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CASE REPORT WITH REVIEW OF LITERATURE

Pheochromocytoma associated with ectopic ACTH-producing tumor and hyper-interleukin-6emia: a case report with review of literature

Hironori Nakahira[1], Shozo Miyauchi[2], Kyoko Watanabe[2], Kazuyuki Akesaka[2], Keizo Ono[2], Osamu Ebisui[2], Teruki Miyake[3], Shinya Furukawa[4], Yoichi Hiasa[3] and Bunzo Matsuura[5]

[1] *Clinical Training Center, Ehime Prefectural Central Hospital, Ehime 790-0024, Japan*
[2] *Department of Diabetes and Endocrinology, Ehime Prefectural Central Hospital, Ehime 790-0024, Japan*
[3] *Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime 791-0295, Japan*
[4] *Health Services Center, Ehime University, Ehime 790-8577, Japan*
[5] *Department of Lifestyle-related Medicine and Endocrinology, Ehime University Graduate School of Medicine, Ehime 791-0295, Japan*

Abstract. Pheochromocytomas occur in the adrenal medulla and present with various symptoms associated with excessive catecholamine production. Although pheochromocytomas associated with ectopic ACTH-producing tumors and hyper-interleukin-6emia (hyper-IL-6emia) have been reported, those associated with both diseases simultaneously have not been reported. In pheochromocytomas with ectopic ACTH-producing tumors and hyper-IL-6emia, the disease characteristics and relationship between each hormone and cytokine are unknown. Herein, we report a case of a 56-year-old woman with stroke whose computed tomography scans of the abdomen revealed a right adrenal tumor on systemic examination. Endocrinological examination revealed elevated plasma levels of catecholamines and their metabolites in the urine and elevated levels of plasma ACTH, serum cortisol, and serum dehydroepiandrosterone sulfate, leading to a diagnosis of right pheochromocytoma and associated ectopic ACTH-producing tumor. Furthermore, hyper-IL-6emia was detected as a key indicator of anemia due to inflammatory hematopoietic disorders. The patient's general condition improved with drug therapy, including 1,000 mg/d of metyrapone, 2 mg/h of phentolamine, 8 mg/d of doxazosin, and systemic management. Dexamethasone suppression tests demonstrated suppressed serum cortisol and IL-6 levels, and dexamethasone dose-dependently increased plasma adrenaline and noradrenaline levels. These findings indicate that excess glucocorticoids play a stimulatory role in catecholamine secretion and a concentration-suppressive role in serum IL-6 levels in pheochromocytomas associated with ectopic ACTH-producing tumors and hyper-IL-6emia. The presence of rare comorbidities should be considered if the clinical findings cannot be explained by the pathophysiology of a pheochromocytoma alone because pheochromocytomas can be associated with the production of other hormones and cytokines.

Key words: Pheochromocytoma, Ectopic adrenocorticotropic hormone-producing tumor, Hyper-interleukin-6emia, Catecholamines

Introduction

Pheochromocytoma is a tumor of the adrenal medulla that manifests with a spectrum of clinical symptoms owing to excessive catecholamine (CA) secretion. In addition to its neoplastic nature, pheochromocytomas can be associated with the ectopic production of various hormones and cytokines. Although there have been documented cases of pheochromocytomas secreting ACTH or interleukin-6 (IL-6), instances in which ectopic ACTH production and hyper-IL-6emia coexist have not been reported. Detailed clinical characteristics of dual-secreting pheochromocytomas, including the relationship between hormonal factors and cytokines, are poorly understood. Herein, we report a rare case of a pheochromocytoma associated with an ectopic ACTH-producing tumor and hyper-IL-6emia.

Case Report

A 56-year-old woman who had a stroke was transferred to a nearby emergency hospital. She was initially diagnosed with hypertension at that hospital. Her blood

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Correspondence to: Shozo Miyauchi, Department of Diabetes and Endocrinology, Ehime Prefectural Central Hospital, 83 Kasuga, Matsuyama, Ehime 790-0024, Japan.
E-mail: c-shmiyauchi@eph.pref.ehime.jp

examination revealed high levels of CAs (adrenaline [Ad]: 5.62 ng/mL; noradrenaline [NAd]: 33.46 ng/mL; and dopamine 0.62 ng/mL), ACTH (183.0 pg/mL), and cortisol (184.0 μg/dL). Plain computed tomography (CT) scans revealed a right adrenal tumor. She was transferred to our hospital because of deterioration in her general condition. She had no relevant family or medical history.

