

Sudden Onset of Pyrexia and Severe Blood Pressure Elevation Due to IL-6 Production by Pheochromocytoma

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Abstract

We report a case of pheochromocytoma presenting with a sudden change in clinical manifestation. The change in the serum Interleukin-6 (IL-6) and histological examination indicated that this clinical presentation was caused by IL-6 elevation secondary to pheochromocytoma. This rare tumor should be considered in the differential diagnosis of fever of unknown origin, and prompt and appropriate administration of an alpha-1 blocker is highly recommended, especially for patients with large pheochromocytomas.

Keywords: Pheochromocytoma; IL-6; Emergency

Introduction

Pheochromocytoma is a relatively rare cause of hypertension which accounts for less than 0.1% of all cases [1]. Its typical clinical symptoms are headache, sweating and palpitation due to excessive catecholamine release, but atypical cases are also encountered. Pheochromocytoma can be successively treated by surgery; however, adrenal resection, considered an extremely difficult operation several decades ago, without identification of this condition is very risky. Currently, elective surgery is preferred after blocking the effects of catecholamine.

Pheochromocytoma secretes several biologically active neuropeptides, cytokines, and hormones in addition to catecholamines [2,3], and some of them have extreme and atypical effects on the clinical manifestations of the condition; therefore in some cases, emergency intervention is required. Here, we report a case of pheochromocytoma in a patient with a high level of IL-6, who required emergency admission due to an abrupt clinical alteration during the assessment of an undiagnosed adrenal tumor. Some substances such as IL-6 may suddenly change the clinical presentation of the patient. Therefore, such rapid changes should be considered during diagnosis, and treatment against not only catecholamines but also cytokines such as IL-6 should be appropriately initiated during assessment of adrenal masses suspected to be pheochromocytoma.

Case Report

A 47-year-old man was referred to a local medical center for examination of an adrenal mass. He was diagnosed as hypertension 3 years before the current presentation and was consequently treated with amlodipine (10 mg), telmisartan (80 mg), and trichlormethiazide (2 mg). His Blood Pressure (BP) was 120/60 mmHg at the current examination. He was also diagnosed with diabetes mellitus 2 years prior to this presentation, but his diabetes was well controlled by medical and diet therapy. On the day of the Magnetic Resonance Imaging (MRI) examination at the outpatient clinic, he experienced nausea and sudden severe back pain and was admitted to the hospital. He also had severe hypertension, disturbance of consciousness, and pyrexia that did not respond to antibiotic therapy. He was subsequently transferred to our hospital for further evaluation and treatment.

Physical examination revealed a body temperature of 38.7°C, BP of 200/120 mmHg despite additional treatment with doxazosin, and

presence of an abdominal mass of approximately 10 cm in width. The disturbance of consciousness was relieved on arrival (Glasgow Coma Scale, E4 M5 V6). Leukocytosis (white blood cell count, 22000/ μ L; 78.9% segmented forms) and an elevated C-reactive protein (CRP) level (44.26 mg/dL) suggested that a bacterial infection may have caused the high fever. However, empirical antibacterial therapy proved ineffective and no lesions indicating bacterial infections were detected by detailed examinations. The plasma epinephrine (4570 pg/mL) and norepinephrine (3286 pg/mL) levels and urinary norepinephrine (2812 μ g/day) and normetanephrine (12.84 mg/day) levels were also remarkably high (Table 1).

Abdominal Computed Tomography (CT) demonstrated a left adrenal mass measuring approximately 12 cm in diameter (Figure 1) [1-3]. Iodine-metaiodobenzylguanidine (MIBG) scintigraphy revealed

		pre-	post-adrenalectomy
WBC	/ μ L	22000	6780
Hb	g/dL	10.2	13
Plt	$10^4/\mu$ L	63.5	27.5
AST	U/L	63	17
ALT	U/L	28	21
CRP	mg/dL	44.26	1.84
IL-6	pg/mL	30.2	3.7
TNF- α	pg/mL	1.1	2.1
IFN- γ	IU/mL	<0.1	<0.1
metanephrine	mg/day	54.76	0.07
normetanephrine	mg/day	12.84	0.26

Table 1: Laboratory data.

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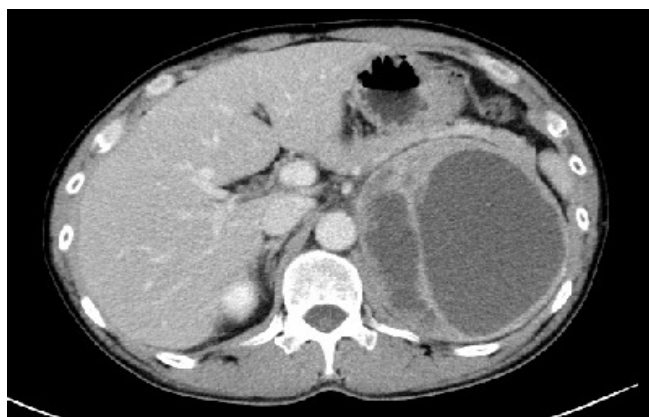


Figure 1: Abdominal CT showed 12x10x5 cm tumor including low density area in the left suprarenal region.

accumulation of the isotope in the left suprarenal region, suggesting that the abdominal mass was a pheochromocytoma.

