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CASE

New-Onset Acute Heart Failure After Intravenous Glucocorticoid Pulse Therapy in a Patient with Graves' Ophthalmopathy

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A 53-yr-old previously healthy man was admitted to our hospital for thyrotoxicosis without ophthalmopathy. Initial therapy with propylthiouracil caused an acute elevation of liver enzymes. Then, he received a first course of ^{131}I therapy (20 mCi). At the end of 6-mo follow-up after ^{131}I, he was still thyrotoxic and developed moderately severe ophthalmopathy. The patient refused thyroid surgery and decided to undergo second course of ^{131}I therapy (30 mCi). Concomitantly with the ^{131}I, we opted to give high-dose pulse glucocorticoid therapy (PGT) to prevent further deterioration of GO. The patient was started on intravenous methylprednisolone pulse therapy 1 g daily in a cycle (one cycle every 2 wk, each cycle comprising two infusions on alternate days). After the end of the second day of PGT administration, he suddenly developed onset of acute pulmonary edema and hypertension. There was no previous history of cardiac disorder or conditions predisposing to cardiac failure other than thyrotoxicosis. A presumptive diagnosis of fluid overload and/or hypertension-induced acute heart failure was made. After prompt investigations excluding cardiogenic causes, we thought that this condition was triggered by PGT that was superimposed on thyrotoxicosis-related hemodynamic instability. Graves' patients with uncontrolled thyrotoxicosis should be under careful surveillance when PGT is planned. To our knowledge, this is the first reported case of life-threatening acute pulmonary edema caused by PGT in GO.

Key Words: Graves' ophthalmopathy; thyrotoxicosis; high dose pulse glucocorticoid therapy; acute heart failure; acute pulmonary edema.

Introduction

Graves' ophthalmopathy (GO) is a chronic debilitating infiltrative eye disease that is often characterized by a single flare of the autoimmune process. As in other autoimmune diseases, many previous studies have shown the therapeutic benefits of glucocorticoid therapy in GO *(1)*. The efficacy of high-dose intravenous pulse glucocorticoid therapy (PGT) has also been well documented *(2,3)*.

Serious adverse cardiovascular effects of PGT are very rare and have been mainly reported in other autoimmune diseases *(4,5)*. Acute administration of glucocorticoid may produce adverse hemodynamic effects by promoting the retention of salt and water *(6)*. It also increases both systolic and diastolic blood pressures as well as the pulse pressure *(7)*.

Thyrotoxicosis is also associated with hemodynamic impairment including decreased systemic vascular resistance and cardiac contractility, and increased cardiac output, heart rate, blood volume, and blood pressure *(8–10)*. Thyrotoxicosis is also occasionally associated with heart failure in the absence of preexisting cardiac disease *(10)*. Increased thyroid hormone levels following radioactive iodine (RAI) therapy has generally been attributed to increased thyroid hormone release from degenerating follicles and may further compromise cardiac function *(11)*.

We report a case of acute pulmonary edema following administration of PGT during GO treatment. The current patient had at least two of the risk factors including thyrotoxicosis and PGT.

Case Report

A 53-yr-old man was admitted to our department for evaluation of profound weight loss (approx 15 kg in 3 mo), fatigue, palpitation, excessive sweating, emotional liability, and insomnia. The past medical history was unremarkable. He denied using tobacco, alcohol, and illicit drugs. He had no history of hypertension, diabetes mellitus, or coronary artery disease. On physical examination, he appeared ill, cachectic, and anxious. His pulse was 122 beats/min, regular; blood pressure 130/80 mmHg; respiratory rate 22

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Table 1
Results of Thyroid Studies During Follow-up

Test	Before first RAI	Before second RAI	During AHF	Normal values
TSH (mIU/mL)	<0.001	<0.001	<0.001	0.35–5.5
Free T3 (pmol/L)	17.6	12.6	3.75	2.8–7
Free T4 (pmol/L)	71.7	65.4	48.2	10–23
Anti-TPO (U/mL)	237	3221		0–40
Anti-Tg (U/mL)	6.5	9.6		0–40
TRAb (U/L)	1	147		0–10

RAI: radioactive iodine; AHF: acute heart failure; TSH: thyrotropin; Anti-TPO: antithyroid peroxidase antibody; Anti-Tg: antithyroglobulin antibody; TRAb: TSH receptor antibody.

breaths/min; temperature was 36.4°C. The hair was brittle and the skin was warm and moist with excessive sweating. He had tremors of the outstretched hands. Extraocular eye movements were intact without exophthalmos and a soft tissue involvement, although lid lag was present. There was diffuse, nontender thyroid hyperplasia without palpable nodules; no bruit was noted over the thyroid area. Cardiac examination revealed a regular tachycardia with no heart murmurs.