On physical examination, her height was 162.0 cm, body weight was 41.4 kg, and body mass index was 15.9 kg/m^2. Her Glasgow Coma Scale score was E3V4M6. The patient's body temperature was 38.4°C, pulse rate was 122/min, blood pressure was 121/62 mmHg, oxygen saturation was 96% (in ambient air). Her skin was hyperpigmented. Her blood tests revealed an increased white blood cell count, anemia, prerenal renal failure due to dehydration, and electrolyte abnormalities with hypernatremia and hypokalemia. Endocrinological examination revealed elevated levels of catecholamine metabolites (metanephrine: 8.48 mg/d; normetanephrine: 9.96 mg/d) in the urine. In addition, ACTH, cortisol, and dehydroepiandrosterone sulfate were also elevated, suggesting ACTH-dependent Cushing's syndrome. Furthermore, her circadian rhythms of ACTH and cortisol levels were absent. Anemia was suspected as an inflammatory hematopoietic disorder based on poor hematopoietic response and increased serum levels of IL-6 (100 pg/mL, reference range: ≤7.0 pg/mL). Her chest and abdomen dynamic CT scan showed a well-defined borderline mass 77.0 mm in length in the right retroperitoneum, and her left adrenal gland was diffusely enlarged. The right-side tumor was partially heterogeneously contrasted with small internal calcifications. The left adrenal gland was mildly enlarged and reactive changes and hyperplasia were suspected. Furthermore, no tumors were identified other than the adrenal tumor, including in the lungs or pancreas. A 123I-metaiodobenzylguanidine scintigraphy performed by a previous physician did not show hyperaccumulation consistent with an adrenal gland. Contrast-enhanced pituitary magnetic resonance imaging scans showed no findings suggestive of a pituitary tumor. Due to the patient's poor general condition, positron emission tomography-CT was not performed.

An α-adrenergic blockade (phentolamine and doxazosin) and β-adrenergic blockade (landiolol and bisoprolol) were administered for the pheochromocytoma with symptom improvement. Her serum cortisol levels improved after treatment with a corticosteroid synthesis inhibitor (metyrapone) for ACTH and cortisol excess due to the ectopic ACTH-producing tumor. These treatments also improved her serum IL-6 levels. After the patient's general condition stabilized, each loading test was performed. The 1-deamino-8-D-arginine vasopressin and CRH load tests did not meet the criteria for Cushing's disease. The results of the dexamethasone suppression tests are shown in Table 1. Plasma Ad and NAd levels measured simultaneously increased from baseline and were higher with 8 mg dexamethasone than with 1 mg dexamethasone. Subsequently, dexamethasone 0.5 mg and 16 mg suppression tests were added 2 weeks after the first dexamethasone suppression tests, and the levels of Ad and NAd were higher at 16 mg than at 0.5 mg dexamethasone or baseline. In contrast, 1 mg and 8 mg of dexamethasone suppressed the serum levels of cortisol and IL-6. These results revealed a dose-dependent increase in Ad and NAd levels and the suppression of IL-6 levels.

Based on the results of the imaging and endocrinological examinations, the patient was clinically diagnosed with a right-sided pheochromocytoma associated with an ectopic ACTH-producing tumor and hyper-IL-6emia. After the diagnosis of pheochromocytoma and confirmation of an ectopic ACTH-producing tumor, retroperitoneoscopic tumor resection was performed. The levels of plasma CAs, ACTH, cortisol, and IL-6 normalized postoperatively (Table 2), suggesting that the patient had a pheochromocytoma that simultaneously produced ACTH and IL-6. Pathological examination showed pleomorphic cells resembling adrenal medullary cells with abundant vascularized cord-like to focal proliferation, consistent

Table 1 Results of dexamethasone suppression test under metyrapone administration (overnight method)

