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Case Report

Acute Inflammatory Syndrome and Intrahepatic Cholestasis Caused by an Interleukin-6-Producing Pheochromocytoma with Pregnancy

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Abstract We herein describe the case of a 30-year-old woman who experienced high fever during the puerperal period and was diagnosed with pheochromocytoma. Acute inflammatory syndrome, as indicated by the elevated serum levels of interleukin-6 (IL-6), and cholestatic liver dysfunction were observed. Since this condition resolved before the operation, it was probably caused by massive central necrosis within the tumor. The IL-6 production from the tumor cells was confirmed by immunohistochemistry. When a case of pheochromocytoma accompanied with acute inflammatory syndrome is encountered, the possibility that the tumor itself might produce some cytokines should be considered, even in the presence of massive necrosis within the tumor.

Key words : acute inflammatory syndrome, IL-6, pheochromocytoma, pregnancy

Introduction

Pheochromocytoma is an adrenomedullary catecholamine-secreting tumor, which accounts for less than 0.1% of all cases of hypertension¹. Furthermore, it is rarely diagnosed during either pregnancy or the puerperal period^{2,3}, and such an incidence occurs in 2 of 30,246 pregnant patients (0.007%) at the Mayo Clinic⁴. Large pheochromocytomas often exhibit various types of necrosis, probably because the levels of intratumoral catecholamines—strong vasoconstrictor substances—are extremely high.

Pheochromocytomas have also been reported

to secrete several biologically active neuropeptides, cytokines, and hormones in addition to catecholamines^{5,6}. Interleukin (IL)-6 is one of the cytokines produced by the pheochromocytomas, and its overproduction causes acute inflammatory responses⁶⁻⁹.

We herein describe the case of a 30-year-old woman who presented with an IL-6-producing pheochromocytoma with massive necrosis; the pheochromocytoma was diagnosed for the first time during the puerperal period.

Case report

A 30-year-old woman was first diagnosed with hypertension in the 24th week of gestation. However, her blood pressure (BP) remained below 130/80 mmHg; thus, no medication was administered. In the 36th week of gestation, proteinuria

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was first detected. During a regular checkup in the 37th week, her BP was elevated to 200/146 mmHg, and the amount of urine protein had increased. She did not show symptoms of pheochromocytoma such as headache, sweating, palpitations, and orthostatic hypotension. Consequently, she was diagnosed with preeclampsia. She was admitted to our center for emergency maternal, fetal, and neonatal care, and a cesarean operation was performed under intravenous infusion of nifedipine hydrochloride to control her BP. A healthy baby weighing 2,555 g was delivered, and the newborn's Apgar score was good. After delivery, the patient's systolic BP increased from 160 to 200 mmHg, and she was administered 10 mg nifedipine CR to induce Ca blockade. Her clinical course is shown in Fig. 1. In the third week of the puerperal period, her body temperature (BT) increased to 38 °C. The pattern of the fever was remittent. Leukocytosis, with the WBC count of 10,800/ μ L and 85% segmented forms, and the elevated C-reactive protein (CRP) level of 13.2 mg/dL suggested that a bacterial infection may have caused the high

fever. However, empirical antibacterial therapy proved ineffective. Abdominal ultrasonography revealed a mass measuring 10 cm in diameter, which was located in the left upper region of the abdomen. The plasma norepinephrine (NE) level was remarkably high (25,978 pg/mL, normal range [NR]: 100–450 pg/mL) in the seventh week after delivery. By the eighth week after delivery, her BT gradually decreased to within the normal range without the administration of nonsteroidal anti-inflammatory drugs (NSAIDs). She was rehospitalized 10 weeks after delivery for further examination.

