CASE REPORT

Interleukin-6-producing pheochromocytoma presenting with fever of unknown origin

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INTRODUCTION

Pheochromocytoma usually presents with typical signs and symptoms, such as headache, sweating, and palpitations due to excessive catecholamine release. Few publications have reported that these tumors are capable of secreting a variety of bioactive neuropeptides and hormones other than catecholamines, resulting in unusual clinical manifestations.[1-4] Interleukin-6 (IL-6) is a multifunctional molecule that plays an important role in hematopoiesis and immune and inflammatory responses. IL-6 stimulates the activation and differentiation of B and T lymphocytes, induces fever and regulates the acute-phase protein synthesis of proteins such as C-reactive protein (CRP) and fibrinogen.[5] IL-6 is mainly produced by lymphocytes and monocytes but can also be produced by other cell types including fibroblasts, keratinocytes, mesangial cells, endothelial cells, and adrenal cortical cells.[6,7] We report an 18-year-old normotensive, female patient who had an interleukin-6-producing pheochromocytoma and presented with fever of unknown origin associated with elevated levels of inflammatory markers.

CASE REPORT

An 18-year-old girl sought medical help for her ongoing malaise and fever following an upper respiratory tract infection. She had experienced weight loss of 3 kg, but did not have typical paroxysmal symptoms. Her physical examination showed no pathological findings except a temperature of 38.7℃. Her blood pressure was measured to be 90/60 mmHg. Laboratory data revealed both an elevated erythrocyte sedimentation rate (130 mm/h) and an elevated C-reactive protein level (98 mg/dl, normal; 0–5). Specific and nonspecific blood and urine cultures were negative for microbiological pathogens. Viral serological markers were negative as well. The total blood count revealed hypochromic and microcytic anemia (Hb: 8.6 g/dl, Hct: %25, MCV: 75 fl, RDW: 18.9%, MCHC: 33.3 g/dl) with marked thrombocytosis (PLT: 901000/μl) and slight neutrophilic leukocytosis (WBC: 12600/μl, neutrophils: 9700/μl), which was confirmed later with both peripheral blood and bone marrow smears. Her liver enzymes were within the normal range.

A fever between 37.5℃ and 41℃ persisted. Contrast-enhanced magnetic resonance imaging of the upper abdomen indicated a smooth-contoured right adrenal mass with a diameter of 5.5 cm, which was hypointense and heterogeneous on T1-weighted images, whereas it was hyperintense and heterogeneous on T2-weighted images, with nodular contrast enhancement toward the center of the mass (Figure 1). This patient was referred to our department for further evaluation. The morning fasting serum cortisol level, the plasma aldosterone level and the renin activity of the patient in the prone and upright positions were within the normal ranges. The urinary normetanephrine level was elevated to a level of 3612 μg/24 hours (normal; 105–354). These findings supported the diagnosis of pheochromocytoma. Almost immediate cessation of the fever and a gradual normalization of the clinical inflammatory marker levels were achieved after four weeks of adrenergic blockade with doxazosin. At admission, the serum interleukin-6 level was measured to be 12.5 pg/mL (normal <3.0 pg/mL), which then became 9.9 pg/mL in the second month of the adrenergic blockade. The IL-6 level decreased

