Recurrent exudative pericarditis in the course of adult-onset Still's disease — two case reports

Abstract

Exudative pericarditis is a disease of varied aetiology requiring inclusion of both infectious and non-infectious causes in its differential diagnosis. The possible diagnoses include adult-onset Still's disease (AOSD), a rare systemic inflammatory disease of unknown aetiology. AOSD typically develops in patients between 16 and 35 years of age and is characterised by fever, arthralgia, transient salmon-coloured rash and other abnormalities including pharyngitis, serositis (particularly pleuritis and pericarditis) and laboratory abnormalities, such as elevated white blood cell count and elevated markers of inflammation. We report two cases of AOSD with recurrent exudative pericarditis.

Key words: adult-onset Still's disease, pericarditis, diagnosis, treatment

Introduction

Exudative pericarditis is a heterogenous group of diseases whose common feature is the accumulation of fluid in the pericardial sac, mainly as a result of inflammation of the pericardial membranes initiated by various aetiologic factors.

Infectious causes should always be looked for in cases of pericarditis accompanied by severe systemic symptoms, high fever and progressive deterioration of the patient’s condition [1]. Similarly, a fulminant course of pericarditis can also be seen in cancer (especially in haematopoietic malignancies) [1, 2]. Other causes of acute exudative pericarditis include connective tissue diseases, autoimmunisation-related pericardial complications of myocardial infarction and post-pericardiotomy syndrome [1–3].

We report two cases of recurrent exudative pericarditis in young men diagnosed with adult-onset Still's disease (AOSD).

Case 1

In the middle of May 2007 a 17-year-old patient developed symptoms of infection with malaise, sore throat and cervical lymphadenopathy. Despite the prescribed outpatient empirical antibiotic therapy the symptoms exacerbated in June 2007 with fever of up to 39°C and non-specific chest pain. An echocardiogram revealed pleural effusion with signs of impending tamponade in the form of collapse of the right ventricular and right atrial free walls. A total of 600 ml of serous fluid was evacuated, which was not sent for testing. The
disease were all negative. The presence of rheumatoid factor (RF), antinuclear antibodies (ANA) or antineutrophil cytoplasmic antibodies (ANCA) was not confirmed.

Given the clinical picture and the bronchoscopic findings — despite the negative tuberculin skin test, genetic testing for tuberculosis (both in the pleural fluid and the bronchial discharge) and normal ADA levels in the pleural fluid — a suspicion of tuberculous pericarditis was undertaken and antituberculous treatment was initiated (rifampicin [RMP], isoniazid [INH], ethambutol [EMB]). The patient was also given periodically concomitant non-steroid anti-inflammatory drugs (NSAIDs). A transient maculopapular rash on the skin of the trunk and in the frontal region, which was considered to be a manifestation of an allergic reaction to the antibiotics.

Several days after the initiation of antituberculous treatment the general condition of the patient improved, the temperature normalised, markers of inflammation returned to normal values and the volume of fluid in the pleural cavities and in the pericardial sac decreased. The patient was discharged home and remained under the care of the Clinic of Pericardial Diseases at the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland.

Following three months of antituberculous treatment, in the beginning of October 2007, the disease recurred with a high hectic fever accompanied by chest pain, pain in the left shoulder and pain in the cervical spine. Again, testing revealed elevated markers of inflammation and elevated
white blood cell count peaking just below 20 thousand/mm³ with a neutrophil predominance. Echocardiography revealed a large quantity of fibrin in the pericardial sac. These findings were additionally accompanied by a slight splenomegaly on abdominal ultrasound. The repeat blood and urine cultures and the numerous serological tests did not confirm an infectious aetiology of the symptoms: RF, ANA, ANCA were all still negative. By that time, we had been in receipt of negative results of all the previously ordered cultures for tuberculosis (pleural fluid and bronchial discharge cultures).

Given the entire clinical picture and the previous history, a suspicion of recurrent exudative pericarditis in the course of adult-onset Still’s disease was raised. A decision to discontinue antituberculous treatment and to initiate prednisone at the dose of 0.5 mg/kg/day was made. Serum ferritin was normal (although, unfortunately, this parameter was determined after the treatment had been initiated). The patient’s general condition soon improved, the fever and arthralgia resolved, and the echocardiographic picture greatly improved. The patient continues to be under the care of Clinic of Pericardial Diseases at the Institute of Tuberculosis and Lung Diseases. Glucocorticosteroids were tapered off for 8 months and then completely discontinued. The patient has not experienced a recurrence so far.