	6:00	23:00	Dex 1 mg	Dex 8 mg	6:00	Dex 0.5 mg	Dex 16 mg
ACTH (pg/mL)	85.9	110.0	27.4	32.9	56.8	11.0	3.3
CS (mg/dL)	14.4	10.6	3.5	5.1	14.9	1.9	1.9
Ad (ng/mL)	0.98	N/A	1.96	2.10	0.30	0.24	0.59
NAd (ng/mL)	7.34	N/A	11.45	11.60	5.33	4.32	9.41
DA (ng/mL)	0.13	N/A	0.08	0.03	0.02	0.02	0.02
IL-6 (pg/mL)	73.2	N/A	21.6	6.5	10.7	5.7	2.2

Abbreviations: Dex, dexamethasone; CS, cortisol; Ad, adrenaline; NAd, noradrenaline; DA, dopamine; IL-6, interleukin-6; N/A, not applicable. The dexamethasone suppression test was carefully performed after stabilizing the patient's condition with administration of doxazosin, bisoprolol, and metyrapone.

Table 2 Changes in hormone levels during treatment

	On Admission Day 4	Preoperative Day 39	Postoperative Day 46
ACTH (pg/mL)	252.0	38.6	18.0
CS (mg/dL)	56.5	14.2	9.9
DHEA-S (ng/mL)	5,025	840	N/A
Ad (ng/mL)	5.58	0.25	<0.01
NAd (ng/mL)	31.04	4.45	0.19
DA (ng/mL)	1.77	0.02	<0.01
IL-6 (pg/mL)	100.00	11.4	4.9

After admission, the patient was treated with phentolamine, doxazosin, bisoprolol, and metyrapone. Retroperitoneoscopic tumor resection was performed on day 42 of hospitalization.
Abbreviations: ACTH, adrenocorticotrophin; CS, cortisol; DHEA-S, dehydroepiandrosterone sulfate; Ad, adrenaline; NAd, noradrenaline; DA, dopamine; IL-6, interleukin-6; N/A, not applicable.

with pheochromocytoma. Immunostaining was positive for chromogranin A and synaptophysin, with an Mib-1 labeling index of approximately 1–3%. Immunostaining for ACTH and IL-6 was negative. Additionally, immunostaining for CRH was performed and was also negative.

Discussion

The present case was diagnosed as a pheochromocytoma during the investigation of the underlying disease causing stroke. Concurrently, an ectopic ACTH-producing tumor and hyper-IL-6emia were identified. The interactions between these conditions and their impact on the clinical presentation and laboratory results were carefully considered. This analysis demonstrated that the hormones and cytokines involved exhibit intricate interactions, playing a pivotal role in the underlying mechanisms of pathogenesis and pathophysiology.

In the present case, both pheochromocytoma and ectopic ACTH-secreting tumors were present; however, some symptom characteristics of each disease were absent. A literature review showed that the clinical symptoms characteristic of both pheochromocytomas and ectopic ACTH-producing tumors include hypertension, headache, weight loss, and impaired consciousness, as well as symptoms of high cortisol levels, such as moon face, central obesity, thinning of the skin, proximal myopathy, and impaired glucose tolerance (Table 3) [1-8]. Several reports have documented cases without Cushingoid appearance [7, 9, 10]. In this case, the patient also did not exhibit Cushingoid features or impaired glucose tolerance. These findings may be attributed to the rapid progression of the disease, which likely led to an acute increase in cortisol levels. In addition, the ACTH and cortisol values in seven of the eight reported cases were 38.5 to 995 pg/mL and 32.3 to 150 μg/dL, respectively, and the values in this case were both within these ranges.

