CLINICAL IMAGE*

Catatonia as a presenting symptom of ectopic adrenocorticotropic hormone syndrome caused by thymic carcinoid tumor

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Introduction Ectopic adrenocorticotropic hormone (ACTH)–producing tumors were first described in the 1960s and have been identified in various tumors, such as small cell lung cancer, gastrointestinal tumors, ovarian tumors, and pheochromocytoma. Ectopic ACTH syndrome is known to account for less than 10% of all Cushing syndrome cases. Among them, ectopic ACTH syndrome caused by thymic carcinoid tumors, which was first described by Wick et al[1] in the 1980s, is a rare cause of Cushing syndrome. Clinical manifestations of Cushing syndrome are centripetal obesity, hyperglycemia, hypertension, purple striae, and neuropsychiatric symptoms. Catatonia is a psychomotor immobility which manifests as hypokinesia, akinesia, negativism, and mutism. This symptom is associated with psychiatric conditions such as schizophrenia, bipolar disease, major depressive disorder, and drug abuse. However, it is known that catatonia is also related to other general medical conditions. There were few case reports that showed the manifestation of catatonia as a presenting symptom of ectopic ACTH syndrome.[2] We report a case of ectopic Cushing syndrome due to thymic carcinoid tumor with unusual presentation of acute psychotic symptoms such as catatonia.

Case description **Clinical situation** A previously healthy 57-year-old man presented to our hospital due to lower extremity edema and fatigue, which started a few months earlier. He was recently diagnosed with diabetes mellitus and hypertension. However, he did not show any typical Cushingoid features such as moon face, central obesity, buffalo hump, and purple striae. At the outpatient clinic, a chest X-ray revealed well-defined opacity at the right cardiac border (FIGURE 1A), and chest computed tomography (CT) showed a mass of approximately 6.5 cm in size along the anterior mediastinum (FIGURE 1B). He was admitted for further evaluation of abnormal findings confirmed by imaging studies.

Course of events Positron emission tomography–computed tomography (PET-CT) showed hypermetabolic uptake of anterior mediastinal mass confirmed by chest CT (FIGURE 1C). Bilateral adrenal hyperplasia was found on an abdominal CT scan (FIGURE 1D). Laboratory tests revealed

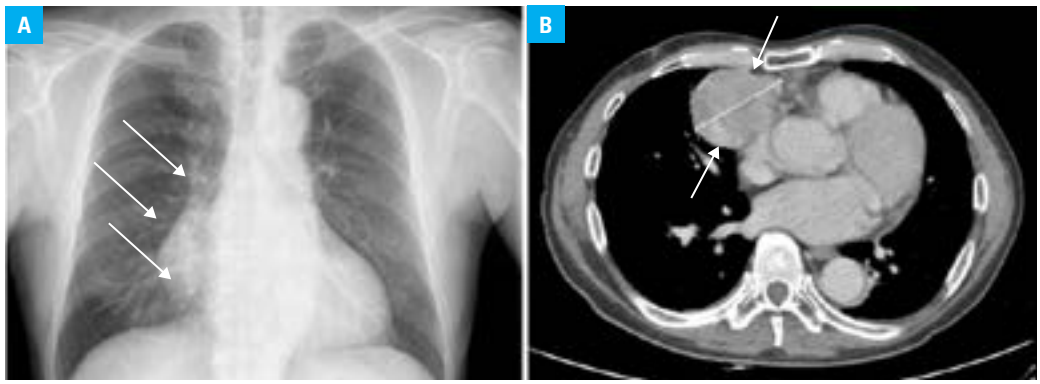

FIGURE 1 Results of imaging tests; **A** – chest X-ray showing mass opacity (arrows) next to the right cardiac border; **B** – chest computed tomography scan showing approximately 6.5-cm mass (arrows) along the right cardiac border

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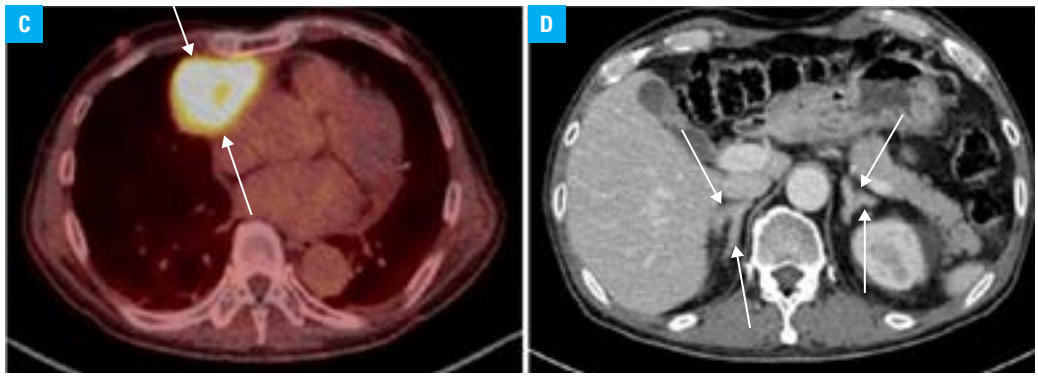