Phentolamine injection (0.5mg/day) in addition to oral administration of doxazosin decreased BP to some extent, but occasional left abdominal pain increased BP again to 180/114 mmHg. Pyrexia and abdominal pain were alleviated by administration of 1300 mg of acetaminophen and 150 mg of tramadol on the day of admission; however, because the heart rate increased to 170 beats/min on the next day, administration of arotinolol (10 mg/day), an alpha/beta blocker, was initiated. The patient's heart rate decreased to 80 beats/min after beta blockade, and subsequently, imaging was performed: MRI of the abdomen demonstrated a mass measuring 10 cm in diameter in the upper left region of the kidney. T1-weighted images showed that the peripheral part of the mass was enhanced but the center was not, suggesting the existence of massive necrosis (Figure 2). On the basis of these findings, the tumor was diagnosed as a pheochromocytoma and surgical adrenalectomy was scheduled.

Until the operation, intensive medical therapy was administered, and the patient's condition stabilized, although he still had a fever of approximately 38°C, leukocytosis, and elevated CRP levels. At this point, there was no suspicion of bacterial infection, and the serum IL-6 level was 30.2 pg/mL (normal < 4.0 pg/mL). With regard to liver function, levels of AST and ALT were elevated along with those of the acute inflammatory markers. The results of serological tests for hepatitis B and C were negative, and no anatomical obstruction to the bile flow and bile duct dilatation were observed on abdominal ultrasonography. After the operation, the level of the abovementioned enzymes decreased to within the normal range.

Thirty days after admission, open left adrenalectomy was performed using an anterior transperitoneal approach. The resected tumor, which measured 5 x 10 x 12 cm, was well capsulated and histological examination of the tumor showed an area of massive central necrosis. The tumor had round to oval nuclei and abundant basophilic glandular cytoplasm; they were arranged in an alveolar fashion and were separated by thin fibrovascular septae (Figure 3).

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

After the surgery, the BP and HbA1c concentration reduced to 110/60 mmHg and 5.6% respectively, although all medications were discontinued. The IL-6 level reduced to 3.7 pg/mL, and levels of other cytokines such as TNF-alpha and INF-gamma were all within normal limits.

Discussion

Owing to the progress in imaging techniques and measurement of hormone concentration, hypertension secondary to pheochromocytoma is not difficult to diagnose, and the pheochromocytoma can successfully treated by surgery except for malignant tumors. Although pheochromocytoma is often observed as an abdominal mass and detected by its characteristic symptoms caused by hormone overproduction, an incidentally discovered adrenal mass should be carefully examined, because non-hormone-overproducing (non-functioning) adrenal tumors also occur frequently.

Although secondary hypertension is responsive to medication to a certain extent, other types of hypertension are difficult to treat, and such patients are often referred to specialists. Such refractory hypertension is rather easily controlled by the new advanced antihypertensive drugs. However, some tumors secrete specific cytokines, and in such cases, special treatment should be administered.

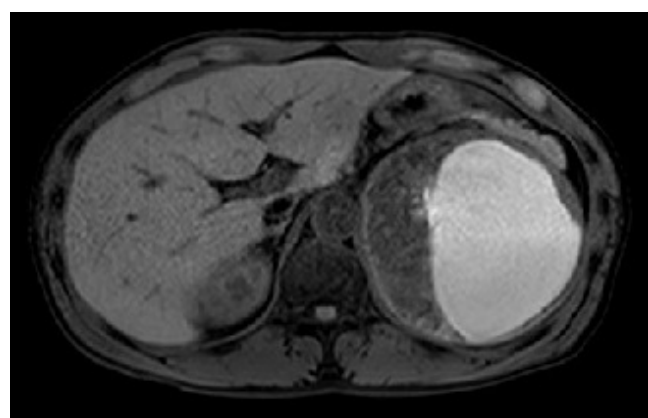


Figure 2: T1-weighted MR image. Peripheral part of the mass was enhanced, while the center was not.

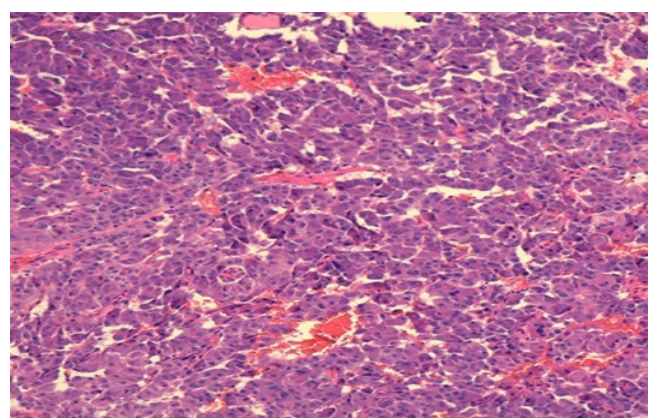


Figure 3: HE staining of the specimen(x10). Round to oval nuclei and abundant basophilic glandular cytoplasm suggesting pheochromocytoma.