In the present case, metyrapone improved the blood levels of ACTH, cortisol, and CAs, and the dexamethasone suppression tests demonstrated a dose-dependent increase in the blood levels of Ad and NAd. The interactions among CAs, ACTH, cortisol, and IL-6 in pheochromocytomas associated with ectopic ACTH-producing tumor and hyper-IL-6emia are shown in Fig. 1. These interactions include: ACTH secreted from ectopic ACTH-producing tumors stimulate cortisol secretion in normal adrenal glands; consequently, the increased cortisol binds to glucocorticoid receptors (GRs) in tumor cells, promoting the expression of tyrosine hydroxylase and phenylethanolamine-N-methyltransferase; this leads to increased CAs secretion by CA-secreting cells [11]; moreover, elevated cortisol levels also enhance pro-opiomelanocortin expression in ACTH-producing cells *via* GRs, resulting in increased ACTH secretion from ectopic ACTH-producing tumors. This creates a positive feedback loop in which ACTH stimulates cortisol production, which in turn promotes ACTH secretion. Consequently, this loop may lead to elevated plasma ACTH, serum cortisol, and plasma CA levels. In the present case, metyrapone suppressed cortisol production, breaking the cortisol-ACTH positive feedback loop, and resulting in decreased ACTH secretion. Consequently, cortisol-induced stimulation of CA secretion was also reduced, leading to lower blood CA levels. Additionally, combination treatment with phentolamine or doxazosin suppressed the CA-stimulating effect, ultimately improving the patient's general condition. The dexamethasone suppression test, performed after the patient's condition improved with treatment, demonstrated a dose-dependent increase in the blood levels of Ad and NAd, supporting the role of excess glucocorticoids in stimulating CA secretion in pheochromocytomas associated with ectopic ACTH-producing tumors. Therefore, high concentrations of glucocorticoids may significantly contribute to the

Table 3 Review of literature of patients with ectopic ACTH-producing pheochromocytoma or pheochromocytoma with hyper-IL-6emia

Author	Year	Age (years)	Sex	ACTH (pg/mL)	Cortisol (μg/dL)	IL-6 (pg/mL)	Symptoms	Examination	Other
ectopic ACTH-producing tumor									
A. Nishihara, *et al.*	2003	55	F	619	84.7	N/A	hypertension, transient disturbance of consciousness	WBC ↑, Hb ↓, hyperglycemia, diabetes, hepatobiliary enzyme ↑, coagulopathy	
A. Nozawa, *et al.*	2004	69	F	N/A	N/A	N/A	fever, impaired consciousness	diabetes	thyroid tumor, Hyperparathyroidism, suspected of MEN II A variant fatal case
Y. Tahara, *et al.*	2009	70	F	38.5	36.6	N/A	hypertension	hypercholesterolemia, diabetes	
G. Tanikawa, *et al.*	2009	55	F	619	84.7	N/A	hypertension, transient disturbance of consciousness	WBC ↑, Hb ↓, hyperglycemia, diabetes, hepatobiliary enzyme ↑, coagulopathy	
C. Ballav, *et al.*	2012	49	F	550	63	N/A	hypertension, headache, generalized swelling, palpitation, facial erythema, supraclavicular fat, deposits, bruises, purple striae, proximal myopathy	hyperkalemia	no hyperpigmentation
I. Sakuma, *et al.*	2016	56	F	995	85.6	N/A	hypertension, general malaise, impaired consciousness, edema, central obesity, moon face, skin thinning	hyperglycemia, ketoacidosis WBC ↑, PLT ↓, FDP ↑, → DIC	
M. Inoue, *et al.*	2018	46	M	270	32.3	N/A	hypertension, headache, rapid weight loss, hyperhidrosis, tachycardia	hyperglycemia, diabetes, hypokalemia, dehydration with diabetic ketoacidosis, hepatobiliary enzyme ↑	no Cushingoid appearances
N. M. Durrani, *et al.*	2022	30	F	590	150	N/A	drowsiness, bilateral lower limb, weakness, headache, hypertensive, Cushingoid face, proximal myopathy, skin pigmentation, acanthosis nigricans	N/A	with a history of diabetes mellitus, hypertension and hypothyroidism
Hyper-IL-6emia									
A. Salahuddin, *et al.*	1997	31	M	N/A	N/A	20	abdominal pain, hematemesis, cough, hypertension, tachycardia	WBC, PLT ↑, Hb ↓, ALP, Bil ↑	patient with neurofibromatosis alcoholic
C. Shimizu, *et al.*	2001	35	F	N/A	N/A	262	fever, headache	WBC, PlT, ESR, CRP ↑, Hb ↓, ALP ↑, fibrinogen ↑, coagulopathy, malnutrition	liver enzymes were normal
J. M. Kang, *et al.*	2005	31	M	N/A	N/A	300	fever, headache, weight loss	WBC, PLT, CRP ↑, Hb ↓, hepatobiliary enzyme ↑, bilirubin ↑, coagulopathy, malnutrition	
S. Yarman, *et al.*	2011	18	F	N/A	N/A	12.5	fever, weight loss	WBC, PLT, ESR, CRP ↑, Hb ↓	liver enzymes were normal
M. Kuroki, *et al.*	2021	32	F	N/A	N/A	78.8	fever, tachycardia, headache, general malaise	WBC, CRP ↑, Hb ↓, coagulopathy, malnutrition	liver enzymes were normal
K. Nagai, *et al.*	2022	48	F	N/A	N/A	268	fever, tachycardia, headache, hypertension	PLT,↑ Hb ↓, CRP ↑, AST, ALT, ALP, γ-GTP ↑, coagulopathy	