On admission, physical examination revealed a height of 153 cm, a weight of 40.9 kg, and a BT of 36.8 °C. Her pulse rate was 100 beats/min and BP was 120/72 mmHg under treatment with nifedipine CR at a dosage of 10 mg/day. No changes in the fundus oculi suggestive of hypertension were observed. Complete blood count showed anemia and thrombocytosis, but the leukocyte count had returned to within the normal range. The serum level of CRP remained elevated by 6.6 mg/dL. An impaired glucose

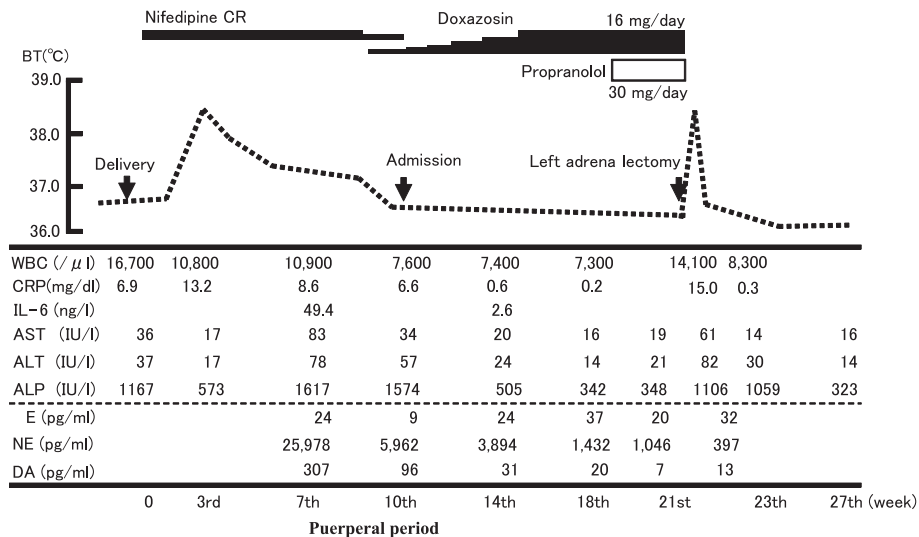


Fig. 1 Clinical course : From 3 to 8 weeks after delivery, the patient's body temperature (BT) fluctuated between 37 and 38 °C, and the WBC counts and the serum C-reactive protein (CRP) levels were increased. The serum level of interleukin 6 (IL-6) was confirmed to be high in the sixth week of the puerperal period; in the 13th week after delivery, this level returned to normal without any anti-inflammatory treatment. The plasma level of norepinephrine (NE) gradually decreased from 25,978 to 1,046 pg/mL before the resection of the tumor. After the BP and pulse rate were controlled, left adrenalectomy was performed. On the day following the operation, the patient's BT again increased to 38 °C.

tolerance with insulin resistance and a deficiency of insulin secretion in the early phase were revealed by a 75-g oral glucose tolerance test (OGTT). The level of plasma NE decreased to 5,962 pg/mL at the 10th week after delivery. The levels of urinary NE and normetanephrine were significantly elevated to 2,011 $\mu\text{g}/\text{day}$ (NR: 48.6–168.4 $\mu\text{g}/\text{day}$) and 17.1 mg/day (NR: 0.09–0.33 mg/day) respectively, while the plasma and urine levels of epinephrine (E) and metanephrine were both within the normal range.

Magnetic resonance imaging (MRI) of the abdomen demonstrated a mass measuring 10 cm in diameter in the upper left region of the kidney; On T1-weighted images, the periphery of the mass was enhanced, while the center was not, thus suggesting the existence of massive necrosis (Fig. 2). ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy revealed the accumulation of the isotope in the left suprarenal region. On the basis of the above data, the tumor was diagnosed as pheochromocytoma.

After the definite diagnosis of pheochromocytoma was established, doxazosin was administered, starting at a dosage of 2 mg/day, which was gradually increased up to 16 mg/day. In addition, 30 mg propranolol was administered for

tachycardia. Consequently, the systolic BP was lowered to levels ranging from 90 to 130 mmHg, and the pulse rate ranged from 80 to 90 beats/min.

