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AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 2 COMPLICATED BY ACUTE ADRENAL CRISIS AND PERICARDIAL TAMPONADE IN THE SETTING OF NORMAL THYROID FUNCTION

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Abstract

We describe herein a 48-year-old Caucasian woman with a history of autoimmune polyglandular syndrome type 2 who presented with pericarditis, pericardial effusion, and pericardial tamponade preceded by acute adrenal crisis in the setting of normal thyroid function. The case highlights the importance of a rare yet important complication of autoimmune polyglandular syndrome type 2 that mandates early recognition and intervention.

Case Report

A 48-year-old Caucasian woman with a past medical history of autoimmune polyglandular syndrome (APS) type 2 with Addison's disease (stable on 3 mg prednisone daily and 0.1 mg fludrocortisone daily) and autoimmune primary hypothyroidism presented with fatigue, malaise, sudden onset of left-sided chest pressure (worse with inspiration), and associated shortness of breath. She denied any dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, palpitations, weakness, fever, chills, presyncope, or syncope. Her family history was significant for Hashimoto's thyroiditis in her father and sister and type 1 diabetes mellitus in her brother. She works as a geriatric nurse practitioner and denied any history of smoking, alcohol, or drug abuse.

In the emergency department, her vital signs were notable for hypotension (systolic blood pressure 90-100, diastolic blood pressure 40-60) and tachycardia (heart rate 110-120). Physical examination was remarkable for decreased breath sounds, dullness to percussion, and decreased tactile fremitus on the right side of the chest. Jugular venous pressure was elevated at 12 cm. Laboratory workup was significant for leukocytosis (white blood cells: 16,300 cells/ μ L) with a neutrophil count of 84.9%, hyponatremia (sodium: 131 mEq/L), hypophosphatemia (phosphate: 1.7 mg/dL), hypomagnesemia (magnesium: 1.4 mg/dL) and hypocalcemia (calcium: 6.7 mg/dL, ionized calcium: 1.04 mg/dL). Thyroid profile was within normal limits (T4: 8.4 μ g/dL, TSH: 0.56 mIU/L, total T3: 91 ng/dL). A 12-lead electrocardiogram revealed sinus tachycardia with a low voltage QRS. Chest X-ray showed slightly enlarged cardiac silhouette but otherwise no acute cardiopulmonary abnormality. Computed tomography angiography of the chest showed no evidence of pulmonary embolism and revealed a moderate right-sided pericardial effusion with maximal thickness of 1.7 cm (Figure 1). Two-dimensional echocardiogram showed a normal left ventricular ejection fraction of 60%, a moderate-sized pericardial effusion, and

impaired diastolic filling of the right atrium and right ventricle hemodynamically consistent with an early tamponade physiology (Figure 2; Video 1).

The patient was admitted with the diagnosis of moderate-to-severe pericardial effusion leading to pericardial tamponade and acute adrenal crisis in the backdrop of autoimmune polyglandular syndrome type 2. Cardiothoracic surgery was consulted and a subxiphoid pericardial window was created to allow therapeutic drainage of 300 mL of thin yellow pericardial fluid. Her electrolytes were replaced, and she was started on stress dose steroids to replenish the glucocorticoid/mineralocorticoid reserve due to hypocortisolemia. After the tamponade was relieved, her blood pressure normalized and her steroids were tapered accordingly. Her pericardial drainage continued to wean down, with the drain removed after 48 hours of hospitalization. Pericardial biopsy revealed acute inflammatory cells with fibrin deposition and reactive mesothelial hyperplasia. Pericardial fluid cultures were negative and the cytology did not reveal any malignant cells. After discharge, follow-up cardiac evaluation with a repeat echocardiogram showed normal function of the heart.

Discussion

The estimated prevalence for APS type 2 (APS 2) is reported to be 1.4 to 4.5 cases per 100,000 persons.¹ It has a genetic predisposition and usually occurs at the age of 30 to 40 years, with women three times more likely to be affected than men.² First-degree relatives of patients with APS 2 are at increased risk of autoimmune disorders. The disease was initially defined as Schmidt syndrome in 1926.³ More common than type 1 APS, APS 2 is characterized by the combination of Addison's disease (the defining component), type 1 diabetes mellitus, and/or autoimmune primary hypothyroidism, and it encompasses a variety of organ-specific autoimmune conditions. Other described conditions associated with APS 2 are celiac disease, vitiligo, pernicious anemia, myasthenia gravis, chronic autoimmune hepatitis, and

Figure 1. Moderate sized circumferential pericardial effusion measuring up to 1.7 cm in thickness.