FIGURE 1 Results of imaging tests; **C** – positron emission tomography–computed tomography scan showing hypermetabolic mass (arrows) in the right anterior mediastinum; **D** – abdominal computed tomography scan showing diffuse adrenal thickening of both adrenal glands (arrows)

severe hypokalemia (2.5 mmol/l) and a glycated hemoglobin A_{1c} level of 8.5%. The complete blood count at baseline showed white blood cells (WBC) of 18.36×10^3/µl, hemoglobin of 13.0 g/dl, and platelet count of 194 000/µl. His blood pressure at admission was 138/107 mmHg. Based on hypokalemia and hypertension, we measured the aldosterone-renin ratio to exclude primary aldosteronism. Plasma aldosterone levels were 10.2 ng/dl (reference range, 3.7–24 ng/dl) and plasma renin activity was slightly decreased (0.27 ng/ml/h; reference range, 0.3~2.9 ng/ml/h). We further measured serum cortisol and plasma ACTH levels to assess thymic carcinoid tumors and ectopic Cushing syndrome. High morning ACTH levels of 241.5 pg/ml (0–60 pg/ml) and very high cortisol levels of 107.0 µg/dl (5–25 µg/ml) were found on hormone examination. During the first day of admission, the patient developed hallucinations and delusions. On the fifth day, he fell into stupor and had rigid posture. He did not respond to external stimuli. His pupil reflex was normal and the Glasgow Coma Scale score was E1V1M1. Brain CT was performed to distinguish neurologic causes such as stroke, but it did not show any evidence of acute cerebral hemorrhage or infarction. Epilepsy was not identified on electroencephalography.

Clinical resolution To control acute psychiatric symptoms caused by hypercortisolemia, continuous intravenous etomidate infusion was started. In addition, the patient was transferred to the intensive care unit to monitor complication of etomidate infusion, such as sedative effect. Serum cortisol levels decreased to 25.0 µg/dl one day after etomidate infusion at 2.5 mg/h. As the cortisol level decreased to normal, the psychiatric symptom improved dramatically. For optimal treatment of ectopic Cushing syndrome, total thymectomy through video-assisted thoracoscopic surgery was performed on hospital day 8. After the surgery, plasma ACTH and serum cortisol levels decreased to 2.8 pg/ml and 14.2 µg/dl, respectively. Immunohistochemical staining with Ki-67, CD56, and synaptophysin showed positive immunoreaction compatible with neuroendocrine tumor. Immunohistochemistry staining for ACTH was also positive. The pathological findings were consistent with atypical thymic carcinoid tumor with ACTH production.

After surgery, high fever, cough, sputum, and desaturation occurred. Chest CT demonstrated multifocal consolidation and cavitary lesions in the bilateral lung fields. Empirical antibiotics and antifungal agents were administered. Percutaneous needle aspiration biopsy for the cavitary lesion confirmed by chest CT was done for diagnostic purposes. The biopsy showed fungal hyphae stained with Grocott's methanamine silver and periodic acid–Schiff. Liposomal amphotericin B and trimethoprim–sulfamethoxazole were administered to manage fungal pneumonia and *Pneumocystis jiroveci* pneumonia. Pneumonia resolved after a 2-week antifungal treatment, and the patient is followed on an outpatient basis with a supplemental dose of hydrocortisone.

Discussion ACTH secretion by thymic carcinoid tumor is a very rare condition and constitutes less than 1% of all Cushing syndrome cases. Because of its rarity, it is difficult to distinguish ectopic ACTH-secreting tumor from pituitary ACTH-producing tumor. The diagnosis of Cushing syndrome can be established when at least 2 different types of tests show abnormal results out of the following: overnight dexamethasone suppression test, 24-hour urine cortisol, and late night salivary/serum cortisol levels. After establishing the diagnosis, it is important to differentiate between ACTH-producing pituitary tumor and ectopic ACTH syndrome when ACTH-dependent Cushing syndrome is suspected. High-dose dexamethasone suppression test is helpful for distinguishing ectopic Cushing syndrome from Cushing disease. In the case of ectopic Cushing syndrome, serum cortisol is not suppressed by high-dose dexamethasone. Inferior petrosal sinus sampling also can be used as a diagnostic test. However, this patient presented acute psychotic symptoms before confirming the baseline hormone test results. Therefore, the full workup for a differential diagnosis was not performed due to the emergency status. Symptoms of typical Cushing syndrome were not shown in this case. Newly diagnosed diabetes and hypertension may be symptoms of Cushing syndrome. Ectopic Cushing syndrome can manifest with atypical features without typical symptoms

such as moon face, buffalo hump, central obesity, and purple striae. However, it is unusual for patients with Cushing syndrome to present with acute psychotic symptom such as catatonia. Catatonia is a psychomotor immobility, which is manifested by stupor.[3] Catatonia is mainly manifested in patients with psychiatric disorders, but it can also occur in patients with other general medical conditions, so it is important to accurately diagnose the underlying causes. It could be helpful to consult a psychiatrist because catatonia usually occurs in psychiatric patients.

The optimal treatment of ectopic ACTH syndrome is surgical resection of the ACTH-producing tumor. However, acute psychosis is an emergency that requires urgent medical treatment. Adrenal steroidogenesis blockers and glucocorticoid receptor antagonists are the currently available drugs for hypercortisolism.[4] Mifepristone, which is a glucocorticoid receptor blocker, can improve hypercortisolism rapidly, but it is not commercially available in Korea. Among adrenal steroidogenesis blockers, etomidate is the most rapid-acting drug in reducing serum cortisol levels.[5] In this case, dramatic improvement of acute psychosis was achieved through etomidate continuous infusion.

Lessons to be learned from the case Our case shows that ectopic Cushing syndrome can manifest with atypical psychotic symptoms such as catatonia. Therefore, it is necessary to recognize the catatonia symptoms when patients with ectopic Cushing syndrome present with psychomotor immobility. In addition, because antipsychotics may exacerbate these symptoms, it is necessary to find and resolve the underlying causes of catatonia. Intravenous etomidate could be an effective treatment to lower cortisol levels immediately in the case of catatonia caused by ectopic ACTH syndrome.

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