A case of pheochromocytoma associated with liver abscess and intestinal pseudo-obstruction

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Abstract: Pheochromocytomas can present with various symptoms. Nonspecific manifestations of pheochromocytoma include intestinal pseudo-obstruction and weight loss. Here, we present a case of pheochromocytoma in which prolonged intestinal pseudo-obstruction due to excess catecholamines was one of the factors leading to the development of a liver abscess. An 18-year-old male patient with a history of status epilepticus and severe intellectual disability was transferred to our hospital for a thorough examination of fever and constipation that had lasted for 2 months. When admitted to our hospital, he had fever, and his body mass index was 9.5 kg/m². Upon comprehensive examination of the patient’s fever, the blood culture was found positive for Bacteroides. Computed tomography showed findings of intestinal pseudo-obstruction and a low density region in the liver that indicated a liver abscess. Imaging studies also revealed a right adrenal mass and endocrinological test showed elevated plasma norepinephrine and urine normetanephrine levels. In addition, the right adrenal mass showed uptake on 123I-metaiodobenzylguanidine scintigraphy. These findings led to a definite diagnosis of pheochromocytoma. The patient was eventually diagnosed with a pheochromocytoma coexisting with a liver abscess. After treating the liver abscess with antibiotics and ultrasound-guided drainage, an adrenalectomy was performed. The pathological findings were consistent with pheochromocytoma. Postoperatively, the catecholamine excess normalized and intestinal pseudo-obstruction and weight loss improved. We suspected that prolonged intestinal pseudo-obstruction resulted in bacterial translocation and development of a liver abscess. To the best of our knowledge, this is the first report of a pheochromocytoma associated with a liver abscess. Moreover, the clinical presentation of this patient was unusual for pheochromocytoma, as the patient did not have typical symptoms such as hypertension or tachycardia, but rather presented with constipation, intestinal pseudo-obstruction, and weight loss. This case provides valuable insight regarding the impact of catecholamine excess on the intestinal tract and body weight.

Keywords: intestinal pseudo-obstruction, liver abscess, pheochromocytoma, weight loss

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long-term intestinal pseudo-obstruction caused by excessive catecholamines was one of the factors contributing to the development of a liver abscess.

Case report
An 18-year-old male patient was transferred to our hospital for a thorough examination of fever and constipation that had lasted for 2 months. He was admitted to the previous hospital for treatment of fever and was being closely examined, but the cause of fever and constipation remained unknown. Computed tomography (CT) performed at the previous hospital revealed a right adrenal mass. However, because there was no endocrinologist, a thorough examination of the adrenal mass was not performed. The patient had a history of status epilepticus at the age of 8 years and was diagnosed with a severe intellectual disability. The patient had never been diagnosed with hypertension. His diet was administered via tube feeding through a gastric tube. He had been prescribed with antiepileptic drugs for a long duration for treatment of epilepsy. In addition, he had been taking proton-pump inhibitors (PPIs) for more than a year for treatment of reflux esophagitis.

When admitted to our hospital, he was noticeably underweight with a height of 153 cm, weight of 23.0 kg, and body mass index (BMI) of 9.5 kg/m². He gained up to 28 kg 8 years ago, but then lost weight, reaching 23 kg 2 years ago, and has not gained weight since then. He was unable to communicate, and his body temperature was 38.8°C. His pulse rate and blood pressure were 100 bpm and 118/50 mmHg, respectively. Physical examination revealed that his abdomen was distended and tympanic to percussion. The bowel sounds were hypoactive. Laboratory data showed a high white blood cell count and C-reactive protein level, indicating inflammation. Elevated levels of liver enzymes were also observed. The CT scan and abdominal radiograph showed marked colonic and small bowel gas, consistent with intestinal pseudo-obstruction. An internal low density mass measuring $4.5 \times 6.5 \times 6.5$ cm was detected in the right adrenal gland. In addition, a new low density region was observed in the liver near the right adrenal gland; this region was not observed in the CT scan performed at the previous hospital 2 months before admission. Blood culture on admission revealed *Bacteroides*, and the low density area in the liver was diagnosed as a liver abscess. Endocrinological results showed elevated plasma norepinephrine and elevated urine normetanephrine. The adrenocorticotropic hormone (ACTH) was not suppressed denying excessive cortisol production from the adrenal mass. Plasma renin activity and aldosterone levels were elevated, suggesting intravascular dehydration. The thyroid function test showed low levels of free triiodothyronine and free thyroxine without elevated levels of thyroid-stimulating hormone, suggesting a nonthyroidal illness (Tables 1 and 2). $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy showed uptake in the right adrenal mass (Figure 1(A)). No uptake was observed in the low density areas of the liver (Figure 3). The presence of adrenal nodules with uptake on $^{123}$I-MIBG scintigraphy and high catecholamine levels led to a definite diagnosis of an adrenal pheochromocytoma. No family history of medullary thyroid cancer or pheochromocytoma was reported, and the genetic test results showed no mutations in RET, SDHB, SDHC, SDHD, TMEN127, MAX or VHL genes.