Sjogren's syndrome.⁴ The association of APS 2 with pericarditis and pericardial tamponade is rare, and to the best of our knowledge only nine cases have been reported previously in the literature.⁵⁻⁸ One case of nonischemic cardiomyopathy and APS 2 requiring heart transplant has also been reported in the literature.⁹

Autoimmune polyglandular syndrome type 2 is a complex genetic disorder in which both HLA haplotype and non-HLA genes contribute to the disease risk. Our genetic understanding of APS 2 is based on the knowledge of its individual components. The genes encoding for the major histocompatibility complex (MHC) class II molecules confer risk for Addison's disease development, and the haplotypes HLA-DR3/4-DQ2/8, DRB1*0404 (HLA-DR4 subtype), DQA1*0501,DQB1*0201, and DQA1*0301,DQB1*0302 have all been implicated.¹⁰⁻¹² Similarly, the non-MHC genes such as CTLA-4 and PTPN22 also add to the susceptibility of disease development.¹⁰ Since the presence of an autoimmune condition as a lone entity is rare, development of one should raise suspicion for the other. For example, 1.5% of patients with type 1A diabetes mellitus have adrenal 21-hydroxylase autoantibodies, and approximately one-third of these patients go on to develop Addison's disease.¹¹⁻¹²

Our patient developed acute pericarditis due to either autoimmune or viral etiology, which lead to an intense inflammatory reaction and rapid accumulation of pericardial fluid. The resultant increased intrapericardial pressure led to compression of all cardiac chambers and ultimately cardiac tamponade. The acute adrenal crisis was likely the preceding event and possibly set the stage for the chain of events including pericarditis, pericardial effusion, and tamponade. In addition, the Addison's crisis led to marked hypovolemia with resultant limited cardiac inflow and reduced filling pressures on the right side of the heart, further worsening pericardial tamponade. Interestingly, her thyroid profile was completely normal, further suggesting hypocortisolism as the precipitating event.

Figure 2 and Video 1. Moderate to large sized near circumferential pericardial effusion with evidence of right atrial diastolic collapse suggestive of early tamponade physiology.

Pericardial effusion and cardiac tamponade, although a rare complication, could be the initial manifestation of APS 2. Unexplained pericardial effusion and tamponade in a young female should raise the suspicion of autoimmune polyglandular syndrome. Early recognition is mandatory, and relieving the tamponade is lifesaving.

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Keywords: pericardial effusions, pericardial tamponade, adrenal crisis; autoimmune polyglandular syndrome type 2

References

1. Chen QY, Kukreja A, Maclaren NK. The Autoimmune Polyglandular Syndromes. In: De Groot LJ, Jameson JL, eds. *Endocrinology*, 4th ed. Philadelphia: W.B. Saunders, 2001: 587-99.
2. Schatz DA, Winter WE. Autoimmune polyglandular syndrome. II: Clinical syndrome and treatment. *Endocrinol Metab Clin North Am*. 2002 Jun;31(2):339-52.
3. MB S. Eine biglandulare Erkrankung (Nebennieren und Schilddrüse) bei morbus Addisonii. *Verh Dtsch Ges Pathol*. 1926;21:212-18.
4. Betterle C, Lazzarotto F, Presotto F. Autoimmune polyglandular syndrome Type 2: the tip of an iceberg? *Clin Exp Immunol*. 2004 Aug;137(2):225-33.
5. Tucker WS Jr, Niblack GD, McLean RH, et al. Serositis with autoimmune endocrinopathy: clinical and immunogenetic features. *Medicine (Baltimore)*. 1987 Mar;66(2):138-47.
6. Torfoss D, von de Lippe E, Jacobsen D. Cardiac tamponade preceding adrenal insufficiency--an unusual presentation of Addison's disease: a report of two cases. *J Intern Med*. 1997 Jun;241(6):525-8.
7. Alkaabi JM, Chik CL, Lewanczuk RZ. Pericarditis with cardiac tamponade and addisonian crisis as the presenting features of autoimmune polyglandular syndrome type II: a case series. *Endocr Pract*. 2008 May-Jun;14(4):474-8.
8. Palmer WC, Kurklinsky A, Lane G, Ussavarungsi K, Blackshear JL. Cardiac tamponade due to low-volume effusive constrictive pericarditis in a patient with uncontrolled type II autoimmune polyglandular syndrome. *Acute Card Care*. 2014 Mar;16(1):23-7.

9. Nielsen TD, Steenbergen C, Russell SD. Nonischemic cardiomyopathy associated with autoimmune polyglandular syndrome type II. *Endocr Pract.* 2007 Jan-Feb;13(1):59-62.
10. Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. *Nat Rev Endocrinol.* 2010 May;6(5):270-7.
11. Yu L, Brewer KW, Gates S, et al. DRB1*04 and DQ alleles: expression of 21-hydroxylase autoantibodies and risk of progression to Addison's disease. *J Clin Endocrinol Metab.* 1999 Jan;84(1):328-35.
12. Falorni A, Laureti S, Santeusano F. Autoantibodies in autoimmune polyendocrine syndrome type II. *Endocrinol Metab Clin North Am.* 2002 Jun;31(2):369-89, vii.