Case Report

Elisa Baranski Lamback*, Grazia Morandi, Eleni Rapti, Georgi Christov, Paul A. Brogan and Peter Hindmarsh

Addison's disease presenting with perimyocarditis

https://doi.org/10.1515/jpem-2017-0278
Received July 17, 2017; accepted October 25, 2017

Abstract

Background: Polyglandular autoimmune syndrome (PGA) and eosinophilic granulomatosis with polyangiitis (EGPA) do not seem to represent a coincidental association.
Case presentation: A case of a 15-year-old boy is reported who presented with severe systemic inflammation, perimyocarditis and cardiogenic shock, in whom EGPA was initially suspected and later diagnosed with autoimmune adrenalitis with PGA.
Conclusions: The severity of the systemic inflammation and perimyocarditis suggests a more widespread autoimmune-mediated process. Autoimmune adrenal insufficiency should be considered in all cases of pericarditis and perimyocarditis, especially when the severity of clinical manifestations exceeds the expected for the severity of the cardiac findings, as timely identification and prompt treatment may be life-saving.

Keywords: Addison's disease; eosinophilic granulomatosis with polyangiitis; polyglandular autoimmune syndrome.

***Corresponding author: Elisa Baranski Lamback,** MD, Internal Medicine and Endocrine Unit, Federal University of Rio de Janeiro, Rua Professor Rodolpho Paulo Rocco, 255, Ilha do Fundão, Rio de Janeiro/RJ 21941-913, Brazil, Phone: +5521 39382748, E-mail: elisalamback@gmail.com
Grazia Morandi: Pediatric Section, University of Verona, Verona, Italy
Eleni Rapti: Endocrinology Section, AHEPA Hospital, Thessaloniki, Greece
Georgi Christov: Department of Cardiology, Great Ormond Street Hospital for Children, UCL Institute of Child Health, London, UK
Paul A. Brogan: Infection, Inflammation, and Rheumatology Section, Great Ormond Street Hospital for Children, UCL Institute of Child Health, London, UK
Peter Hindmarsh: Department of Pediatric Endocrinology and Diabetes, Great Ormond Street Hospital for Children, UCL Institute of Child Health, London, UK

Introduction

Autoimmune adrenalitis commonly occurs as part of a polyglandular autoimmune syndrome (PGA) [1]. Serositis and systemic inflammation have been reported to be associated with PGA [2], although the association of pericarditis (with or without myocarditis) and adrenocortical crisis has been described in only a few case reports.

Case presentation

A 15-year-old boy, 62 kg, presented with a 2-week history of upper viral respiratory tract infection, dizziness and chest pain. Apart from a long-standing history of asthma, he was otherwise well. In his local hospital, a chest radiography was performed (which was unremarkable) and he was discharged, although it was noted in retrospect that he had a sodium concentration of 128 mmol/L (137–145). Two days later, he was found to be in cardiogenic shock. On admission, he had a fever, high C-reactive protein (CRP) of 267 mg/L (<20) and erythrocyte sedimentation rate (ESR) of 121 mm/h (0–10), eosinophilia [0.91×10^9/L (0.1–0.8)], elevated troponin I of 58 ng/L (<34), but normal creatine kinase of 158 U/L (55–370), moderately elevated pro-b-type natriuretic peptide of 781 pg/mL (23–157), with acute kidney injury [creatinine 206 μmol/L (54–99), urea 14.5 mmol/L (2.5–7.5)], prolonged prothrombin time [14.1 s (9.6–11.8)] and hypoalbuminemia [31 g/L (35–50)], but normal transaminases and bilirubin. An electrocardiogram showed diffuse ST-segment elevation, compatible with pericarditis. He was normoglycemic and had a family history of type 1 diabetes (T1D). A transthoracic echocardiogram demonstrated global impairment of ventricular function and moderately large pleural and pericardial effusions. The pericardial effusion (Figure 1) was causing more significant than expected respiratory-related variation reaching up to 50% at the mitral inflow probably related to potentiation of hemodynamic effect by the left ventricular dysfunction. A percutaneous pericardiocentesis was performed with evacuation of 120 mL of yellow viscous opaque fluid which showed to be a