Abbreviations: N/A, not available; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; FDP, fibrin/fibrinogen degradation products; DIC, disseminated intravascular coagulation; ALP, alkaline phosphatase; Bil, bilirubin; ESR, erythrocyte sedimentation; CRP, C-reactive protein; AST, aspartate aminotransaminase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyltransferase.

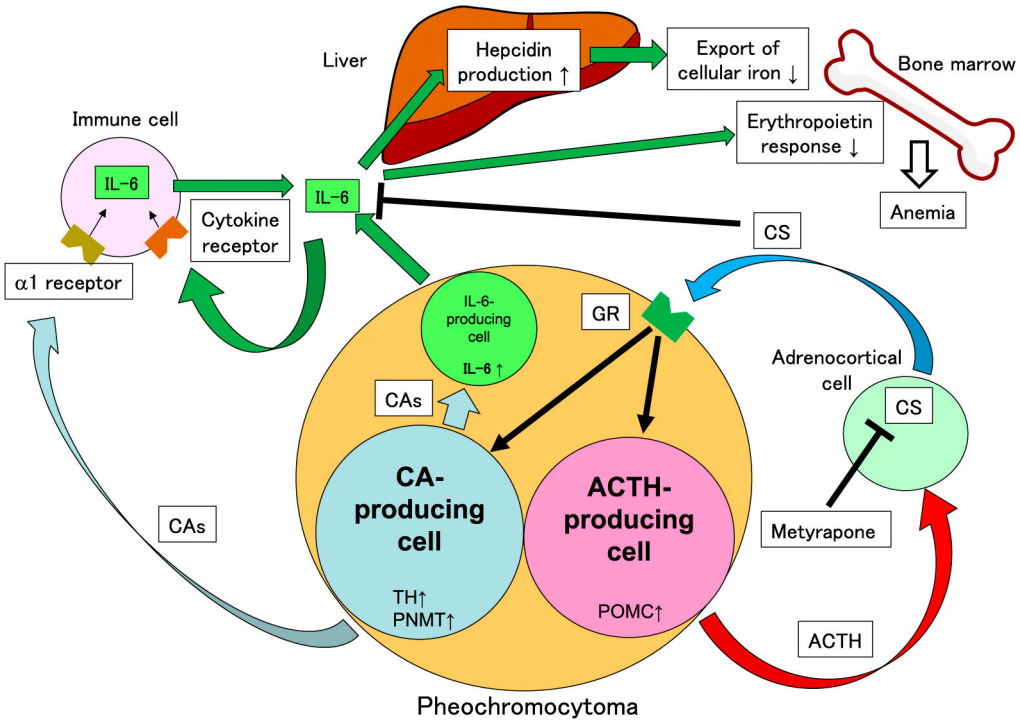


Fig. 1 Interactions among CAs, ACTH, cortisol, and IL-6 in pheochromocytomas associated with ectopic ACTH-producing tumors and hyper-IL-6emia.

Abbreviations: CA, catecholamine; CS, cortisol; IL-6, interleukin-6; GR, glucocorticoid receptor; TH, tyrosine hydroxylase; PNMT, phenylethanolamine-N-methyltransferase; POMC, pro-opiomelanocortin.

hypersecretion of CAs and ACTH in these tumors.