In the seventh week after delivery, the serum level of IL-6 was measured in order to confirm ectopic IL-6 secretion from the tumor; at this time the patient's BT fluctuated between 37 and 38 $^{\circ}\text{C}$, and the serum IL-6 level was found to be high. However, the serum levels of IL-6 and CRP gradually returned to normal without any medication in the 14th and 18th week after delivery, respectively, when her BT was completely normal. The level of plasma NE also gradually decreased to 1,046 pg/mL over a 5-month period after delivery. With regard to the liver function, the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), predominantly the type 2 isozyme, were elevated along with the elevated levels of the acute inflammatory markers. The results of the serological tests for hepatitis A, B, and C viruses were negative. In addition, anatomical obstruction to the bile flow and bile duct dilatation were not observed on abdominal ultrasonography images. The levels of the abovementioned enzymes gradually decreased to within the normal range by 18 weeks after delivery, when the serum levels of IL-6 and CRP had already returned to normal. These findings indicated that the cholestatic liver dysfunction was related to the inflammatory responses.

Thereafter, an open left adrenalectomy was performed using an anterior transperitoneal approach. The resected tumor, which measured 11 \times 9 \times 8 cm and weighed 320 g, was well capsulated and showed massive central necrosis (Fig. 3). Histological examination of the tumor showed an area of central necrosis due to infarction (Fig. 4A). The tumor cells had round to oval nuclei and abundant basophilic granular cytoplasm; they were arranged in an alveolar fashion and were separated by thin fibrovascular septa (Fig. 4B).

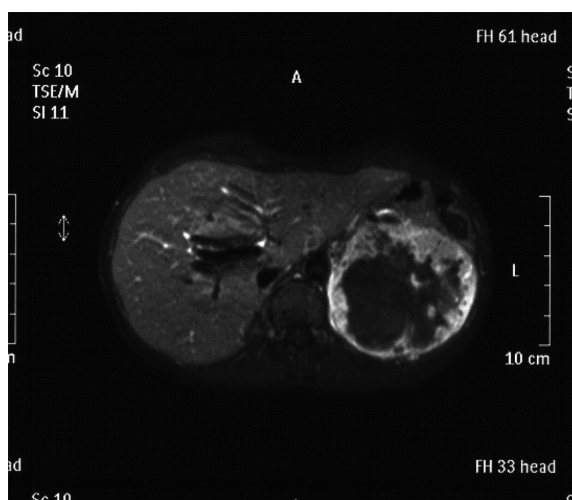


Fig. 2 Abdominal magnetic resonance imaging (MRI) : A mass measuring 10 cm was observed. The center of the tumor was not enhanced, while the periphery was enhanced on T1-weighted images.

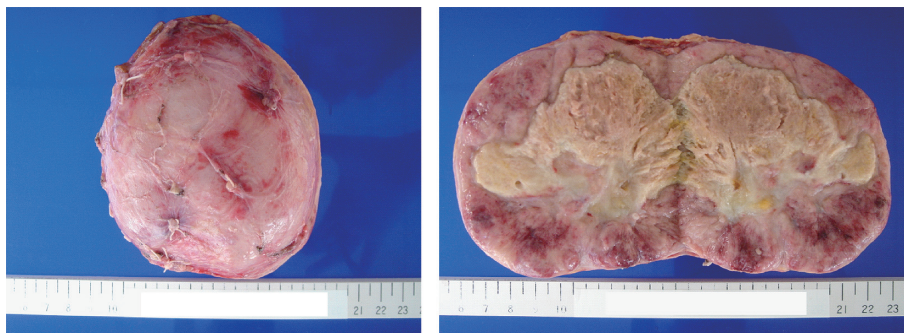


Fig. 3 Macroscopic finding of pheochromocytoma showing massive central necrosis.