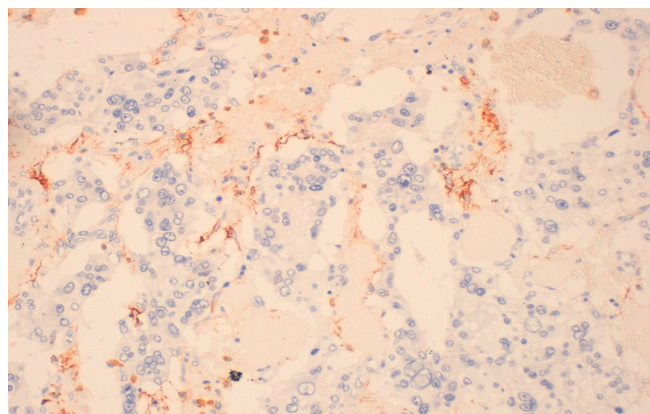


Figure 4: Immunohistochemical staining of removed adrenal gland using the anti-IL-6 antibody (x20). Positive staining was observed at the surrounded cells of the tumor.

Before the elective surgery, appropriate medical treatment must be administered to stabilize the patient's general conditions. In the current patient, high fever and high CRP levels were observed, but bacterial infection was ruled out because no definite foci of bacteria were observed on detailed examinations, and empirical antibiotic therapy was ineffective. Therefore, we concluded that pyrexia, high CRP levels, and liver dysfunction were caused by IL-6 or other cytokines that were secreted by the adrenal pheochromocytoma, and we consequently performed surgical intervention. The fever, high CRP level, and liver dysfunction alleviated with the normalization of IL-6 levels after surgery.

Some IL-6 producing pheochromocytomas have been previously reported [3-10] and in some cases, the IL-6 decreased before the tumor was removed [5,7,10]. Non-steroidal anti-inflammatory drug (NSAID) [7] and alpha- and beta- adrenergic blockade [5] were suggested for suppressing for IL-6 production from the pheochromocytoma, because catecholamines accelerate IL-6 production [11,12] and this effect is attenuated by alpha1- or beta-adrenoreceptor antagonists [13]. However, the serum IL-6 level did not decrease before the operation in some cases despite administration of an alpha1-adrenoreceptor antagonist [3,4,6,8,9]. Therefore the hypothesis that alpha1- and beta-adrenergic blockade reduces IL-6 production does not hold true for all cases of IL-6-producing pheochromocytoma.

In our case, IL-6 was measured before and after surgery and we noted a decrease in the IL-6 levels after adrenalectomy but could not confirm the effect of adrenergic blockade on IL-6 production. The effect of adrenergic blockade varies among cases, as shown in the abovementioned reports. This variety of responses may be related to the IL-6-secreting cells, because in our patient, IL-6 was produced from surrounding cells not from the tumor cells, and a few previous studies reported IL-6 production from pheochromocytoma cells. The serum IL-6 in our patient was thought to be secreted from the surrounding cells, as massive necrosis occurred within the tumor, which accelerated the production of IL-6 from cells such as helper T cells and macrophages.

In some cases, after treatment with NSAIDs or adrenergic blockade, the IL-6 level of IL-6-producing pheochromocytoma decreased before the operation in some cases [5,7,10]. Since we did not measure the IL-6 level when administering the alpha-1 blocker, the reduction in the IL-6 level after treatment could not be confirmed. However, owing to the

stabilization of heart rate after adrenergic blockade and the large size of the tumor, we could not rule out the possibility that the hypertension and diabetes were caused by the development of the tumor and the associated IL-6 elevation, as reported previously [5]. Considering the clinical course and IL-6 production in our case, the amount of IL-6 secreted by the surviving tumor as well as the surrounding cells, which contributed to the serum IL-6 elevation, might be important in managing pheochromocytoma.

Although we could not demonstrate the direct secretion of IL-6 from the tumor cells, the serum levels of IL-6 in our patient was high compared with the serum IL-6 levels in previously reported IL-6-producing pheochromocytoma [5,6,8]. Therefore, the clinical courses of this condition may not depend on whether IL-6 was directly secreted from the adrenal cells or secondary to the necrotic change of the tumor.

The size of the tumor might also be a decisive factor in the clinical course of this disease, as large pheochromocytomas often exhibit various types of necrosis, probably because the levels of intratumoral catecholamines, which are strong vasoconstrictor substances, are very high. If we consider the indirect secretion of IL-6 from the surrounding cells in addition to the direct secretion of IL-6 from the tumor cells, various results by alpha1- and beta blockade could be explained.

In conclusion, indirect secretion of IL-6 from the surrounding cells of the tumor cannot be disregarded in cases of pheochromocytoma. Clinicians should consider the pathophysiological state of the patient and prescribe medication according to the hypertensive state.

Conclusion

Pheochromocytoma may cause paraneoplastic syndrome with pyrexia in addition to marked increase in IL-6 level. This rare tumor has to be considered during a vast differential diagnosis of fever of unknown origin. Further, prompt and appropriate administration of alpha-1 blocker is highly recommended, especially for patients with large pheochromocytomas.

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