs of the retroperitoneum are extremely rare. Primary malignant tumors of the adrenal gland are those such as adrenal cortex carcinoma, malignant pheochromocytoma, malignant lymphoma, and neuroblastoma. Adrenal NET is well known as pheochromocytoma that originates in the adrenal medulla, and is generally benign, but can occasionally develop into malignancy. Conversely, adrenal small cell neuroendocrine carcinoma is extremely rare and is poorly understood. To our knowledge, this is only the third case report in English of primary small cell neuroendocrine carcinoma of the adrenal gland [3, 4]. One case already had distant metastasis and chemotherapy (etoposide and cisplatin) was performed [3]. The other case had tumor thrombus extending into renal vein, so nephrectomy was performed at the same time [4]. Therefore, this case was the first case that is confined to the adrenal gland.

Some studies recommended surgical excision if the adrenal tumor size is 4 cm or greater because the tumor is likely malignant [5, 6]. Mantero et al. reported that patients with carcinoma were significantly younger than patients with adenoma (median 46; range 17–84; vs. 57, 16–83 year; $p=0.05$), and a cut-off at 4.0 cm had the highest sensitivity (93%) in differentiating between benign and malignant tumors [6]. Laparoscopic adrenalectomy has become the 'gold standard' for the surgical treatment of benign adrenal neoplasms and is increasingly used for malignant tumors [7]. However, the use of laparoscopy for malignant tumors is still a matter of debate [7]. Some retrospective series have reported increased recurrence, peritoneal carcinomatosis, positive margins, and local recurrence rates for laparoscopic surgery compared to open surgery [8–12]. In our case, local recurrence was observed at 6 months after surgery, so it may have been better to perform open surgery.

Fig. 2 **a** Cut surface of the resected specimen showed white solid tumor tissue with necrosis tissue. **b** There are small cell proliferation with high nucleus-to-cytoplasm ratio and irregular necrosis was observed. (hematoxylin–eosin, Bar=100 μ m). **c** The number of

positively Ki-67 stained nuclei in the tumor is significantly increased (Bar=100 μ m). **d** Tumor cells show diffuse positivity for synaptophysin stain (Bar=100 μ m)

Recent studies reported the diagnostic efficacies of PET-CT to detect where adrenal lesions are a metastatic or benign growth. Dynamic CT showed a sensitivity of 61–100%, a specificity of 82–97%, and MRI showed a sensitivity of 79–100%, and a specificity of 82–100% [13]. On unenhanced CT scan, metastasis have more inhomogeneous and high attenuation than adenomas. On dynamic CT scan, relative percentage washout of less than 37–50% or absolute percentage washout of less than 60% may be regarded as metastases. Relative percentage washout is calculated with the following formula: washout percentage = $100 \times ([EA - DA] / EA)$, where EA is attenuation (in Hounsfield units) on contrast-enhanced scans and DA is attenuation on delayed contrast enhanced scans (usually at 10 min after starting injection). Absolute percentage washout is calculated as $100 \times ([EA - DA] / [EA - \text{attenuation value at unenhanced CT}])$ [13]. On chemical shift MRI, MRI show less than 20% decrease signal intensity change between in-phase and opposed-phase in malignant nodules [13]. Conversely, PET-CT demonstrated a sensitivity of 93–100% and a specificity of 90–96% [13]. Therefore, PET-CT appears to have a somewhat greater and more consistent accuracy than CT and MRI. It has been shown that glucose transporter type

1 plays a crucial role in determining FDG uptake in small cell neuroendocrine carcinoma [4]. Dong et al. reported that PET-CT showed intense FDG uptake of the left adrenal tumor with thrombosis of the left renal vein. The patient underwent left adrenalectomy and nephrectomy. PET-CT clearly showed not only the primary tumor but also metastatic site, so PET-CT may be a valuable tool for the detection and staging of small cell neuroendocrine carcinoma of the adrenal gland [4].

There has been no proven therapy reported for adrenal small cell neuroendocrine carcinoma. In lung small cell carcinoma, surgical resection is recommended for localized types, and pre- and postoperative chemotherapy is often reported. Conversely, for advanced lung small cell carcinoma, the effectiveness of chemotherapy including cisplatin has been shown, and cisplatin and etoposide is considered standard treatment [14–17]. Furthermore, resection of primary tumor with or without lymph node resection in patients with pancreatic or gastrointestinal NET is associated with improved survival. In the case of NEC, chemotherapy treatment such as cisplatin and etoposide is recommended according to treatment of lung small cell carcinoma [18–20]. Referring to the treatment policy of these other organs, in

this case, it may have been better to perform regional lymph node resection after adrenalectomy.

In addition, chemotherapy such as cisplatin and etoposide therapy may be reasonable if general condition is good post-operation or upon tumor recurrence. However, in the adrenal gland, it is unclear whether radical surgery was appropriate and what chemotherapy regimen should be given for small cell neuroendocrine carcinoma, so further study is necessary.

Adrenal mass is often misdiagnosed as a nonfunctioning adenoma unless endocrine activity is present. We therefore need to raise awareness of the potential for adrenal malignancy tumor such as the rarer small cell neuroendocrine carcinoma. Our case is the first case of small cell neuroendocrine carcinoma that is confined to the adrenal gland. Even though localized in the adrenal gland, the small cell neuroendocrine carcinoma displayed aggressive behavior. Clinician should keep this rare scenario in mind.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent The patient provided a written informed consent for his case report to be published anonymously.

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