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Learning from errors

Cardiac tamponade as the first manifestation of systemic lupus erythematosus in children

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Summary

Systemic lupus erythematosus (SLE) is a serious chronic autoimmune disease with intense inflammatory response and damage in many target organs including joints, skin, kidneys, heart and nervous system. Cardiac tamponade is extremely rare as a cardinal presentation of SLE in children with only a few cases reported in the literature. We report two cases of a 9-year-old boy and an 11-year-old girl presenting with acute cardiac tamponade and later recognition of elevated anti-double-stranded DNA (anti-dsDNA) titre. We also present a literature review about similar cases in children and we stress on the importance of screening all cases of acute cardiac tamponade in children with antinuclear and anti-dsDNA antibodies to avoid any delay in SLE diagnosis and treatment.

BACKGROUND

These two case reports are important as an alert for paediatricians to keep a high index of suspicion for systemic lupus erythematosus (SLE) diagnosis in children where SLE may be atypical; in presentation particularly in cases presenting with isolated acute cardiac tamponade. In such cases early SLE diagnosis will prompt a thorough evaluation and diligent follow-up which can minimise the disease comorbidities and improve its outcomes.

CASE PRESENTATION

Case 1

A previously healthy 9-year-old boy presented to the Rafik Hariri University Hospital emergency room, because of low-grade fever, easy fatigability, exertional dyspnoea and epigastric pain of a few days duration. On physical examination he was pale, tachycardiac with distant heart sounds and congested neck veins.

Case 2

A previously healthy 11-year-old girl presented to another hospital with dyspnoea and chest pain.

She was diagnosed to have cardiac tamponade and a pericardial drainage with a pericardial window was performed, revealing 450 ml of serosanguinous fluid. Gram stain and cultures performed on the pericardial fluid were negative. She was discharged on dexamethasone and cefpodoxime proxetil orally. Nine days later, she presented to the American University Hospital of Beirut emergency unit with relapsing dyspnoea and chest pain. Her system review revealed absence of anorexia, gastrointestinal symptoms, neurological symptoms, joints pain, skin rash, urinary symptoms or haematuria. Her physical examination showed hepatomegaly, no friction rub and bilateral decreased basal air entry.

INVESTIGATIONS

Case 1

The chest x-ray showed mild bilateral pleural effusion with enlargement of the cardiac silhouette. A cardiac ultrasound confirmed the diagnosis of cardiac tamponade. Laboratory studies revealed haemoglobin of 7.3 g/dl, white blood cells (WBC) 4800/mm^3, neutrophils 77%, lymphocytes 13%, monocytes 10% and platelet count 139 000/mm^3. Urinalysis showed negative sugar and protein with 10–14 WBC/HPF, 10–12 red blood cells (RBC)/HPF and 1–2 granular casts. Pericardiocentesis revealed 400 ml of purulo-sanguineous fluid that was sent for gram stain and bacterial cultures, acid-fast bacteria stain and tuberculosis culture, fungal smears and culture and for cytology. Biochemical profile of the pericardial fluid showed a white cell count of 48 000/mm^3 (92% segmented) and red cell count of 144 000/mm^3, glucose undetected, protein 45 g/l (Nl<30 g/l), lactic dehydrogenase 659 IU/l (Nl<200 IU/l).

Case 2

The chest x-ray revealed pneumonic consolidation in the left lower lobe with small ipsilateral pleural effusion, and increase in the cardiac silhouette. Echocardiography showed a small pericardial effusion. Laboratory studies showed a haemoglobin of 14.4 g/dl, white cells count 27 500/mm^3 with normal differential count and normal platelet count, erythrocyte sedimentation rate (ESR) 18 mm/h, C reactive protein (CRP) 100 mg/l (Nl up to 2.5 mg/l), creatinine 0.5 mg/dl (Nl 0.6–1.2 mg/dl), aspartate transaminase 18 IU/l, alanine transaminase 21 IU/l, alkaline phosphatase 120 IU/l (Nl 20–385 IU/l) and γ-glutamyl transferase 24 IU/l (Nl 10–50 IU/l). Pericardiocentesis was not repeated. Urinalysis revealed pH 8, specific gravity 1.005, protein negative, glucose negative, WBC 6–8/HPF, RBC rare/HPF, no casts seen.

DIFFERENTIAL DIAGNOSIS

Cardiac tamponade usually follows progressive pericardial effusion that occurs secondary to several infectious and non-infectious aetiologies. Infectious agents include a number of viral, bacterial, fungal and parasitic agents. Non-infectious causes include acute conditions like chest trauma or chronic conditions such as autoimmune inflammatory disorders like acute rheumatic fever, juvenile rheumatoid arthritis and SLE, chronic renal failure, hypothyroidism and neoplastic diseases.