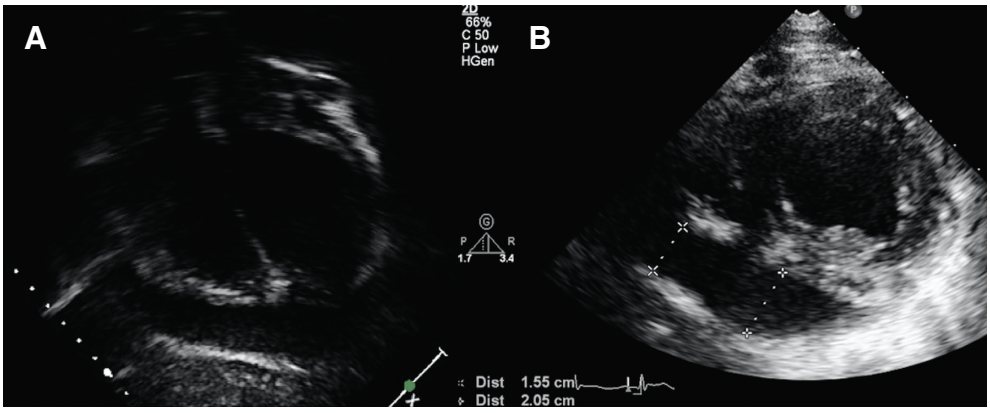

Figure 1: Echocardiography image on admission.
(A) Subcostal view showing moderate pericardial effusion and (B) modified short axis view showing the posterior pocket. The pericardial effusion was moderate with separation of around 15 mm with a larger posterior pocket.

polymorphonuclear exudate with 23/nL white blood cells (95% neutrophils, 1% lymphocytes, 3% monocytes, 1% eosinophils) with a high total protein of 56 g/L and low triglycerides of 0.74 mmol/L (0.38–1.58). He received vasopressor and inotropic agents, and hydrocortisone for 3 days. Despite the clinical manifestations of cardiogenic shock, the lactates were only mildly raised (<3 mmol/L). Infective screening failed to isolate any organism. Anti-neutrophil cytoplasmic antibodies and other non-organ-specific autoantibodies were negative (rheumatoid factor, antinuclear antibodies, β-2-glycoprotein immunoglobulin [Ig] G and IgM, anticardiolipin IgG, smooth muscle antibody, anti-gastric parietal cell antibodies, mitochondrial antibody, reticulin antibody, liver-kidney-microsomal type 1 antibody). Vasculitis screening was negative and thyroid function was normal. He had a borderline lupus test (dilute Russell viper venom test), with normal serum C3 and C4.

A systems review revealed that he had some degree of alopecia, but no hyperpigmented skin; and serial biochemical monitoring revealed chronic hyponatremia [130 mmol/L (124–136)] with elevated potassium concentrations [5.7 mmol/L (3.6–5.0)]. The diagnosis was of idiopathic perimyocarditis, perhaps triggered by an intercurrent viral infection.

During an initial 2-week hospital stay, he showed gradual clinical, biochemical and echocardiographic improvement. A cardiac magnetic resonance performed at 2 weeks from the acute incident revealed a structurally normal heart, mildly dilated left ventricle with impaired global systolic function [ejection fraction of 46% (55–70%)] and multifocal edema (consistent with myocarditis).