The symptoms and signs at presentation were suggestive of hyperthyroidism. Thyroid function studies showed a suppressed thyrotropin hormone (TSH) of < 0.001 mIU/mL (normal range, 0.35–5.5) and elevated free T_4 of 71.7 pmol/L (normal range, 10–23), and free T_3 of 17.6 pmol/L (normal range, 2.8–7). Antithyroid peroxidase antibody (anti-TPO) titer was elevated to 237 U/mL (normal range, < 40). Antithyroglobulin antibody (anti-Tg) titer was found to be 6.5 U/mL (normal range, < 40). Serum concentrations of free T_4, free T_3, TSH, anti-TPO, and anti-Tg were determined by chemiluminescent assay using commercially available kits (DPC kits; Diagnostic Products Corporation, Los Angeles, CA, USA). Circulating TSH receptor antibody (TRAb) level was 1 U/L (normal range, 0–10) (TRAK-Assay, Brahms Diagnostica GmbH, Berlin, Germany). Thyroid function, thyroid autoantibodies, thyroid ultrasound, and a thyroid scan findings were consistent with the diagnosis of Graves' disease (see Table 1).

He was initially treated with propranolol and propylthiouracil (PTU) to control his hyperthyroidism. However, PTU was discontinued after a week because he showed a marked and rapid increase of serum aminotransferase enzymes (AST 171 IU/L, ALT 206 IU/L). When serum aminotransferases had returned to normal, he received a first course of ^{131}I therapy (20 mCi). The patient was then lost to follow-up, but returned after 6 mo. He was still thyrotoxic, and had developed moderately severe GO with a clinical activity score (CAS) of 5. The diagnosis of GO was based on ophthalmologic investigation, in combination with increased eye muscle size and retrobulbar soft tissue edema on orbital magnetic resonance imaging. Proptosis measured with a Hertel exophthalmometer was 24 mm in the right eye and 25 mm in the left eye. Moderately severe GO is defined as marked soft tissue swelling, and/or proptosis > 25 mm, and/or inconstant diplopia, but without optic nerve involvement. CAS takes into consideration seven manifestations of disease: spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, eyelid edema or fullness, conjunctival injection, chemosis, and swelling of the caruncle. One point is given for any manifestation; the final score is the sum of all manifestations present *(12)*. Circulating TSH-R antibody level was also increased to 147 U/L.

Therapy options for the treatment of his hyperthyroid condition and GO were discussed with the patients. He refused surgery and decided to undergo a second course of RAI. Therefore, he received 30 mCi ^{131}I therapy, plus PGT to prevent further deterioration of GO. The therapeutic scheme was methylprednisolone pulse therapy 1 g daily diluted in 250 cc of saline solution (NaCl 0.9%) in slow intravenous infusion in a cycle (one cycle every 2 wk, each cycle consisted of two infusions on alternate days).

PGT was started on the day after ^{131}I therapy. There was no adverse consequence on the first day of PGT administration. On the second day, at the end of PGT infusion, the patient experienced the sudden onset of respiratory distress, dyspnea, cyanosis, profuse sweating, and shivering. Physical examination showed an awake, anxious patient with severe dyspnea sitting upright on the bed. Initial vital signs were an oral temperature of 36.7°C, blood pressure of 180/120 mm Hg, heart rate of 146 beats/min, and a respiratory rate of 36 breaths/min together with severe hypoxemia (SpO_2 = 74%). Cardiopulmonary examination showed engorged jugular veins, a regular tachycardic rhythm without a murmur, bilateral diffuse crackles, and decreased breath sounds, especially in the dependent areas of lung fields. The abdomen was soft and nontender. The extremities were without edema. Supplemental oxygen, intravenous access, and cardiac monitoring were initiated with a diagnosis of acute heart failure. An electrocardiogram (ECG) was performed and showed sinus rhythm with a heart rate of 145 beats/min. The patient was given intravenous furosemide, nitroglycerin, and morphine sulfate. He underwent bedside chest radiography within the first few minutes of the episode, which revealed bilateral, patchy alveolar infiltrates with a normal cardiac silhouette consistent with acute pulmonary edema. Blood gas analysis findings were pH 7.04, $PaCO_2$ 83 mmHg, and PaO_2 86 mmHg while breathing oxygen through a mask at a rate of 6 L/min. He became progressively more dyspneic and cyanotic, and required endotracheal intubation. During the endotracheal intubation copious pink exudate was noted, and the patient was immediately transferred to the intensive care unit (ICU).

During follow-up in ICU, a Swan–Ganz catheter was inserted. The central venous pressure was 20 cm H_2O (normal range, 3–11 cm H_2O), and pulmonary wedge pressure

was 30 mmHg (normal range, 6–12 mmHg). The pulmonary artery pressures were 58/28 mmHg (mean 47). The patient was given supportive management, with low doses of nitroglycerin, diuretics, and a high concentration of inspired oxygen in combination with bronchodilators during his stay in ICU. Ventilatory assistance was required. A working diagnosis of acute onset pulmonary edema without a clear etiology was entertained at this time. Three sets of cardiac enzymes and serial ECGs ruled out an acute coronary syndrome. Renal function and liver function parameters were also normal. Transthoracic echocardiogram showed depressed cardiac function (an ejection fraction of 35%), with evidence of left ventricular failure and volume overload. Subsequently, coronary angiography showed entirely normal coronary anatomy. With continued medical management including diuresis to maintain a negative fluid balance, the patient's cardiopulmonary status began to improve and pulmonary edema resolved. The patient was successfully weaned off ventilatory support 2 d after the onset of pulmonary edema and was well enough to be discharged back to the ward on the 4th ICU day.

