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Case Report

A Rare Case of Addison's Disease Presenting With Intermittent Pancytopenia and Cardiac Tamponade

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ABSTRACT

Objective: To report the first case, to our knowledge, of intermittent pancytopenia and cardiac tamponade occurring together in association with Autoimmune Addison's Disease (AAD).
Methods: A 21 year-old woman presented on three different occasions with multiple complaints. Her evaluation was significant for intermittent pancytopenia (white blood cell, 1.3-3.0 $\times$ 10^3/μL [normal 4.5-11 $\times$ 10^3]; hemoglobin, 8.8-9.6 g/dL [11-16]; and platelets, 102-117 $\times$ 10^3/μL [150-400 $\times$ 10^3/μL]) and pericardial effusion with cardiac tamponade. Further investigation including a morning serum cortisol level of 0.6 μg/dL (5.27-22.45 μg/dL), adrenocorticotropic hormone level of 1027 pg/mL (normal 6-50 pg/mL), and positive 21-hydroxylase antibodies confirmed the diagnosis of primary adrenal insufficiency due to AAD. Treatment with steroids resulted in prompt hemodynamic recovery with normalization of all blood cell lines.
Results: The diagnosis of AAD is often delayed or overlooked. Pancytopenia occurring in AAD is most likely due to either marrow suppression in the setting of acute illness and exacerbated by hypoadrenalism or possibly an autoimmune-mediated marrow reaction. Pericarditis with cardiac tamponade has been described in AAD occurring in the setting of polyglandular autoimmune syndrome type II. The pathogenesis involves autoimmune inflammation of the pericardium, which precipitates an acute inflammatory reaction and rapid fluid accumulation.
Conclusion: Pericarditis with cardiac tamponade and intermittent neutropenia may be rare manifestations of an Addisonian crisis.

Introduction

Autoimmune Addison's disease (AAD) is the most common cause of primary adrenal insufficiency in developed countries and may present in a myriad of ways.[1] We describe a case of a patient who presented with cardiac tamponade and neutropenia as manifestations of AAD. To our knowledge, this is the first case reported of these two entities occurring together in association with AAD.

Case Report

A 21-year-old woman with a 4-year history of postural orthostatic tachycardia syndrome (POTS), treated with fludrocortisone, and recent travel to Cambodia presented to the emergency department of an outside hospital with a 1-week history of diarrhea and vomiting. She was hypotensive with a blood pressure of 85/56 mmHg and tachycardic with a heart rate of 112 beats per minute (bpm). Her laboratory results are shown in Table 1. She was admitted and treated for travelers' diarrhea with parenteral hydration and antibiotics. She clinically improved and was discharged without further investigation.

She represented 25 days later, with a 1-day history of weakness and postural instability. She also complained of chest and back pain associated with shortness of breath. Her vitals on presentation were as follows: temperature of 96 °F, heart rate of 110 bpm,

Abbreviations: AAD, autoimmune Addison's disease; AI, adrenal insufficiency; bpm, beats per minute; Hb, hemoglobin; POTS, postural orthostatic tachycardia syndrome; TTE, transthoracic echocardiogram.

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Table
Electrolytes and Complete Blood Cell Count in All Three Lineages on the Day of Initial Presentation Compared With 2 Months After Initiation of Glucocorticoid Therapy

	Initial presentation (before glucocorticoid therapy)	After glucocorticoid therapy
Basic metabolic profile		
Sodium (137-146 mmol/L)	123	139
Potassium (3.5-5.3 mmol/L)	3.7	4.1
Chloride (98-107 mmol/L)	85	103
Bicarbonate (23-32 mmol/L)	20	24
Complete blood count		
White blood cell (4.5-11 $\times$ 10^3/μL)	1.3	6.9
Absolute neutrophil count (1.5-7.8 $\times$ 10^3/μL)	0.3	4.2
Hemoglobin (11-16 g/dL)	10.7	15.2
Platelets (150-400 $\times$ 10^3/μL)	142	221

