Pheochromocytoma Manifesting Persistent Right Shoulder Pain and Hypochondralgia

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We report a 42-year-old female who initially complained of sub-acute onset of right upper quadrant abdominal pain with right shoulder pain. A CT scan incidentally revealed an adrenal tumor, and a final diagnosis of pheochromocytoma was made on the basis of endocrinological examinations. Symptomatically, the pheochromocytoma in our patient mimicked a hepato-biliary disease by presenting abdominal pain accompanying right shoulder pain that was assumed to be referred pain via the right phrenic nerve. Physicians may need to consider the possibility of pheochromocytoma in patients with abdominal symptoms.

Keywords: abdominal pain, adrenal tumor, hypertension, pheochromocytoma, referred pain

Introduction

Pheochromocytoma is a type of neuroendocrine tumor derived from chromaffin cells of the adrenal medulla or extra-adrenal paraganglion. The incidence rate of pheochromocytoma is only a few cases per million per year, accounting for less than 1% of hypertensive patients. Thus, there are few chances for physicians to encounter such patients in primary care settings.

Patients with pheochromocytoma present various clinical symptoms associated with excessive catecholamine. Major symptoms are episodic headache, perspiration, and tachycardia; however, this classic triad of symptoms is not present in all patients. Less common signs or symptoms include palpitation, tremor, pallor, dyspnea, generalized weakness, panic attack-type symptoms, flushing and weight loss. Back pain, orthostatic hypotension, blurred vision, polyuria, polydipsia and constipation are rare but can be associated with the disease.

Abdominal pain, on the other hand, is not expected in cases of pheochromocytoma, though some cases presenting acute abdomen have been reported. We
present a case of pheochromocytoma that presented right upper quadrant pain accompanied by right shoulder pain, mimicking hepato-biliary diseases.

**Case Presentation**

A 42-year-old female visited a hospital complaining of a two-week history of right shoulder pain in February, a winter month in Japan. Although the patient planned to see orthopedics, she was first referred to an outpatient department of internal medicine since the patient also complained of slight pain in the right upper quadrant abdomen. Palliative or provocative factors for these symptoms were not apparent. There was no particular past medical history and she had not been taking any medications. The patient had been aware of paroxysmal palpitation for the past 5 years and getting sweaty for past one year. Her family history included hypertension in her father. She was heterosexual and had no recent history of multiple sexual partners. Her vaginal discharge was unchanged. She had not been able to sleep adequately due to the pain.

On arrival, her blood pressure was 147/97 mmHg and heart rate was 71 beats per minute. She was sweating to some degree. Physical examination of the abdomen showed slight tenderness, but Murphy’s sign was absent. The examination also found orthopedic illnesses at her right shoulder unlikely and an exact site of the pain was not specified. Although blood and urine screening examinations were negative for any characteristic results, including inflammatory reaction, abdominal ultrasound (US) was subsequently performed for investigation of her abdominal pain. The US examination revealed a hypoechoic mass in the right adrenal region (Figure 1A), and contrast-enhanced computed tomography (CECT) using a low-osmolar contrast medium (Iopamidol) was performed with a suspicion of primary or secondary tumor. A well-enhanced right adrenal tumor was visualized (4 × 3 cm) (Figure 1B–D), but no other abnormal findings, such as a gallbladder lesion or an inflammation of the peritoneum, were observed. Although the symptoms did not deteriorate after CECT, her blood pressure was elevated as high as 175/108 mmHg (pulse rare, 66 beats per min). Based on these results, pheochromocytoma was suspected as a possible diagnosis and the patient was referred to our hospital. A detailed interview revealed that the patient had noticed body weight loss (13 kg over a period of 1.5 years), headache and nausea for 2 years, and general malaise and dry mouth for 1 year. Plasma noradrenaline and catecholamine metabolites in 24-hour urine collection were highly elevated (Table 1). Magnetic resonance imaging (MRI) showed the right adrenal tumor to be of high intensity in a T2-weighed image (Figure 1E), and single photon emission CT (SPECT) using 123I-metaiodobenzylguanidine (MIBG) revealed high uptake only at the right adrenal gland (Figure 1F–G). Consequently, a definitive diagnosis of solitary pheochromocytoma at the right adrenal gland was made.