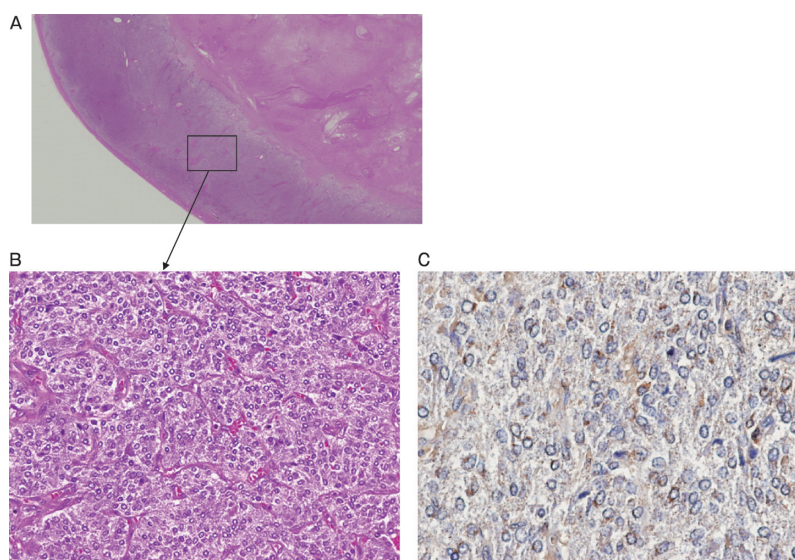


Fig. 4 Histological findings of the pheochromocytoma : (A) On examination under low-power magnification, an area of necrosis within the tumor was evident (hematoxylin-eosin staining, $\times 20$). (B) On examination under high-power magnification, nested arrangement of tumor cells separated by thin fibrovascular septa was noted (hematoxylin-eosin staining, $\times 100$). (C) Immunohistochemical staining of the pheochromocytoma for interleukin-6 (IL-6) showed that the cytoplasm of the tumor cells was positive for IL-6. ($\times 400$)

In order to determine whether the resected tumor produced IL-6, we performed an immunohistochemical study using goat polyclonal antibodies against a C-terminal peptide of mouse IL-6, which cross-reacts with human IL-6. Immunohistochemistry revealed that the tumor cells were positive for IL-6 (Fig. 4C).

On the day after the operation, the patient's BT again increased to 38 °C. Leukocytosis, with the WBC count of 14,100 / μ L and the elevated CRP level of 15.0 mg/dL were observed. We suspected bacterial infection and administered 2 g/day cefazolin for 6 days. After 3 days, the serum levels of AST, ALT, and ALP also

increased. Although the BT returned to normal within 1 week, the normalization of the serum CRP level and complete improvement of hepatic dysfunction were confirmed only 2 and 6 weeks after the operation, respectively (Fig. 1). The levels of plasma NE and urinary normetanephrine returned to normal at 1 week after the operation, and the hypertension was resolved without any medication. In addition, normal glucose tolerance was revealed by a 75-g OGTT performed 2 months after the operation.

Immunohistochemical staining was performed with 4- μ m-thick paraffin-embedded sections. The tissue specimens were deparaffinized in

xylene, rehydrated in a graded series of ethanol solutions, and then washed in phosphate-buffered saline (PBS ; pH 7.6). After the endogenous peroxidase activity was blocked, the nonspecific sites were blocked with 3% bovine serum albumin and 1% nonfat dry milk in PBS for 10 min at room temperature. The sections were incubated overnight with anti-IL-6 goat polyclonal antibodies (1:200; Santa Cruz, CA, USA) at 4 °C. After being washed in PBS, the sections were incubated with biotinylated donkey anti-goat IgG (Santa Cruz, CA, USA), followed by streptavidin-conjugated horseradish peroxidase (DAKO, Denmark). The reaction was revealed with metal-3, 3'-diaminobenzidine, and the sections were then counterstained with hematoxylin.

Discussion

Pheochromocytoma is rarely detected during pregnancy²⁻⁴ ; however, an exact diagnosis in such cases is important to prevent the potentially devastating consequences for both the mother and the fetus, which can be easily avoided by recognizing the disease in a timely manner. Hypertension during pregnancy is often caused by preeclampsia; however, pheochromocytoma should also be considered as one of the possible causes when severe hypertension occurs before the 20th week of gestation, especially when the BP is labile or headaches, palpitations, and diaphoresis are present¹⁰. Proteinuria has been reported to be associated with preeclampsia and rarely with pheochromocytoma, and it thus plays an important role in the differential diagnosis

between preeclampsia and pheochromocytoma¹¹.