One week later, he was unwell, vomiting and confused, with a worsening of his myocardial function and segmental hypokinesia and recurrence of the pericardial effusion. However, markers of cardiac cytolysis and congestion were negative. He also had persistent unexplained hoarseness, caused by paresis of the right vocal cord which was not considered a typical consequence of his prior intubation. Other results of note included microcytic anemia and a new rise of CRP of 212 mg/L and ESR of 110 mm/h, and serial scrutiny of the differential white count revealed eosinophilia >10%. His preceding history of asthma, with acute severe sterile perimyocarditis, renal impairment, peripheral hypereosinophilia and vocal cord paralysis (speculatively caused by mononeuritis multiplex) were considered suggestive of eosinophilic granulomatosis with polyangiitis (EGPA) initially [3], although important differential diagnoses included other causes of hypereosinophilic myocarditis (including eosinophilic leukemia or lymphoma). Based on the suspected diagnosis of EGPA, his treatment was based on a typical induction of remission regimen with methylprednisolone, followed by prednisolone and cyclophosphamide. This brought quick and stable improvement and there was no need of pericardial drainage.

Endocrine results of note were an elevated adrenocorticotropic hormone (ACTH) [at 8 am: 634 ng/L (10–50)], low cortisol (1.27 μg/dL) and positive anti-21-hydroxylase antibodies. Aldosterone was undetectable [<60 pmol/L (90–700)], with a high plasma renin activity [52.6 nmol/L/h (0.5–3.1)]. Repeat testing along with a high fractional excretion of sodium of 2.5% confirmed the diagnosis of primary adrenal autoimmune insufficiency. Fludrocortisone and sodium supplementation were started, as well as replacement with hydrocortisone, with normalization of the adrenal biochemistry and resolution of the hyponatremia. Repeat echocardiography and cardiac MRI

were unremarkable. Other organ-specific autoantibodies were negative (anti-thyroperoxidase, anti-glutamic acid decarboxylase, anti-insulin IgG, anti-thyroid-stimulating hormone receptor and anti-tissue transglutaminase).

With no recrudescence of his systemic inflammation following four doses of cyclophosphamide, he was switched to daily oral azathioprine, with gradual slow taper of the daily prednisolone, and remains in remission.

Discussion

This case reports the association between an EGPA-like presentation with severe systemic inflammation with hypereosinophilia, life-threatening perimyocarditis and autoimmune adrenalitis. A literature review using PubMed database was performed with the following keywords: ["Addison disease" AND "pericarditis"], ["hypocortisolism" AND "pericarditis"], ["adrenal crisis" AND "pericarditis"] and ["autoimmune polyglandular syndrome" AND "pericarditis"]. We included case reports or case series, irrespective of the publication date. We identified 14 cases of the association between pericarditis and primary adrenal insufficiency, of which 11 were of autoimmune etiology (Table 1). Our case describes the youngest patient, to date, with autoimmune hypocortisolism presenting in association with perimyocarditis and cardiac tamponade.

Pericarditis can have an infectious, autoimmune, inflammatory or idiopathic etiology [12]. Although hypothyroidism causes pericardial effusion, endocrinological mechanisms have not been implicated in the etiology of acute pericarditis. There are several reports of patients with adrenal failure presenting with acute pericarditis

Table 1: Case reports of primary adrenal insufficiency and pericarditis.