Oral administration of doxazosin was initiated and surgery was planned. Preoperatively, she continued to have slight abdominal and right shoulder pain. Doxazosin was slowly loaded, up to 8 mg per day, and laparoscopic adrenalectomy was successfully performed under general anesthesia. The resected adrenal tumor was 37 × 40 mm in size, and pathologically, tumor cells containing basophilic cytoplasm showed a zellballen pattern, suggesting pheochromocytoma. No evidence of intratumor hemorrhage or malignant pathology was obtained.

Postoperative urine examination did not show excretion of excessive catecholamine, and the tumor was considered to have been completely resected. The clinical course after the surgery was uneventful without any medication, and preoperative activation of renin-aldosterone system due to intravascular volume loss was normalized after the surgery (Table 1).

**Discussion**

With the development of imaging methods, many cases of pheochromocytoma have been incidentally detected. In a case series, it was reported that 49% of pheochromocytoma cases were discovered by chance. Another report showed that more than half of adrenal pheochromocytoma cases were asymptomatic and were unmasked by image investigation for other reasons. Previous cases of pheochromocytoma presenting abdominal pain were reported to be caused by intratumor haemorrhage. In our patient, however,
Figure 1. Radiological findings
A: Abdominal ultrasound (US), B: Contrast-enhanced CT (CECT, early phase), C: CECT (late phase), D: CECT (early phase, coronal), E: Magnetic resonance imaging (MRI, T2-weighed image), and F–G: 123I-MIBG scintigraphy (F: SPECT)

US demonstrated a hypoechoic tumor close to the liver and right kidney (A). CECT and MRI showed early enhancement and high intensity in T2-weighed images, respectively, in the right adrenal region (B–E). Coronal section revealed that the tumor had contact with the diaphragm next to the foramen of the vena cava (D). 123I-MIBG scintigraphy demonstrated a high spot at the same lesion, suggesting solitary pheochromocytoma (F–G).

Table 1. Endocrine data

<table>
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<tr>
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<th>Pre-operation</th>
<th>Post-operation</th>
<th>(normal range)</th>
<th>units</th>
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<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adrenaline</td>
<td>0.02</td>
<td>0.02</td>
<td>(≤0.10)</td>
<td>ng/mL</td>
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<tr>
<td>Noradrenaline</td>
<td>9.00</td>
<td>0.59</td>
<td>(0.10–0.50)</td>
<td>ng/mL</td>
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<td>Dopamine</td>
<td>0.03</td>
<td>≤0.01</td>
<td>(≤0.03)</td>
<td>ng/mL</td>
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<tr>
<td>ACTH</td>
<td>10.4</td>
<td>35.2</td>
<td>(7.2–63.3)</td>
<td>pg/mL</td>
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<tr>
<td>Cortisol</td>
<td>7.5</td>
<td>11.5</td>
<td>(8.0–25.0)</td>
<td>µg/dL</td>
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<td>Plasma renin activity</td>
<td>2.8</td>
<td>0.5</td>
<td>(0.3–2.9)</td>
<td>ng/mL/h</td>
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<td>Aldosterone</td>
<td>49.9</td>
<td>8.4</td>
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<td>ng/dL</td>
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<td>Neuron-specific enolase</td>
<td>15.76</td>
<td>11.41</td>
<td>(≤16.30)</td>
<td>ng/mL</td>
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<tr>
<td><strong>Urine</strong></td>
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<td></td>
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<tr>
<td>Adrenaline</td>
<td>11.0</td>
<td>7.2</td>
<td>(3.0–41.0)</td>
<td>µg/day</td>
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<td>Noradrenaline</td>
<td>3638.5</td>
<td>118.5</td>
<td>(31.0–160.0)</td>
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<td>Dopamine</td>
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<td>Metanephrine</td>
<td>0.20</td>
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<td>(0.04–0.18)</td>
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<tr>
<td>Normetanephrine</td>
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<tr>
<td>Vanillylmandelic acid</td>
<td>23.9</td>
<td>4.2</td>
<td>(1.5–4.3)</td>
<td>mg/day</td>
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</table>
radiological and histological examinations did not reveal any hemorrhagic findings. Additionally, although clinical courses of the previous cases were acute onset, our patient complained of pain for two weeks (sub-acute course). In these points, the occurrence of her abdominal pain was unique, compared to the previous cases. The main cause of the abdominal pain was uncertain; however, there are a few possibilities for the pathophysiology.