For the treatment of liver abscess, antibiotic (ampicillin/subactam, 12 g/day) was initiated. In addition, ultrasounds-guided drainage of the liver abscess was performed on the fourth and eleventh day of hospitalization, and yellowish pus was aspirated with positive culture results for *Escherichia coli* and *Bacteroides*. Percutaneous drainage and antibiotic therapy improved the inflammatory response and fever (Figure 2). After treatment of liver abscess, an alpha-adrenergic receptor antagonist, phentolamine, was administered intravenously, and the dose was increased to 1.8 mg/h to reverse catecholamine-induced blood volume contraction preoperatively and to prevent severe hypotension after tumor removal. Two months after hospitalization, the patient underwent a right adrenalectomy. The tumor weighed 60 g, and the pathological findings were consistent with pheochromocytoma. The Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP) score was 6, and the tumor was graded as moderately differentiated.³

Postoperatively, blood pressure and pulse remained stable; blood pressure was around 100/60 mmHg, and pulse rate was 60–70 bpm. In addition, the plasma norepinephrine and urine normetanephrine levels normalized (Table 2). Constipation and intestinal gas retention com-
A year after surgery, the patient gained back 7 kg, and his BMI improved to 12.3 kg/m².

**Discussion**

The notable findings of this case were its unique clinical presentation and the co-occurrence of pheochromocytoma and liver abscess. To the best of our knowledge, this is the first report of a pheochromocytoma associated with a liver abscess.

First, the clinical presentation of this case is unique. The classic symptoms of pheochromocytoma include headache, palpitations, sweating, and hypertension. Among these, sustained or paroxysmal hypertension is the most common sign of pheochromocytoma. For instance, Philips reported that paroxysmal hypertension and sustained hypertension occur in 45% and 50% of patients with pheochromocytoma, respectively, and only 5% of patients remain normotensive. In our case, frequent blood pressure measurements showed no evidence of paroxysmal hypertension. In addition, tachycardia associated with fever was completely improved after surgery (Figure 1(B)).

### Table 1. Laboratory results on admission.

| Variable                  | Reference range | Results  |
|---------------------------|-----------------|----------|
| Complete blood count      |                 |          |
| White-cell count, μl      | 4000–8000       | 21,600   |
| Neutrophil, %             | 40.0–70.0       | 78.4     |
| Lymphocyte, %             | 27.0–47.0       | 15.4     |
| Monocyte, %               | 2.0–8.0         | 5.8      |
| Basophil, %               | 0.0–1.0         | 0.2      |
| Eosinophil, %             | 0.2–7.0         | 0.0      |
| Hemoglobin, g/dl          | 14–18           | 9.8      |
| Platelet count, μl        | 20.0–40.0 × 10⁴| 47.4 × 10⁴|

### Table 1. (Continued)

| Variable                  | Reference range | Results  |
|---------------------------|-----------------|----------|
| Endocrinological findings |                 |          |
| Aldosterone, pg/ml        | 35.7–240        | 303.6    |
| PRA, ng/ml/h              | 0.3–2.9         | 11.0     |
| ACTH, pg/ml               | 7.2–63.3        | 52.6     |
| Cortisol, μg/dl           | 4.4–21.1        | 21.1     |
| TSH, μlU/ml               | 0.50–5.00       | 1.19     |
| FT3, pg/ml                | 2.30–4.00       | 1.15     |
| FT4, ng/dl                | 0.90–1.70       | 0.62     |

ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; Cre, creatinine; CRP, C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; Glu, glucose; γGTP, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-Chol, high-density lipoprotein-cholesterol; IP, inorganic phosphorus; K, potassium; Na, sodium; PRA, plasma renin activity; T-bil, total bilirubin; T-Chol, total cholesterol; TG, triglyceride; TSH, thyroid-stimulating hormone.
observed during the infection; however, neither tachycardia nor sweating was observed after the fever resolved. Instead, constipation, intestinal pseudo-obstruction, and weight loss were observed as clinical manifestations of the pheochromocytoma.