Author	Diagnosis	Age, years, gender	Recurrent pericarditis	Presentation
Tucker [2]	PGA 2 (AD + ATD)	27, female	Yes	N/A
Tucker [2]	PGA 2 (AD + ATD)	31, female	Yes	N/A
Tucker [2]	AD + primary idiopathic hypogonadism	50, male	Yes	N/A
Torfoss [4]	Newly diagnosed PGA 2 (AD + ATD)	42, male	Yes	One month earlier: sinusitis; 5 days of muscle aches; 4 h of acute severe respiratory-dependent chest pain. Hypotensive
Torfoss [4]	Newly diagnosed PGA 2 (AD + ATD)	36, male	Yes	Two months earlier: fever and raised CRP; 2 days of fever, respiratory-dependent chest pain. Hypotensive and fever
Bhattacharyya [5]	Newly diagnosed AD	18, male	No	One year unwell, with intermittent vomiting. Circulatory collapse
Alkaabi [6]	PGA 2 (AD + ATD)	34, female	Yes	Long-lasting lethargy, nausea, weight loss, chest pain
Alkaabi [6]	Newly diagnosed PGA 2 (AD + ATD + hypogonadism)	58, male	Yes	Long-lasting lethargy, nausea, weight loss, chest pain
Alkaabi [6]	PGA 2 (AD + ATD)	35, female	Yes	Long-lasting lethargy, nausea, weight loss, chest pain
Taxter [7]	Newly diagnosed adrenoleukodystrophy	11, male	No	Two days of chest pain
Palmer [8]	PGA 2 (AD + ATD) Uncontrolled AD (compliant with fludrocortisone but stopped prednisone 6 months prior)	54, male	Yes	Four days of worsening weakness, subjective fevers, nausea and malaise leading to decreased oral intake. Profoundly hypotensive
Khalid [9]	PGA 2 (AD + ATD)	48, female	No	Fatigue, malaise, sudden onset of left-sided chest pressure. Hypotensive
Traficante [10]	Newly diagnosed adrenoleukodystrophy	Prenatal	N/A	Pericardial effusion was seen at a routine ultrasound examination
Kawahara [11]	Newly diagnosed tuberculous primary adrenal insufficiency with recurrent nontuberculous pericarditis	60, male	Yes	Three days of epigastric pain
Present study	Newly diagnosed AD (probably PGA 4)	15, male	Yes	Two-week history of upper viral respiratory tract infection, dizziness and chest pain. Cardiogenic shock

AD, Addison's disease; ATD, autoimmune thyroid disease; PGA, polyglandular autoimmune syndrome.

(Table 1). It is unknown if the combination of adrenal failure and acute pericarditis has a direct cause-effect relation or if there exists a common etiological factor for the triggering of the adrenal destruction and the pericarditis [4]. As infection is one of the commonest precipitating factors for acute crisis [13], it is possible that viral infections could precipitate both. Acute pericarditis can also develop from autoimmunity. In patients with PGA, autoimmune mechanisms have been suggested as the common etiologic factors [2, 6].

More recently, pericarditis has been suggested to arise from chronic hypocortisolism, even in the absence of autoimmunity (in adrenoleukodystrophy [7, 10], isolated ACTH deficiency [14] and tuberculous adrenalitis [11]). Considered together, these cases [7, 10, 11, 14] indicate that a patient with adrenal failure can exhibit acute pericarditis with no obvious underlying immune mechanism.

These observations stating that hypocortisolism could be related to pericarditis are in contrast to other cases that show that pericarditis can occur in the absence of adrenal insufficiency in the context of PGA, as described by Algün et al. [15]. These case reports seem to indicate that pericarditis could be a feature of a more widespread systemic autoimmune process that includes PGA in some individuals.

Moreover, endocrinopathy-related serositis can also occur after asymptomatic intervals of disease-controlled hypocortisolism, perhaps due to its pathogenesis involving not only endocrine failure, but also derangements in the immune complex and immunogenic status [16]. Furthermore, endocrinopathies can be diagnosed before serositis [2]. The acute adrenal crisis could be the preceding event and possibly lead to pericarditis, pericardial effusion and tamponade [9].

In some case reports, Addison's disease (AD) was either already known or was diagnosed in the context of PGA associated with cardiac tamponade [2, 4, 6]. In our review, in the majority of cases, adrenal insufficiency was diagnosed during the pericarditis episode, and although treated, the pericarditis recurred emphasizing that systemic autoimmunity may require treating in its own right, in addition to treatment of adrenocortical insufficiency. Recurrence of pericarditis requires administration of immunosuppressive drugs. While our patient presented with clinical features suggestive of EGPA [3], we are not aware of any previous reports of EGPA-like and PGA, and we suggest that this case demonstrates a propensity to systemic autoimmunity with PGA as a feature, perhaps contributed to by human leukocyte antigen (HLA) association (given the family history of T1D). While the exact etiology and classification of the clinical diagnosis remains uncertain, we suggest that the severity of the perimyocarditis and systemic inflammation in our case warrants a longer-term immunosuppressant treatment, as per that of the severe life-threatening multisystemic inflammatory disorder, in addition to treatment for adrenocortical insufficiency.