Case 2

The second case concerns a 23-year-old male who has also been under the care of the Clinic of Pericardial Diseases at the Institute of Tuberculosis and Lung Diseases. He has experienced episodes of recurrent pericarditis of unknown aetiology several times in the past few years. He has periodically taken NSAIDs. At the age of 16 the patient was diagnosed with hypertension classified as idiopathic following a thorough evaluation at a reference facility.

In May 2009, during one of the recurrent episodes of exudative pericarditis, the patient was hospitalised at the Department of Cardiology, Hypertension and Internal Diseases at Bródno Provincial Hospital in Warsaw, Poland with a several days’ history of sore throat without any signs of purulent tonsillitis. On admission the patient complained of chest pain that became worse on deep respiration. These symptoms were accompanied by a hectic fever exceeding 39°C. Laboratory findings included elevated white blood cell count to 16 thousand/mm³ with a predominance of granulocytes (80%) and elevated CRP to 51 mg/dl. Echocardiography revealed small amounts of fluid in the pericardial sac (up to 4 mm behind the right atrial wall). The multiple blood and urine cultures were all negative. Anti-streptolysin-O reaction was negative. Titres of IgM antibodies to parainfluenza virus, CMV, EBC and Coxsackie viruses were low. No antibodies to HIV were present. Serology for atypical infections caused by Mycoplasma pneumoniae, Legionella pneumophila and Borrelia burgdorferi were all negative. Tuberculin skin test was negative and the chest X-ray revealed no changes in the pulmonary parenchyma. Tests for serum ANA, ANCA and RF were negative. Levels of thyroid hormones were normal.

Despite empirical antibiotic therapy (ceftriaxone, ciprofloxacin, gentamicin) the hectic fever (of up to 40°C) failed to resolve and the white blood cell counts and CRP levels continued to rise (up to 19 thousand/mm³ and up to 270 mg/dl, respectively). A transient salmon-coloured rash on the trunk developed and subsided as the body temperature decreased. Subsequent echocardiograms revealed increasing amounts of fluid in the pericardial sac of up to 16 mm accompanied by severe chest pain. At that stage a chest CT scan was obtained, which revealed fluid in the pericardial sac in similar amounts those as demonstrated by echocardiography, a small amount of fluid in the left pleural cavity and traces of fluid in the right pleural cavity. Several slightly enlarged lymph nodes were also revealed, namely the lymph nodes in the anterior superior mediastinum (up to 9 mm), the right paratracheal lymph nodes (up to 15 mm), the lymph nodes in the aortic window (up to 13 mm). There was also a considerable enlargement of the subcarinal lymph node (up to 25 mm). No pathological changes within the pulmonary parenchyma were revealed.

The patient was consulted by the Clinic of Pericardial Diseases at the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland. Given the clinical picture (fever, rash, signs of polyserositis), the lack of data to confirm an infectious or malignant aetiology of the symptoms and the absence of ANA and RF, a preliminary diagnosis of adult-onset Still’s disease was made. Prednisone at the dose of 0.5 mg/kg/day was proposed. The patient’s condition soon improved, the fever and the skin rash subsided, the markers of inflammation completely normalised and the fluid in the pericardial sac underwent resorption. Serum ferritin levels determined at that time were normal. The patient was discharged home in a good general condition and referred for further care and tre-
atment to the Clinic of Pericardial Diseases at the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland. During the subsequent months of follow-up there were no recurrences when the glucocorticosteroids were being tapered off.

Discussion

Adult-onset Still’s disease (AOSD), whose diagnosis was established in both of the reported cases, mainly affects patients between 16 and 35 years of age and is classified as a rare seronegative form of rheumatoid arthritis first described by Bywaters in 1971 [4]. The prevalence of AOSD in the population is estimated at 0.16–1.47 per 100,000 [5, 6] and fluid in the pericardial sac is detected in 30–40% of the patients, although not all of these cases present with symptomatic pericarditis [7].

The onset of the disease can be sudden and is mainly associated with a triad of symptoms: a high hectic fever accompanied by a transient salmon-coloured rash appearing at fever peaks, and arthralgia. Other manifestations include: sore throat, lymphadenopathy (mainly cervical lymphadenopathy), polyserositis, splenomegaly and liver dysfunction [8, 9].