In this case, hyper-IL-6emia may have affected the pathogenesis of the disease (Fig. 1). The patient had inflammatory anemia, which is difficult to explain by pheochromocytoma or an ectopic ACTH-producing tumor alone and provided a key to the diagnosis of hyper-IL-6emia. IL-6 is an inflammatory cytokine with various effects, including acute-phase response, angiogenesis, neutrophil activation, and immune response [12]. The anemia due to hematopoietic disorders observed in our case may have been caused by impaired iron metabolism *via* hepcidin synthesis and secretion in the liver by IL-6 [13]; consequently, this reduced erythropoietin responsiveness in the bone marrow due to IL-6 [14, 15].

The dexamethasone suppression tests demonstrated that blood IL-6 levels were lower than baseline levels after dexamethasone loading. This suggests that excess glucocorticoids have an inhibitory effect on IL-6 levels. In the review of the literature of pheochromocytoma cases complicated by hyper-IL-6emia, the IL-6 levels in the six reported cases were 12.5 to 300 pg/mL. Furthermore, fever, headache, anemia, and elevated white blood cell counts were observed in all patients; moreover, other complications such as increased platelet counts, liver dysfunction, abnormal blood coagulation, elevated erythrocyte sedimentation rate, and C-reactive protein (CRP) have also been reported (Table 3) [16-21]. IL-6 levels in the present case were within the range reported in other cases, and fever, anemia, liver dysfunction, blood coagulation abnormalities, and elevated CRP were also observed. However, the liver dysfunction and elevated CRP levels were relatively mild. A possible reason for the lack of completion of typical hyper-IL-6emia symptoms is that the effects of IL-6 may have been partially suppressed by hypercortisolemia due to the ectopic ACTH-producing tumor (Fig. 1). Hence, the symptoms caused by hyper-IL-6emia may be attenuated when an ectopic ACTH-producing tumor and hyper-IL-6emia are combined with a pheochromocytoma.

The etiology of hyper-IL-6emia in this case could have been from the pheochromocytoma itself and/or released from immune cells. Although some studies have reported IL-6 production by tumor cells, some others have reported enhanced IL-6 production from immune cells due to CAs [21]. In the present case, IL-6 levels were high despite the presence of excess cortisol from an ectopic ACTH-producing tumor, suggesting that excess CAs may have been involved in the increased IL-6 levels. In contrast, IL-6 levels decreased in the dexamethasone suppression test, despite increased plasma Ad and NAd concentrations. Therefore, further detailed studies are required to elucidate the involvement of cortisol and CAs

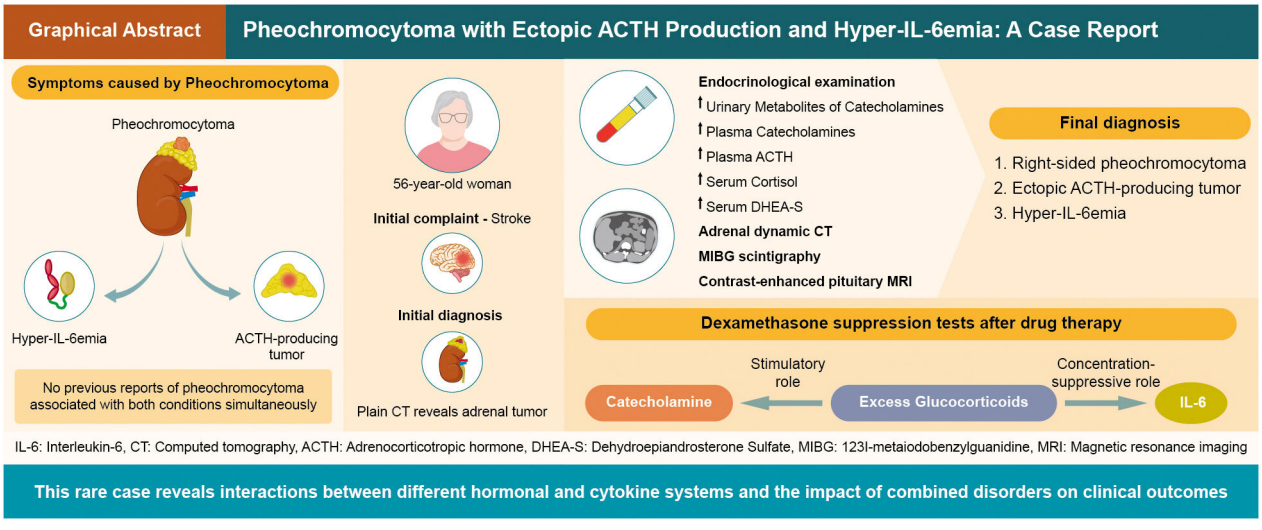
in the pathogenesis of increased IL-6 levels.