TREATMENT

Our two cases received antibiotics; the first case received in addition a course of antituberculosis treatment that was discontinued after negative tuberculosis culture. Cardiac tamponade was drained in both cases by pericardiocentesis and a pericardial drain was left in place in the first case because of progressive fluid collection. That case also required methyl prednisolone pulse therapy for associated interstitial nephritis and was discharged on oral steroids and antimalarial drugs, whereas our second case was discharged on amoxiclavulinic acid, ibuprofen and antimalarial drugs.

OUTCOME AND FOLLOW-UP

Both patients presented with chest pain and respiratory symptoms and were diagnosed to have cardiac tamponade by echocardiography soon after presentation. In the first case, the physicians were misled by the purulo-sanguineous nature of the pericardial fluid, its predominant segmented WBCs, its low glucose and its elevated protein and LDH. Diagnosis of purulent pericarditis was made and treatment with intravenous cefotaxime and vancomycin was started. Pericardial fluid recollected progressively and antituberculosis treatment was started upon recommendation of the infectious disease team who also recommended a panel of viral antibody titres that were negative. He underwent pericardiotomy and pericardial drain was left in the pericardial space for continuous drainage. On the second hospital week urinalysis showed + 3 proteinuria, and 24 h urine collection a few days later showed a proteinuria of 4 g/24 h. His liver function tests were normal. On the 28th hospital day he developed seizures with normal biochemical profile and cerebrospinal fluid tests. His ECG was abnormal and he was started on valproate to control the seizures. Rheumatological work-up was performed in his fourth hospital week in view of multisystem involvement, and showed an ESR of 40 mm/h, positive antinuclear antibody (ANA) titre, elevated anti-double-stranded DNA (anti-dsDNA) titre 122 IU/ml (Nl <20 IU/l) and negative anti-Sm antibody, anticardiolipin and anti-Ro antibody titres. His C3 and C4 complement levels were normal. Kidney biopsy was conducted for staging of his renal disease in the fifth hospital week, which showed acute tubulo-interstitial nephritis with glomerular mesangial cell proliferation, focal endo-capillary proliferation and evidence of interstitial fibrosis and tubular atrophy (15%). At that time SLE diagnosis was established and the patient was started on pulse methylprednisolone therapy. His condition improved gradually with decrease in the amount of pericardial fluid drainage. He was discharged 2 weeks later in good clinical condition on oral prednisone to be followed up in the nephrology and rheumatology clinics.

The second case had recurrent chest symptoms and there was partial relief of her chest symptoms after her initial pericardiotomy in spite of treatment with oral steroids and oral antibiotics. Her recurrent respiratory distress was attributed to her recent pneumonia and persistent pericarditis. Steroids were tapered progressively during her second hospital admission and she was started on intravenous ceftriaxone and vancomycin as treatment for her pneumonia and on ibuprofen for her pericarditis. She underwent a panel of viral antibody titres that was negative and in view of which a work-up to rule out collagen vascular diseases was carried out and revealed an elevated level of anti-dsDNA with a value of 30.2 IU/ml (Nl <20 IU/ml), and negative ANA titre. Follow-up anti-dsDNA 2 months later showed further increase in anti-dsDNA titre to 49.8 IU/ml. Her tuberculin intradermal skin test was negative.

DISCUSSION

Acute cardiac tamponade is a life-threatening condition and is fatal if not treated promptly. It develops when the pressure inside the pericardial space increases to more than the pressure in the cardiac chambers leading to reduction in diastolic filling, in cardiac output and in systemic blood pressure. Its diagnosis should be suspected clinically in any child presenting with respiratory distress and cardiopulmonary compromise; however, the definite diagnosis is made by echocardiography.[1 2] It usually follows progressive pericardial effusion that may occur secondary to several infectious and non-infectious aetiologies.