Constipation and intestinal pseudo-obstruction are occasionally observed complications of pheochromocytoma caused by hypersecretion of catecholamines, which act on alpha-2-adrenergic receptors of intestinal smooth muscle cells to decrease intestinal movement. Thosani et al. reported that 6%

### Table 2. Results of catecholamines before and after adrenalectomy.

| Variable | Reference range | Before surgery | After surgery |
|----------|----------------|----------------|--------------|
| **Catecholamines in plasma** | | | |
| Norepinephrine, pg/ml | 100–500 | 1403 | 484 |
| Epinephrine, pg/ml | 0–100 | 87 | 81 |
| Dopamine, pg/ml | 0–30 | 45 | 15 |
| **Catecholamines in 24-h urine** | | | |
| Total catecholamines in 24-h urine, μg/day | 34–198 | 515 | 195 |
| **Metanephrines in 24-h urine** | | | |
| Metanephrine, mg/day | <0.18 | 0.24 | 0.13 |
| Normetanephrine, mg/day | <0.28 | 8.36 | 0.28 |

**Figure 1.** (A) Imaging findings results of the CT scan and 123I-MIBG scintigraphy. CT scan revealed an internal low density mass in the right adrenal gland, and 123I-MIBG scintigraphy confirmed uptake in the same mass. (B) Change in abdominal radiograph. Abdominal radiographs on admission (a), after phentolamine administration (b), and after surgery (c). Marked intestinal distension and gas were partially relieved by phentolamine administration and were completely improved by adrenalectomy. CT, computed tomography; MIBG, 123I-metaiodobenzylguanidine.
Figure 2. Clinical course. The top section shows the changes in the CT scan, and the bottom section shows the change in the white blood count and C-reactive protein. Antibiotic treatment and ultrasound-guided drainage improved the inflammatory response. The low density region of the liver indicating abscess disappeared on the 38th day. The picture shows a sample taken from drainage (A). Yellowish pus was aspirated with positive culture results for *Escherichia coli* and *Bacteroides*. The black arrows indicate the pheochromocytoma, and the dotted line indicates the liver abscess.

CRP, C-reactive protein; CT, computed tomography; WBC, white blood count.

Figure 3. 123I-MIBG scintigraphy showing the adrenal mass and liver abscess. The top row shows the CT scan (a) and 123I-MIBG scintigraphy (b) images. The bottom row provides a description of the image. The circle indicates the adrenal mass, and the white arrows indicate the liver abscess. Area of the liver abscess showed no uptake on 123I-MIBG scintigraphy.

CT, computed tomography; MIBG, 123I-metaiodobenzylguanidine.
of patients with paragangliomas or pheochromocytomas experienced constipation. In addition, they reported that constipation is a complication usually observed in patients with primary tumors larger than 5 cm, as in this case, or with extensive metastatic disease. Administration of an alpha-adrenergic receptor antagonist, phentolamine, and tumor reduction is known to be effective approaches for improving bowel movement in pheochromocytoma patients. Although phentolamine was partially effective in our case, the patient’s constipation and intestinal pseudo-obstruction were completely resolved only after tumor resection.

Weight loss is also a sign of pheochromocytoma and occurs because of a catecholamine-induced hypermetabolic state. In a study of 360 patients with pheochromocytomas and paragangliomas, Krumeich et al. showed that norepinephrine and normetanephrine levels were inversely associated with weight. In addition, Petrák et al. demonstrated that chronic catecholamine overproduction leads to a hypermetabolic state characterized by increased resting energy expenditure. They also stated that adrenalectomy normalizes energy metabolism and eventually increases BMI and body fat content. The present case showed a maximum weight of 28 kg at the age of 12 years, but subsequently lost weight, reaching 23 kg at the age of 16 years, and did not gain weight thereafter. Following surgery, however, the patient’s weight gradually improved. This indicates that the weight loss was partly due to pheochromocytoma.

Second, this case was associated with a liver abscess. The most common cause of pyogenic liver abscess is biliary disease, such as choledocholithiasis or cholecystitis. In some cases, however, nonbiliary diseases, such as diverticulitis or appendicitis, can cause liver abscess. In the present case, no abnormalities were observed in the bile duct system. We suspected that prolonged intestinal pseudo-obstruction led to the portal venous system, eventually resulting in a liver abscess. In addition, Elfiky et al. recently reported that patients using PPIs are associated with 2.36 times increased risk of developing liver abscesses because PPIs elevate the gastric pH, thus increasing the risk of bacterial translocation. Our patient had been prescribed a PPI, namely, lansoprazole, for more than a year. Although there are no past reported cases of pheochromocytoma coexisting with liver abscess, we speculate that the patient in this case developed a liver abscess because of a combination of multiple risk factors, including long-term intestinal pseudo-obstruction, low nutrition, tube feeding, and PPI prescription.