In the present case, the laboratory findings and clinical course suggested that the pheochromocytoma was associated with ACTH-producing and IL6-producing tumors. Furthermore, the tumor in the right adrenal gland might have consisted of a mixture of pheochromocytoma and ectopic ACTH-producing cells [6, 18]. However, histopathological evidence of an ACTH-producing tumor or IL-6 production could not be obtained. This may be because ACTH and IL-6 producing cells are very sparse [6, 18] and not produced throughout the tumor, and the specimen may have been taken from a non-producing area. Even though the ACTH production level was high for the tumor as a whole, the ACTH production level per tumor cell was very low, and it could not be detected with the sensitivity of ACTH immunostaining. Alternatively, it is possible that the patient was in a critical condition and treatment was prioritized, resulting in the suppression of ACTH and IL-6 production to undetectable levels by the therapeutic agents. The patient's clinical course demonstrated a normalization of both ACTH and IL-6 levels after tumor resection, indicating the presence of an ACTH-producing tumor and that IL-6 production was likely to have been present, although the site could not be identified.

The coexistence of pheochromocytoma and a CRH-producing tumor is extremely rare. In this case, the possibility of CRH production by the pheochromocytoma was considered and investigated. Immunohistochemical staining for CRH was negative, therefore, the presence of a CRH-producing tumor was ruled out.

Despite the findings of this case report, several limitations were noted. First, catecholamine and cytokine loading tests were not performed in this case, so the response to these stimuli could not be evaluated. Further investigation is required. Second, the dexamethasone suppression test was performed while the patient was still taking medication, which may have had some effect on the results. However, the medication dose was constant; therefore, the response to loading could be valid. Third, the dexamethasone suppression test demonstrated only the temporary effect of high concentrations of glucocorticoids on the pathology and may not reflect the long-term effects of high concentrations of glucocorticoids on other hormones and cytokines. Fourth, advanced analyses such as qPCR to compare POMC and IL-6 with TH and PNMT, as well as *in situ* hybridization to detect ACTH in the tumor tissue, were considered but ultimately not pursued due to feasibility constraints. These points limit direct comparisons and broader generalizations. Nonetheless, this case report provides valuable clinical insights and can be used to validate our findings in future clinical practice.

In conclusion, in this case report we presented a rare case of an ectopic ACTH-producing pheochromocytoma associated with hyper-IL-6emia (Graphical abstract). Although cases of ectopic ACTH-producing pheochromocytomas or IL-6 producing pheochromocytomas have been reported previously, there have been few reports of pheochromocytomas associated with both disorders. Therefore, the description of the clinical picture and pathophysiology of this case is clinically significant. Pheochromocytomas may be associated with the production of other hormones and cytokines; hence, if the pathophysiology of a pheochromocytoma cannot be explained solely by a pheochromocytoma, rare comorbidities should be considered.



Graphical abstract

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Author Contributions

HN wrote the manuscript. HN and SM prepared the conception of the manuscript. HN, SM, KW, KA, KO, and EO performed patient care, data acquisition, analysis, and interpretation. TM, SF, YH, and BM contributed to data analysis, interpretation, and manuscript revision. All authors critically reviewed the manuscript and contributed to the completion of the final manuscript. All authors approved the final manuscript for submission.

Disclosures

None of the authors have any potential conflicts of interest associated with this report.

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Informed Consent

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