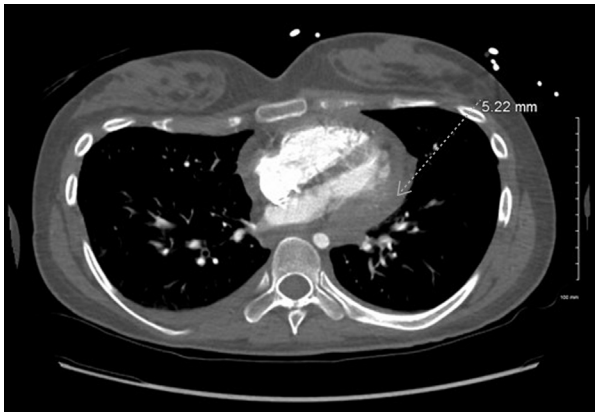

Fig. 1. Computed tomography of the chest revealing 5.22-mm-thick pericardial effusion (arrow).

respiratory rate of 25 breaths per minute, and blood pressure of 67/33 mmHg. Her laboratory results revealed normalization of previous pancytopenia with a white blood cell count of 13.1 $\times$ 10^3/μL, hemoglobin (Hb) level of 11.9 g/dL, and platelet count of 261 $\times$ 10^3/μL. Her laboratory tests also were remarkable for a serum sodium level of 126 mmol/L, potassium level of 6.1 mmol/L, bicarbonate level of 11 mmol/L, chloride level of 99 mmol/L, and creatinine level of 2.0 mg/dL (baseline, 0.4 mg/dL). She underwent further evaluation with a computed tomography examination of the chest and abdomen, which revealed a mild pericardial effusion with mild edema in the mediastinum (Fig. 1) but otherwise was unremarkable including the adrenal glands. The patient was admitted to the intensive care unit, and a transthoracic echocardiogram (TTE) was performed 12 hours later, which demonstrated the presence of a moderate to large pericardial effusion, with echocardiographic signs of pericardial tamponade (Figs. 2 *A* and *B*). She was urgently taken to the cardiac catheterization laboratory for pericardiocentesis. Pericardial tamponade was confirmed with equalization of pressures in all of the heart chambers. Following placement of a pericardial drain, her condition rapidly improved. Subsequent pericardial fluid cultures were negative for bacteria, viruses, and mycobacteria, and cytology was negative for malignant cells. Serum studies for bacterial, viral, and parasitic infections were all negative, and thyroid function tests were normal. An autoimmune workup was unrevealing. On the third day of admission, she again was noted to have pancytopenia with a neutrophil count of 0.5 $\times$ 10^3/μL (without blast cells on peripheral smear), Hb level of 9.6 g/dL, and platelet count of 117 $\times$ 103/μL. The pancytopenia was thought to be related to bone marrow suppression in the setting of acute illness, and no further workup was performed. She was discharged with a 3-month course of colchicine and 2 weeks of ibuprofen as treatment for acute pericarditis. Repeat complete blood count after discharge showed normalization of her blood cell count in all three lineages.

The patient remained asymptomatic until 3 months later when she represented again with substernal chest pain worse in the supine position. On presentation, her temperature, heart rate, and blood pressure were 100.2 °F, 111 bpm, and 95/69 mmHg, respectively. A TTE again demonstrated signs of pericardial tamponade. Emergent pericardiocentesis removed 300 mL of serous fluid, which led to the normalization of pericardial pressures and hemodynamic stability. Pericardial fluid studies were negative for infection and malignancy. On further examination, it was evident that her skin in sun-exposed areas and oral mucosa was hyperpigmented. There was no evidence of vitiligo. Laboratory studies again demonstrated pancytopenia with a white blood cell count of 2.9 $\times$ 10^3/μL, Hb level of 10.4 $\times$ 10^3/μL, and platelet count of 134 $\times$ 10^3/μL (Fig. 3). Her laboratory studies were also remarkable for the following: sodium level of 132 mmol/L, potassium level of 4.2 mmol/L, carbon dioxide level of 13 mmol/L, chloride level of 97 mmol/L, a normal anion gap, and morning serum cortisol level of 0.6 μg/dL with a repeat level of 0.9 μg/dL. She was treated emergently with stress-dose glucocorticoids, and her clinical picture improved dramatically—she was able to be weaned from intravenous vasopressor support within hours. Her course was complicated by transient worsening of her neutropenia to 0.7 $\times$ 10^3/μL, and a bone marrow biopsy was performed and revealed 20% to 30% cellular marrow with maturing trilineage hematopoiesis. Evaluation for specific causes of pancytopenia including peripheral smear review and bone marrow biopsy failed to identify any nutritional, infectious, rheumatologic, or malignant etiology for the pancytopenia. Her blood cell counts dramatically improved after 2 days of intravenous hydrocortisone (neutrophil, >1.3 $\times$ 10^3/μL; Hb, 9.2 g/dL; and platelets, 124 $\times$ 10^3/μL). She continued to improve clinically, and her intravenous steroid was stopped, and 20 mg of prednisone along with 0.1 mg of fludrocortisone was started. Repeat TTE showed resolution of her pericardial effusion. Additional history revealed that she had received two short courses of steroids after her previous two admissions. The patient was discharged in good condition. At follow-up 3 weeks later, she felt much improved, and all her blood cell lines and electrolytes had normalized (Table 1). Figure 3 demonstrates the pattern of intermittent neutropenia during her three presentations. Her adrenocorticotropic hormone level returned significantly elevated at 1027 pg/mL, and her 21-hydroxylase antibody was positive. Thyroid peroxidase and anti-glutamic decarboxylase antibodies were negative. Since then, her glucocorticoid therapy has been tapered, and she is maintained on 25 mg of hydrocortisone and 0.1 mg of fludrocortisone daily. A repeat TTE 5 months after discharge demonstrated no recurrent pericardial effusion.