In our patient, hypertension was detected in the 24th week of gestation ; however, regular check-ups showed that the patient's BP was within the normal range until the 37th week of gestation, and proteinuria was first detected at the 36th week of gestation. An emergency cesarean operation was performed because of the diagnosis of preeclampsia. The existence of pheochromocytoma had not been suspected at that time. Pheochromocytoma was diagnosed during the puerperal period, and the primary clue to the diagnosis was a high fever, which may have been induced by the high serum level of IL-6. Massive central necrosis within the tumor was found on MRI and histological examination; the necrosis was thought to have suddenly occurred after the delivery, when the patient developed a high fever.

Ectopic IL-6 production was confirmed by immunohistochemical staining of the resected tumor specimens for IL-6. Although we did not examine whether our tumor produced the other cytokines as tumor necrosis factor (TNF)- α and IL-1 β , the pheochromocytomas producing plural cytokines have never been reported. To our knowledge, our paper reports the eighth case of an IL-6-producing pheochromocytoma (Table 1). In most previous reports, the serum level of IL-6 returned to normal after an adrenalectomy⁶⁾⁷⁾⁹⁾¹²⁾¹³. However, in 3 patients, including our patient, the serum level of IL-6 decreased gradually before the tumor had been removed. In case no. 5, it was reported that an

Table 1 Comparison of the reported cases of IL-6-producing pheochromocytoma

No.	Age(y)	Sex	Hepatic-function test	CRP (mg/dL)	Pre-IL-6 (pg/mL)	Medication before operation	Reference
1)	42	F	unrevealed	6 +	88	naproxen, Minipress®	Suzuki K. 1991
2)	46	F	unrevealed	40.4	166	unrevealed	Fukumoto S. 1991
3)	31	M	AST ↑, ALP ↑		20 → 12	phenoxybenzamine, propranolol	Salahuddin A. 1997
4)	70	F	unrevealed	3.6	12.9	doxazosin	Takagi M. 1997
5)	35	F	ALP ↑	29.5	262 → normal	naproxen	Shimizu C. 2001
6)	36	F	unrevealed	32.5	20	dipyrrone, paracetamol, methylprednisolone	Minetto M. 2003
7)	31	F	AST↑, ALT↑, ALP↑, γ -GTP↑	30.4	300	naproxen	Kang J.M. 2005
8)	30	F	AST↑, ALT↑, ALP↑	13.2	49.4 → normal	nifedipine, doxazosin, propranolol	This case

ALP, alkaline phosphatase ; ALT, alanine aminotransferase ; AST, aspartate aminotransferase ; CRP, the maximum plasma level of C-reactive protein (CRP) before the operation ; Pre-IL-6, the serum levels of interleukin-6 (IL-6) before the operation

NSAID suppressed IL-6 production from the pheochromocytoma¹⁴), while in case no. 3, α - and β -adrenergic blockade were suggested to have decreased the serum IL-6 level⁸). In our patient, NSAIDs were not used, and as a matter of course, doxazosin, an α_1 -adrenoceptor antagonist was used. With regard to the relationship between catecholamines and IL-6, it has already been reported that catecholamines themselves accelerate IL-6 production¹⁵⁾¹⁶⁾, and this effect is attenuated by α_1 - or β -adrenoceptor antagonists¹⁷⁾. However, in the patients in cases nos. 1 and 4, the serum IL-6 level did not decrease before the operation, in spite of the administration of an α_1 -adrenoceptor antagonist; therefore, the hypothesis that α_1 - and β -adrenergic blockade reduce serum IL-6 levels does not apply to all the cases of IL-6 producing pheochromocytoma. Another explanation for the decrease in the serum IL-6 level of our patient was that the massive necrosis within the tumor accelerated the production of IL-6 from cells such as helper T cells and macrophages, and as the necrosis gradually subsided, the serum IL-6 level decreased. Therefore, the amount of IL-6 secreted by the surviving tumor itself might not directly affect the serum IL-6 level, because in our patient, this level returned to normal before the operation. To our knowledge, only 2 cases of pheochromocytoma with intrahepatic cholestasis have been reported thus far¹³⁾¹⁸⁾, and a liver biopsy revealed both lymphocytic infiltration and cholestasis in the hepatocytes and sinusoids in 1 case¹³⁾. However, other studies have reported that proinflammatory cytokines, including IL-6 and TNF- α , inhibit bile salt uptake by hepatocytes¹⁹⁾²⁰⁾, and IL-6 reduces mRNA expression of transporters that are associated with the uptake and efflux of the bile acids²¹⁾²²⁾. Since the changes in the serum levels of AST, ALT and ALP in our patient were similar to those in the CRP and IL-6 levels, the observed hepatic dysfunction may also have been associated with the overproduction of IL-6. Hepatic dysfunction