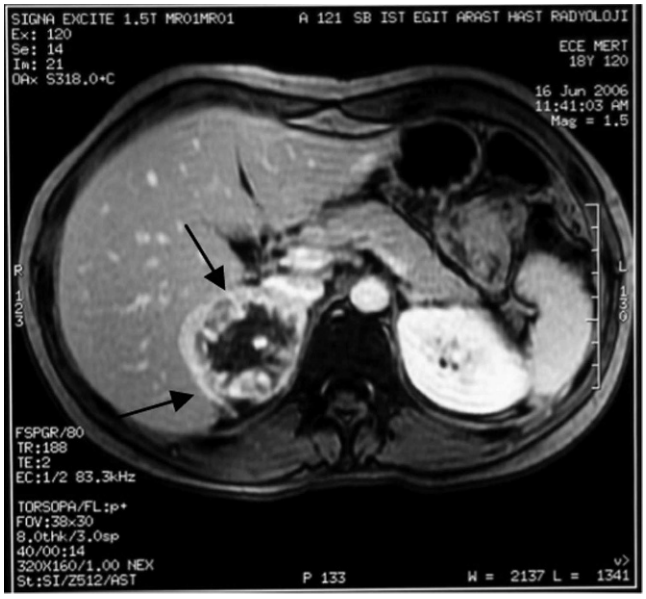
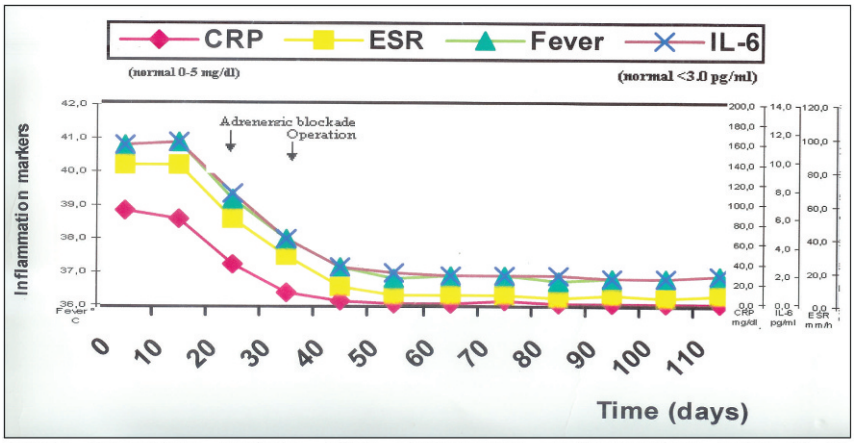


Figure 1 - Hyperintense and heterogeneous right adrenal mass (arrow) on a T2-weighted MRI image.

No potential conflict of interest was reported.



(CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IL-6: Interleukin-6)

Figure 2 - Inflammation markers and IL-6 levels before and after therapy.

to 6.6 pg/mL after complete resection of the tumor, which proved histopathologically to be a pheochromocytoma. The serum interleukin-6 level returned to normal a few weeks after the operation (Figure 2).

DISCUSSION

The unusual presentation of our pheochromocytoma case, with normal blood pressure, fever, and a marked inflammatory response, indicates the complexity of the clinical manifestations of this rare tumor. There have been other reports of adrenal tumors presenting with fever, hypertension, anemia, thrombocytosis, megakaryocytosis, and hyperfibrinogenemia associated with elevated levels of IL-6.[1,4,8-11] Cytokine production by the tumor could occasionally play a crucial role in the emergence of unusual symptoms such as fever and weight loss. IL-6 is clearly associated with the inflammatory response mediated by the differentiation of B-lymphocytes into immunoglobulin-producing plasmacytes and potently stimulates the production of acute inflammatory proteins while decreasing serum albumin levels.[8,9] IL-6 is also the cause of megakaryocytosis.[12,13] IL-6 over-production can be either ascribed directly to the tumor or indirectly accounted for by tumoral production as a consequence of the high levels of circulating norepinephrine. The relief of symptoms and the normalization of the inflammatory marker levels following the decrease in the level of IL-6 after resection of the tumor strongly support the role of IL- 6 in this unusual presentation of our case. Although there are some data demonstrating the effectiveness of non-steroidal anti-inflammatory drugs in reducing IL-6 levels and inflammatory symptoms in patients with pheochromocytomas,[1,4,12] our patient achieved fever remission through the use of alpha-adrenergic receptor blockers, corroborating the results of a previous study.[14] Our patient had no hypertension despite high catecholamine levels. This situation could be explained by the increased nitric oxide synthesis due to IL–6 activity, which might have led to vasodilation.[15,16]

CONCLUSION

Pheochromocytoma may be a cause of paraneoplastic syndrome with pyrexia in addition to inducing a marked increase in the levels of inflammatory markers. IL-6 appears to be the primary mediator. This rare tumor has to be considered in the vast differential diagnosis of fever of unknown origin.

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