Discussion

We describe a 21-year-old woman with a history of POTS who presented twice with pericardial tamponade and pancytopenia and was eventually diagnosed with AAD. The clinical symptoms of AAD are secondary to deficient production of glucocorticoids, mineralocorticoids, and androgens.[1,2] Classical manifestations of AAD include weakness, fatigue, weight loss, orthostatic hypotension, skin and mucosal hyperpigmentation, nausea, vomiting, and salt craving.[2] AAD remains a clinical challenge to diagnose as an estimated 60% of affected individuals are seen by multiple clinicians before establishing diagnosis.[3] It is likely that our patient was suffering with partially treated Addison's since the age of 17 years

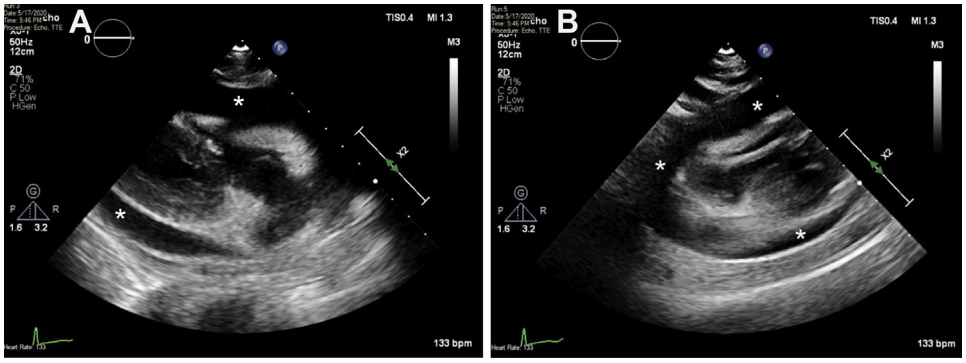

Fig. 2 ***A and B.*** Transthoracic echocardiogram parasternal long axis views revealing moderate to large pericardial effusions marked by the asterisks (*).