Infectious agents include a number of viral, bacterial, fungal and parasitic agents. Viral pericarditis is usually a benign condition that requires symptomatic treatment with non-steroidal anti-inflammatory agents. However, in some cases the effusion is large leading to tamponade which requires pericardiocentesis. Bacterial agents on the other hand, present with purulent pericarditis secondary to direct bacterial invasion, but it may also present with non-purulent effusion secondary to immune-mediated pericarditis which usually occurs during the course of bacterial sepsis. It may also occur in association with chronic non-infectious conditions like chronic renal failure, hypothyroidism and neoplastic diseases or post-trauma. Finally, pericardial effusion also occurs secondary to autoimmune inflammatory disorders like acute rheumatic fever, juvenile rheumatoid arthritis and SLE.[3 4]

Our patients presented with chest pain and respiratory symptoms and both were diagnosed to have cardiac tamponade by echocardiography soon after presentation. In our first case the physicians were misled by the retrieved purulo-sanguineous pericardial fluid, its predominant segmented white blood cells, its low glucose and its elevated protein and LDH. Diagnosis of purulent pericarditis was made and treatment with intravenous antibiotics and pericardial drainage was started. Persistent pericardial effusion and renal involvement with seizures were the clues for SLE diagnosis that was made 5 weeks after the onset of the disease. Our second case had recurrent chest symptoms following surgical pericardiotomy with a pericardial window which were performed to relieve her initial cardio-pulmonary compromise. Both cases had negative pericardial fluid cultures, negative serology profile for the

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Box 1 Systemic lupus erythematosus revised classification criteria (American College of Rheumatology 1997).

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral or nasal ulcers
5. Arthritis:
   A. Non-erosive affecting two or more joints
6. Serositis:
   A. Pleuritis, pericarditis and peritonitis
7. Renal manifestations:
   A. Persistent proteinuria or cellular casts
   B. Consistent renal biopsy
8. Seizure or psychosis
9. Haematologic manifestations :
   A. Haemolytic anaemia
   B. Leucopaenia (<4000 leucocyte/mm^3)
   C. Lymphopaenia (<1500 lymphocyte/mm^3)
   D. Thrombocytopaenia (<100 000/mm^3)
10. Immunological abnormalities:
   A. Positive anti-double-stranded DNA, or anti-Smith antibody test result,
   B. False-positive rapid plasma regain test result, positive lupus anticoagulant test result or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody.
   C. Positive antinuclear antibody result.

most common viral agents and negative intradermal skin tests for tuberculosis. The diagnosis of SLE in both patients was confirmed by positive anti-dsDNA titres in addition to positive ANA titre in our first case. Although anti-dsDNA titre was slightly elevated in our second case, which can be explained by the steroids treatment which she received in the other hospital, that titre continued to increase on follow-up 2 months later.

In 1997, the American College of Rheumatology (ACR) established revised criteria for SLE classification in clinical trials (Box 1). Accordingly, the presence of 4 of the 11criteria establishes the diagnosis of SLE.[4] Our first patient met the ACR criteria for SLE diagnosis in his fifth hospital week; however, our second case met only two of those criteria, which are polyserositis and elevated anti-dsDNA which makes her presentation incomplete or atypical for SLE.

In a study about the diversity of SLE presentation in children, Iqbal *et al*[5] found that one-third of the SLE cases in children present initially with features that are not suggestive of SLE diagnosis. In their retrospective analysis ANA and anti-dsDNA were detected in 97% and 95% of the cases, respectively, at a much higher frequency than any other clinical or biomedical ACR criteria. Another study found that autoantibodies against native DNA (anti-dsDNA, cardiolipin and ANA) are the most relevant antibodies associated with SLE diagnosis.[6] In addition, anti-dsDNA antibodies are closely associated with lupus nephritis which may be present at the onset of the disease or may appear later on in its course. The titres can fluctuate over time and are used to follow-up for the activity of SLE nephritis. On the other hand, various ANA patterns are common among SLE patients, and seroconversion may occur a few years after the onset of the disease.[6] In our first case both ANA and anti-dsDNA titres were significantly elevated 5 weeks after the onset of symptoms and in association with renal involvement and seizures, whereas in the second case only anti-dsDNA titre was slightly elevated by the end of the third week of her illness and without evidence of renal involvement.