In conclusion, PGA should be considered in this case, as our patient has AD and alopecia along with a family history of T1D. The severity of the systemic inflammation and perimyocarditis suggests a more widespread autoimmune-mediated process, although hypocortisolism per se may also have contributed. Irrespective of the cause, this case illustrates that autoimmune adrenal insufficiency should be considered in all cases of pericarditis and perimyocarditis, especially when eosinophilia is detected and the severity of clinical manifestations exceeds the expected for the severity of the cardiac findings. As hyponatremia can be present also in acute heart failure, it can be misinterpreted. Timely identification and prompt treatment for both may be life-saving.

Learning points

- Pericarditis (with or without myocarditis) can be a feature of polyglandular autoimmune syndrome.
- Addison's disease should be considered in all cases of pericarditis and perimyocarditis, especially when the severity of clinical manifestations exceeds the expected for the severity of the cardiac findings.
- In the majority of reported cases, adrenal insufficiency was diagnosed during the pericarditis episode, and although treated, the pericarditis recurred emphasizing that systemic autoimmunity may require treating in its own right.
- Severe perimyocarditis and systemic inflammation warrants a long-term immunosuppressant treatment, as per that of eosinophilic granulomatosis with polyangiitis, in addition to treatment for adrenocortical insufficiency.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and

interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev 2002;23:327–64.
2. Tucker WS Jr, Niblack GD, McLean RH, Alspaugh MA, Wyatt RJ, et al. Serositis with autoimmune endocrinopathy: clinical and immunogenetic features. Medicine (Baltimore) 1987;66:138–47.
3. Eleftheriou D, Gale H, Pilkington C, Fenton M, Sebire NJ, et al. Eosinophilic granulomatosis with polyangiitis in childhood: retrospective experience from a tertiary referral centre in the UK. Rheumatology (Oxford) 2016;55:1263–72.
4. 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;241:525–8.
5. Bhattacharyya A, Jagadeesan S, Wolstenholme RJ, Tymms DJ. Acute adrenocortical crisis and and abnormal electrocardiogram. Hosp Med 1999;60:908–9.
6. 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;14:474–8.
7. Taxter AJ, Bellin MD, Binstadt BA. Pericarditis as the presenting feature of adrenoleukodystrophy. Pediatrics 2011;127:e777–80.
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;16:23–7.
9. Khalid N, Chhabra L, Ahmad SA, Umer A, Spodick DH. Case report: autoimmune polyglandular syndrome type 2 complicated by acute adrenal crisis and pericardial tamponade in the setting of normal thyroid function. Methodist Debakey Cardiovasc J 2015;11:250–2.
10. Traficante G, Biagiotti R, Andreucci E, Di Tommaso M, Provenzano A, et al. Prenatal diagnosis of X-linked adrenoleukodystrophy associated with isolated pericardial effusion. Clin Case Rep 2015;3:643–5.
11. Kawahara J, Shinozaki Y, Takata H, Katsuta S, Kawane T, et al. A case of tuberculous Addison disease with recurrent nontuberculous pericarditis. AACE Clinical Case Rep 2016;2:e199–201.
12. Khandaker MH, Espinosa RE, Nishimura RA, Sinak LJ, Hayes SN, et al. Pericardial disease: diagnosis and management. Mayo Clin Proc 2010;85:572–93.
13. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361:1881–93.
14. Morinaga Y, Yamaguchi H, Tsubouchi C. A case with ACTH deficiency complicated with cardiac tamponade [in Japanese]. Nihon-naibunpitsugakkai-zasshi 2013;88:1004.
15. Algün E, Erkoç R, Kotan C, Güler N, Sahin I, et al. Polyserositis as a rare component of polyglandular autoimmune syndrome type II. Int J Clin Pract 2001;55:280–1.
16. Jolobe OM. Cardiac tamponade preceding adrenal insufficiency – an unusual presentation of Addison's disease. J Intern Med 1998;243:399–400.