The most characteristic laboratory findings include a high leukocytosis with a neutrophilia exceeding 80%, considerably elevated ESR and elevated serum CRP, anaemia with thrombocytosis, and elevated liver aminotransferases. The marked elevation in serum transferase, typical of the acute phase of the disease, is also emphasised [10]. According to many authors, about 50% of patients with AOSD have been shown to have serum ferritin levels exceeding 4000 ng/ml (normal range: 40–200 ng/ml) and even markedly higher. As subsequent observations showed, levels of non glycosylated ferritin increased, while those of glycosylated ferritin significantly decreased [11], which was used in the development of the diagnostic criteria by Fautrel et al. [12, 13].

The diagnosis is based on a constellation of specific clinical manifestations, laboratory findings and exclusion of systemic infections, other systemic conditions (absence of ANA in the serum) and malignancies. No pathognomonic diagnostic test for Still’s disease has been developed so far, which is why many authors, based on observations of various patient groups, have made attempts at establishing criteria that would facilitate the diagnosis of this condition [13–17]. Table 1 summarises the most commonly used diagnostic criteria for Still’s disease. The criteria proposed by Yamaguchi et al. are best-known and characterised by a high sensitivity (93.5%) [17].

The constellation of clinical manifestations and laboratory findings in both of the cases reported here satisfied the diagnostic criteria of AOSD proposed by the above authors. In addition, the age of the patients was typical of this disease. Both patients had a high leukocytosis with relative neutrophil counts exceeding 80% and developed a

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature &gt; 39°C &gt; 1 week</td>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Leucocytosis &gt; 10 × 10⁹/l</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Typical rash</td>
<td>Spleenomegaly</td>
</tr>
<tr>
<td>Arthralgia &gt; 2 weeks</td>
<td>Hepatic disorders</td>
</tr>
<tr>
<td>Negative RF and lack of ANA</td>
<td>Maculo-papular rash</td>
</tr>
</tbody>
</table>

Diagnostic criteria:
- 5 criteria, at least 2 major ones
- After exclusion of infection, neoplasm, collagen tissue diseases

**Table 1. Diagnostic criteria of adult-onset Still’s disease according to selected authors [13, 14, 17]**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All criteria listed below</td>
<td>Major criteria</td>
<td>Major criteria</td>
</tr>
<tr>
<td>Temperature &gt; 39°C</td>
<td>Temperature &gt; 39°C</td>
<td>Temperature &gt; 39°C</td>
</tr>
<tr>
<td>Arthritis or arthralgia</td>
<td>Leucocytosis &gt; 10 × 10⁹/l</td>
<td>Neutrophils 80%</td>
</tr>
<tr>
<td>RF &lt; 1:80</td>
<td>Typical rash</td>
<td>Evanescent erythema</td>
</tr>
<tr>
<td>ANA &lt; 1:100</td>
<td>Arthralgia</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>and at least two criteria from listed below</td>
<td>Minor criteria</td>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Leucocytosis &gt; 15 × 10⁹/l</td>
<td>Glycosylated ferritin &lt; 20%</td>
<td></td>
</tr>
<tr>
<td>Typical evanescent rash</td>
<td>Minor criteria</td>
<td>Diagnostic criteria</td>
</tr>
<tr>
<td>Serositis (pleuritis, pericarditis)</td>
<td>Maculo-papular rash</td>
<td>4 major criteria or 3 major + 2 minor ones</td>
</tr>
<tr>
<td>Hepatomegaly/splenomegaly</td>
<td>Leucocytosis &gt; 10 × 10⁹/l</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
transient skin rash (initially considered to be a manifestation of an allergic reaction to treatment in one of the patients), sore throat and lymphadenopathy. The first patient had splenomegaly and a transient elevation of liver aminotransferases. Both cases had polyserositis (pericarditis and pleuritis). While serum ferritin levels in both patients was normal, it should be noted that this parameter was determined after establishing the diagnosis of Still’s disease and initiating treatment, and — as the authors emphasise — serum levels of this marker correlate well with the activity of the disease and normalise during the recuperation period. Glycosylated ferritin was not determined.

The diagnosis of Still’s disease in adults requires ruling out other conditions characterised by similar manifestations including, first of all, potentially dangerous systemic infections [1]. For this reason, the differential diagnosis of recurrent pericarditis in both cases initially included infectious aetiology.