While there are no reported cases of pheochromocytoma associated with liver abscess, some cases of pheochromocytoma mimicking liver abscesses have been reported in the past. For instance, Sarveswaran et al. reported a case of cystic pheochromocytoma mimicking a liver abscess. Based on these previous reports, we considered it essential to carefully differentiate whether the low density area of the liver in this case was a liver abscess or part of a pheochromocytoma before performing drainage to avoid puncturing the pheochromocytoma and leading to crisis. We diagnosed the low density region of the liver as a liver abscess based on three reasons. First, the blood culture was positive, and it was certain that there was an infection. Second, it was evident that the low density region of the liver had developed rapidly. Finally, there was no uptake on 123I-MIBG scintigraphy in the area (Figure 3).

In conclusion, we report an extremely rare case of pheochromocytoma with a liver abscess. We hypothesize that prolonged intestinal pseudo-obstruction caused by pheochromocytoma led to bacterial translocation and development of the liver abscess in a frail patient. This case also highlights the impact of catecholamine excess on the intestinal tract and body weight.

Declarations

Ethics approval and consent to participate
Written consent was obtained from the patient’s mother for the publication of this case report.

Consent for publication
Not applicable.

Author contributions
Mikiko Okazaki-Hada: Conceptualization; Data curation; Investigation; Resources; Validation; Visualization; Writing – original draft.
Izumi Fukuda: Conceptualization; Supervision; Validation; Writing – review & editing.
Ryuta Nagaoka: Resources; Writing – review & editing.
Mototsugu Nagao: Conceptualization; Validation; Writing – review & editing.

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References
1. Lenders JW, Duh QY and Eisenhofer G et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 1915–1942.
2. Neumann HPH, Young WF Jr and Eng C. Pheochromocytoma and paraganglioma. N Engl J Med 2019; 381: 552–565.
3. Kimura N, Takayanagi R, Takizawa N, et al. Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma. Endocr Relat Cancer 2014; 21: 405–414.
4. Fagundes GFC and Almeida MQ. Perioperative management of pheochromocytomas and sympathetic paragangliomas. J Endocr Soc 2022; 6: 1–8.
5. Phillips RA. Pheochromocytoma. J Clin Hypertens 2002; 4: 62–72.
6. Okumura S, Sumie M and Karashima Y. Perioperative anesthetic management of intestinal pseudo-obstruction as a complication of pheochromocytoma. JA Clin Rep 2019; 5: 35.
7. Funazaki S, Yamada H and Hara K. Pseudo intestinal obstruction caused by malignant paraganglioma. Intern Med 2021; 60: 3507–3508.
8. Thosani S, Ayala-Ramirez M, Román-González A, et al. Constipation: an overlooked, unmanaged symptom of patients with pheochromocytoma and sympathetic paraganglioma. Eur J Endocrinol 2015; 173: 377–387.
9. Sawaki D, Otani Y, Sekita G, et al. Pheochromocytoma complicated with refractory paralytic ileus dramatically improved with intravenous administration of alpha-adrenergic receptor antagonist, phenolamine. J Clin Gastroenterol 2003; 37: 194.
10. Krumeich LN, Cucchiara AJ, Nathanson KL, et al. Correlation between plasma catecholamines, weight, and diabetes in pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 2021; 106: e4028–e4038.
11. Petrák O, Haluzíková D, Kaválková P, et al. Changes in energy metabolism in pheochromocytoma. J Clin Endocrinol Metab 2013; 98: 1651–1658.
12. Rahimian J, Wilson T, Oram V, et al. Pyogenic liver abscess: recent trends in etiology and mortality. Clin Infect Dis 2004; 39: 1654–1659.
13. Kaplan GG, Gregson DB and Laupland KB. Population-based study of the epidemiology of and the risk factors for pyogenic liver abscess. Clin Gastroenterol Hepatol 2004; 2: 1032–1038.
14. Elfiky A, Alsheikh M, Hosry J, et al. Is the use of proton pump inhibitors a predisposing factor for pyogenic liver abscesses. Gastroenterology Res 2021; 14: 184–189.
15. Toyoshima Y, Hosokawa Y, Takada S, et al. A case of cystic pheochromocytoma mimicking liver abscess. Hinyokika Kiyo 2011; 57: 373–376 (in Japanese).
16. Sarveswaran V, Kumar S, Kumar A, et al. A giant cystic pheochromocytoma mimicking liver abscess an unusual presentation: a case report. Clin Case Rep 2015; 3: 64–68.