The patient was transferred back to our ward and treated with a low-sodium (2 g salt per day) diet, fluid restriction (1.5 L/day), furosemide (40 mg intravenously twice daily with potassium chloride 40 mEq orally twice daily), an angiotensin converting-enzyme inhibitor (lisinopril 10 mg orally daily), and metoprolol (sustained-release preparation 25 mg orally daily). A follow-up echocardiogram showed a normal ejection fraction of 65% and complete resolution of previous abnormalities 1 wk after onset of pulmonary edema. Three months after his second course of RAI treatment, he was biochemically hypothyroid, and L-thyroxine replacement therapy was initiated. GO was substantially improved after 6 mo with slight periorbital puffiness and conjunctival injection only. Proptosis measured by exophthalmometer reduced to 19 mm in the right eye and 21 mm in the left eye.

Discussion

PGT has been used to treat a variety of inflammatory disorders. Serious adverse cardiovascular effects of PGT are rare and have been mainly reported in non-Graves' patients, typically those with kidney or heart disease *(4,5)*. Complications including infections, elevated blood glucose levels, neuropsychiatric disturbances such as seizures, mania, psychoses, and hemiplegia have been reported in patients with other autoimmune diseases receiving PGT as well *(13,15)*. PGT-induced severe cardiovascular adverse reactions including death, mostly related to ventricular arrhythmia or myocardial infarction, have also been reported *(13–17)*.

Thyrotoxicosis has an influence on several cardiovascular hemodynamic parameters. Excess thyroid hormone states are accompanied by an increase in total blood volume, a decrease in total systemic vascular resistance, a positive inotropic and chronotropic action, and shortened circulation time. Although both systolic contraction and diastolic relaxation are enhanced, the cardiac contractile reserve is low, a phenomenon that is reversed after antithyroid treatment *(18, 19)*. Thyrotoxicosis is also accompanied by several hemodynamic changes that can produce blood pressure elevations *(20)*. Long-standing untreated hyperthyroidism occasionally may lead to reversible heart failure even in the absence of concomitant cardiac diseases *(18)*. An abrupt rise in thyroid hormone levels following RAI therapy has been well documented and attributed to increased thyroid hormone release from degenerating follicles, which might further compromise cardiac function *(21)*.

In the present case, heart failure did not develop until precipitated by high-dose PGT that further exacerbated cardiac workload. Increased cardiac workload caused significant but reversible left ventricular dysfunction. In our case, acute heart failure did not seem to be directly related to aggravated thyrotoxicosis after RAI treatment, because RAI treatment did not change the serum levels of thyroid hormones during acute heart failure. However, the possibility of intervening nonthyroidal illness that might obscure the thyroid hormone profile cannot be ruled out.

The mechanisms of pulmonary edema are various, as follows: altered permeability, increased pulmonary capillary pressure, decreased oncotic pressure, increased negative interstitial pressure, and mixed *(22)*. Traditionally, it is well known that corticosteroid hormones induce renal sodium and fluid retention by possibly acting through renal mineralocorticoid receptors *(23,24)*. Steroids also increase both systolic and diastolic pressures as well as the pulse pressure, which is unrelated to urinary sodium or fluid retention *(25,26)*. The mechanism by which steroids raise blood pressure in human is still unclear. Steroids have a variety of effects on kidneys, heart, brain, blood vessels, and body fluid volumes, but it is not clear which of these are causal rather than epiphenomena or amplifiers or modulators of the rise in blood pressure *(26)*. Current interest focuses on vascular effects of steroids and the role of the nitric oxide (NO) system. A role for the NO system in steroid-induced hypertension was suggested by studies in the rat, in which L-arginine partially prevented the development of adrenocorticotropic hormone–induced hypertension *(27)*.

In our patient, acute onset pulmonary edema arose shortly after PGT in an otherwise healthy thyrotoxic patient. We thought that fluid overload and hypertension triggered by PGT in the presence of long-standing uncontrolled thyrotoxicosis-related hemodynamic changes contributed to the development of acute pulmonary edema. Although cardiopulmonary adverse effects have been reported with the use of PGT, to the best of our knowledge this is the first case report of severe life-threatening acute heart failure associated with PGT in a Graves' patient. This case highlights the need to consider steroid medications as a cause of deterioration in cardiac function in the context of thyrotoxicosis,

even in the absence of other well-established risk factors for heart failure. Although specialists in other fields have been administering PGT in an outpatient setting, we recommend that patients should be hospitalized for close surveillance during PGT.

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