recurred after the operation, as indicated by inflammatory changes. This dysfunction may have been a side effect of cefazolin, or it may have been induced by the increase in the cytokine levels caused by the stress of surgery. Kanauchi et al reported that the production of both IL-6 and TNF- α increased for 5 postoperative days in response to the stress of laparoscopic adrenalectomy²³⁾. Thus, we presumed that in our patient, the open adrenalectomy for a large pheochromocytoma, which is considerably more stressful than its laparoscopic equivalent, triggered the abovementioned acute consecutive responses.

Among eight cases reported so far, five cases are Japanese. This is probably because of relatively higher prevalence of pheochromocytoma in Japan than in other countries, (0.6% v.s. 0.1~0.3%)²⁴⁾.

In conclusion, we report here the case of a patient who was diagnosed as having a large IL-6-producing pheochromocytoma with massive central necrosis in the seventh week after delivery. On the basis of the observations of the entire course of the patient, it is clear that the changes in the levels of plasma NE and IL-6 were mainly induced by the necrosis of the tumor, and these changes might also have influenced the findings of the liver-function tests. We showed that the pheochromocytoma itself may produce some cytokines, even if the tumor has undergone massive necrosis, which may directly induce an acute inflammatory syndrome. Therefore, there might be a possibility of greater prevalence of similar cases than we presently imagine. The existence of pheochromocytoma should be considered in the differential diagnosis when both labile hypertension and a loss of proteinuria are observed during the gestational period, especially before the 20th week.

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(和文抄録)

急性炎症反応と肝内胆汁うっ滞を呈し、産褥期に初めて 診断された IL-6 産生褐色細胞腫の一例

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私たちは分娩後、発熱を契機に診断された IL-6 産生褐色細胞腫の一例を経験したので報告する。症例は 30 歳、女性。妊娠 24 週目に高血圧を指摘されたが、その後は血圧安定しており、加療なし。37 週目、血圧 200/146 mmHg と急激に上昇し、妊娠高血圧症候群の診断の下、当院救急搬送後、即日帝王切開となった。無事第一子を出産したが、その後も高血圧は改善せず、産褥期 3 週目頃より 38℃ 台の発熱が出現し、原因精査の結果、左副腎に壊死を伴う径 10cm 大の褐色細胞腫の存在が明らかになった。また同時期に血中胆道系酵素、CRP および IL-6 の増加を認めた。その後、解熱とともにこれらの値も徐々に低下し、産褥 18 週目までにはいずれも正常化した。産褥 21 週目、左副腎摘出術を施行。摘出した腫瘍の免疫組織化学的検査の結果、腫瘍からの IL-6 の産生が確認された。

私たちが調べ得た限り、IL-6 を産生する褐色細胞腫の報告は本例を含め 8 例であった。いずれも血中 IL-6 の増加の他、急性炎症反応あるいは肝胆道系酵素の上昇を認めたが、8 例中 3 例（本例含む）は、腫瘍摘出前に血中濃度はすべて正常化していた。特に本例のように腫瘍内部に壊死を伴う場合は、腫瘍細胞からの IL-6 産生を見逃されてきた可能性があり、今後 acute inflammatory syndrome を伴う褐色細胞腫の診断の際には、IL-6 の産生を疑う必要があると考えられた。