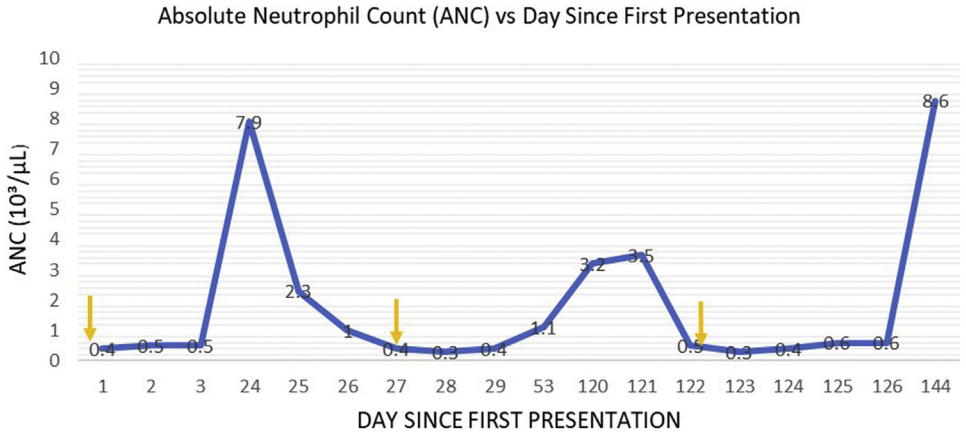

Fig. 3. Graph showing an intermittent pattern of neutropenia with the arrows indicating the onset at each presentation and revealing normalization of neutropenia with the resolution of the acute illness.

as she had presented then with orthostasis, syncope, and fatigue and was diagnosed with POTS, the most common form of orthostatic intolerance in young people, particularly women.[4] She then began treatment with mineralocorticoid alone. This case illustrates the critical importance of excluding adrenal insufficiency (AI) prior to diagnosing patients with POTS.

The patient's exceeding low level of cortisol (0.6 μg/dL) during acute stress was diagnostic for AI,[2] and her markedly elevated adrenocorticotropic hormone level and positive 21-hydroxylase antibodies confirmed the diagnosis of primary adrenal insufficiency due to autoimmune adrenalitis.[5] Her Addison's disease may be the first manifestation of the polyglandular autoimmune syndrome-type II.

Various hematologic abnormalities are seen in AAD, most commonly normochromic normocytic anemia but also eosinophilia and pernicious anemia. [6] Review of the literature has identified only one previous report (in abstract form) of AAD occurring together with intermittent severe neutropenia[7] and one previous report of new-onset AAD presenting with pancytopenia in pregnancy.[8] During each of our patient's admissions over a 4-month period, she either presented with or quickly developed prominent pancytopenia including grade 4 neutropenia (Fig. 3), which resolved with glucocorticoid treatment. We suspect that her pancytopenia occurred most likely coincidentally due to marrow suppression in the setting of acute illness and was exacerbated by her hypoadrenalism or possibly was an autoimmune-mediated marrow reaction although the paucity of reported cases makes this possibility unlikely. Pancytopenia has been reported in Sheehan's syndrome due to thyroid and cortisol deficiency.[9] Autoimmune neutropenia is a rare disease caused by antineutrophil antibodies, and 40% of these present with other cytopenias.[10] Bone marrow hypocellularity has been described in other autoimmune illnesses.[11,12]

Acute pericarditis with a large pericardial effusion can be caused by idiopathic, malignant, and infectious etiologies. In younger patients, autoimmune and viral illnesses are often precipitants of recurrent pericarditis. Proinflammatory cytokines including interleukin 6, interleukin 8, and interferon gamma have been detected in pericardial fluid, suggestive of a localized inflammatory process.[13] Pericarditis with cardiac tamponade has been described in Addison's disease occurring in the setting of autoimmune polyglandular syndrome type II (PGA-II) in approximately 15 cases.[14-19] Similar to viral pericarditis, the proposed mechanism in Addison's is that autoimmune inflammation of the pericardium leads to an acute inflammatory reaction and rapid fluid accumulation. Immune complexes and antibodies have also been found in fluid samples, supporting autoimmune inflammation in the pathogenesis of pericarditis.[20] This inflammation and fluid accumulation can result in increased pericardial pressure and lead to collapse of the cardiac chambers and subsequent tamponade. In Addison's disease, preexisting hypovolemia from aldosterone and cortisol deficiency can lower right ventricular filling pressures and, thereby, lower the threshold for cardiac tamponade. Cardiac tamponade, if untreated, leads to decreased cardiac output and obstructive shock.

Conclusion

Our patient's pericarditis was likely autoimmune-mediated and her marrow suppression probably occurred coincidentally in the

setting of acute illness. Treatment with corticosteroids, as expected, corrected the AI, reduced pericardial inflammation and thereby facilitated reversal of the marrow reaction. Cardiac tamponade and pancytopenia may be rare complications of an Addisonian crisis.

Disclosure

The authors have received no funding and have no multiplicity of interests to disclose.

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