Adrenal glands are innervated by the celiac plexus providing sensory input; thus, visceral pain can occur as a result of pathological change in the adrenal glands. The enlarged adrenal gland itself might have stimulated the sensory nerve and induced the abdominal symptom. Alternatively, elevation of plasma catecholamine might have sympathetically induced the pain by activating nociceptive afferent fibers. However, deterioration of the abdominal pain accompanying catecholamine surge was not evident preoperatively. The reason for improvement of the abdominal pain before the operation was uncertain. However, administration of the alpha-blocker, doxazosin, might have worked for the better.

Right shoulder pain associated with liver diseases is well known as a representative referred pain. The phenomenon develops by a stimulation of right phrenic nerve that innervates diaphragm and a part of peritoneum. Similarly, the right shoulder pain in our case was assumed to occur as a referred pain derived from the adrenal tumor. Phrenic nerve, mainly deriving from the 4th cervical ganglion, passes close to subclavian vessels and enters the thoracic cavity. The right phrenic nerve runs through the right side of the superior vena cava and right atrium, descends between the pericardium and mediastinal pleurisy, and reaches the diaphragm. A part of the phrenic nerve innervates the inferior surface of the diaphragm and gallbladder by passing through the foramen of the vena cava at the central tendon of the diaphragm. The adrenal gland is located at retroperitoneal space and any pathological changes usually do not influence the phrenic nerve. However, the enlarged adrenal gland in our patient adjoined the liver and diaphragm next to the foramen of the vena cava, and which possibly irritated the right phrenic nerve, inducing the right shoulder pain. With a slow-growth tumor, the pain was assumed to develop subacutely.

Since abdominal or shoulder pain is unexpected in patients with pheochromocytoma, the physician did not recall the disease at all as a differential diagnosis during the initial visit and ordered a CECT examination. However, the probability of pheochromocytoma should have been noted, considering the existence of hypertension and an adrenal mass, confirmed by abdominal US. According to a popular theory, CECT can evoke a catecholamine crisis, leading to a serious condition, and it should be avoided if possible. Recently, however, it has been reported that administration of an intravenous low-osmolar contrast does not induce abnormal release of norepinephrine and epinephrine and can be performed in patients with pheochromocytoma. In the present case, a low-osmolar, nonionic contrast medium was used, resulting in rapid elevation of blood pressure without any other harmful events.

Endocrine characteristics of pheochromocytomas regarding dominant secretion of either noradrenaline or adrenaline may also be related to cardiovascular symptoms. The present case showed a noradrenaline-dominant secretory pattern, which is generally known to cause sustained hypertension rather than specific symptoms, such as pallor and tremor, albeit this also has some exceptions. Additionally, it is also important to pay attention to adverse catecholaminergic effects when several drugs including dopamine D2 antagonists, such as metoclopramide, and β-blockers and hormones, such as glucagon and glucocorticoids, are administered to these patients. In the future, an increasing number of asymptomatic or atypical cases of pheochromocytoma may be encountered. Though rare, catecholamine-producing tumors might be included in the differential diagnosis of any complaints or symptoms.

In summary, we presented an atypical manifestation of pheochromocytoma that mimicked hepato-biliary diseases by presenting right hypochondralgia concurrently with right shoulder pain. General practitioners may need to be aware that pheochromocytoma can manifest various symptoms, as shown here, so as not overlook such cases.
Conflicts of Interests
All authors state that there are no conflicts of interests to declare.

References