Table 1 Cardiac tamponade as first manifestation of systemic lupus erythematosus

No.	Reference	Age (years)	Sex	Type of pericardial fluid	ACR criteria	Treatment
1	Case 1	9	M	Purulo-sanguinous	Pleural effusion, nephritis, seizures and elevated ANA and anti-dsDNA titres	Pericardiocentesis methylprednisolone pulse therapy followed by oral steroids
2	Case 2	11	F	Serosanguinous	Pleural effusion and elevated anti-dsDNA titre	Pericardiocentesis NSAIDS, oral steroids and antimalarial
3	Mohseni *et al*[1]	14	F	Bloody	Diagnosis made on autopsy and positive ANA and elevated anti-dsDNA titre	Pericardiocentesis
4	Ulas Saz *et al*[7]	3	F	Bloody	Polyserositis and positive ANA	Pericardiocentesis and oral steroids.
5	Weich *et al*[8]	15	F	Exudative fluid with positive antideaminase test and negative TB culture	Arthralgia, nephritis, leucopaenia, autoimmune hepatitis and elevated anti-dsDNA titre	Pericardiocentesis, anti-TB drugs and oral steroids
6	Malcic *et al*[9]	11	M	Serosanguinous	Positive ANA and elevated anti-dsDNA titre	Pericardiocentesis, oral steroids, NSAIDs and antimalarial
7	Malcic *et al*[9]	10	F	Serosanguinous	Positive ANA and elevated anti-dsDNA	Pericardiocentesis, oral steroids NSAIDs and antimalarial
8	Aiuto *et al*[10]	14	F	Haemorrhagic fluid	Nephritis, positive ANA and elevated anti-dsDNA	Pericardiocentesis and oral steroids
9	Gulati *et al*[11]	8	F	Serous fluid	Arthralgias, haematological manifestations, positive ANA and elevated dsDNA	Pericardiocentesis anti-TB treatment and oral steroids for 1 year
10	Rudra *et al*[12]	14	F	Bloody	Arthralgias, serositis, haematological manifestation and positive ANA	Pericardiocentesis and oral steroids
11	Lerer[13]	15	F	Straw coloured	Nephritis and positive ANA	Pericardiocentesis and oral steroids

ACR, American College of Rheumatology; ANA, antinuclear antibody; NSAIDS, non-steroidal anti-inflammatory drugs; TB, tuberculosis.

In a 21-year retrospective study, Rosebaum *et al* described 71 cases of adult SLE cases fulfilling ACR criteria. Forty-one of the cases developed pericarditis, nine of which developed cardiac tamponade. All cardiac tamponade cases were women and had low C4 levels.[2] To have a better understanding of cardiac tamponade in children with SLE, we performed a review utilising Medline, Embase and Scopus search engines for the words lupus, pericarditis and cardiac tamponade and we limited our search to children from 0 to 18 years of age. Including our cases, we found 11 children presenting with cardiac tamponade as their first SLE manifestation (table 1).

Cardiac tamponade as a first manifestation of SLE in children has been described mostly in girls (F/M: 9/2). ACR diagnostic criteria for SLE was fulfilled in cases 1, 3, 8, 9 and 10 (Table 1) the remaining six cases had less than four diagnostic criteria. All of the reported cases had elevated anti-dsDNA titre, ANA titre or both. Our second case and case number 4 (table 1) were the only SLE cases presenting with isolated polyserositis. Similar to what has been reported in the adult literature the retrieved pericardial fluid in the reported cases was serosanguinous, bloody or purulent.

Case numbers 1, 5 and 9 (table 1) received treatments for tuberculosis, all of them had negative tuberculosis culture. Our first case received a few weeks course of antituberculosis treatment that was discontinued after the negative tuberculosis culture, case 5[8] had a positive antideaminase test and received a 6 months course of antituberculosis treatment while case 9[11] received 1 year of antituberculosis treatment until SLE diagnosis was made after recurrent episodes of pericarditis and cardiac tamponade. Those three cases reflect the importance of complete laboratory investigation of pericardial fluid to avoid any potential risk of missing tuberculosis, and at the same time the importance of screening with ANA and anti-dsDNA titres for early recognition of SLE. All the reported cases required treatment with immediate pericardiocentesis and were discharged on oral steroid therapy. In case number 3,[1] the diagnosis of SLE was made on autopsy. That case had a fulminant disease after a 4-day history of upper respiratory tract symptoms. Her respiratory distress was treated initially with bronchodilators and was found on her day of death to have cardiac tamponade soon after which she sustained cardiopulmonary arrest and did not respond to pericardiocentesis and resuscitation.

SLE cases without major organ involvement are treated with glucocorticoids, antimalarials and non-steroid anti-inflammatory agents. Yet, in severe and refractory cases, an immunosuppressive agent may be used.[14]

Learning points

- Acute cardiac tamponade is a life-threatening event that requires immediate pericardiocentesis.
- Full diagnostic work-up should be performed to rule out infectious, non-infectious aetiologies and rheumatological diseases particularly systemic lupus erythematosus (SLE).
- Delay in SLE diagnosis in children presenting with cardiac tamponade may increase its morbidity and mortality.

Competing interests None.

Patient consent Obtained.

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