The diagnosis of bacterial exudative pericarditis, which is rarely observed in the general population these days (1–5% of the cases of exudative pericarditis) [1, 18], was suggested by the high fever and the high leukocytosis with neutrophil predominance identified in both patients. Arguments against this diagnosis included the serious nature of the pericardial fluid evacuated due to impending cardiac tamponade and the negative results of the numerous blood cultures, the lack of significant improvement despite broad-spectrum antibiotic therapy and the lack of primary foci of bacterial infection in both patients. Bacterial pericarditis is most commonly associated with infections spreading from neighbouring organs, such as pneumonia, pulmonary abscess and pleural empyema [1, 19]. Risk factors include surgery, chest injury, immunosuppression, diabetes mellitus and alcohol abuse [1].

In developed countries, viral infections are the most common infectious cause of pericarditis [1, 3, 20]. This aetiology was also taken into consideration in the reported cases. Viral infection as the cause of pericarditis was suggested by the high fever and the initial manifestation in the form of flu-like symptoms, although high leukocytosis is not typical of viral pericarditis. Serology testing performed in both patients did not confirm viral aetiology of pericarditis in the course of the most common infections, such as Coxsackie viral infections, parainfluenza, cytomegalovirus and EBV infection. It should, however, be noted that in everyday practice it is impossible to include in the differential diagnosis all the potential viral pathogens that can cause pericarditis.

Another infectious factor that was considered in both cases was Mycobacterium tuberculosis. This microorganism accounts for 4–10% of the cases of exudative pericarditis in developed countries [21] and for up to 70–90% of the cases in Sub-Saharan Africa, especially in combination with HIV infection [2, 21–23]. The diagnosis of tuberculous pericarditis is of particular importance due to the grave prognosis, including the risk of the therapeutically challenging constrictive pericarditis [24]. It should, however, be noted that tuberculous pericarditis is usually characterised by a subacute course with less severe general symptoms, including lower body temperatures, than in the cases reported here [25, 26]. Chest CT scans obtained in patients with tuberculous pericarditis sometimes reveal parenchymal changes indicative of past or active pulmonary tuberculosis with a frequently accompanying pleural effusion [27]. In the second patient, the lack of the typical changes on imaging studies and the negative tuberculin skin test both suggested another aetiology. In the first case, on the other hand, the changes in the bronchial tree in the form of anthracotic scars strongly indicative of past tuberculosis potentially suggested tuberculous pericarditis. The improvement of the patient’s general condition observed after initiation of antituberculous treatment additionally seemed to ex juvantibus confirm the diagnosis. It was not until the next recurrence of the disease during antituberculous treatment that this diagnosis was refuted and prompted the doctors to reevaluate the case and to search for other causes of the patient’s exudative pericarditis.

Another group of pathologies, other than infections, in the course of which exudative pericarditis may develop includes malignancies [1, 28, 29] with metastatic breast cancer, metastatic lung cancer and haemopoietic malignancies (lymphomas and leukaemias) being the most common [1, 28]. Given the young age of the reported patients and the fulminant course of the disease the most likely suspects were lymphoid or haemopoietic malignancies. Malignant nature of the exudate was, however, ruled out in both cases, as no malignant masses were identified in or outside the pericardium and no tumour cells were found in the pericardial fluid in the first of the patients.

Another important group of diseases leading to exudative pericarditis that was included in the differential diagnosis in both patients included connective tissue diseases (with systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and rheumatic fever being considered first) [1, 30, 31]. Acute flares of connective tissue...
diseases may be accompanied by elevated body temperature, myalgia and arthralgia. Pericardial effusion is observed in 20–50% of the cases [1]. Pericarditis is common [30, 31], as was the case with our patients. However, the absence of other systemic manifestations, the low ASO titres and the negative tests for ANA and RF suggested another aetiology of exudative pericarditis.

Based on the patients’ histories other, less common causes of recurrent pericarditis were ruled out, both autoimmune (Dressler’s syndrome, post-pericardiotomy syndrome) and non-immune causes (chest trauma, drug reactions) [32]. Metabolic causes of pericarditis (renal failure and hypothyroidism) were ruled out on the basis of normal laboratory values [33–35]. Eventually, the diagnosis of AOSD was established in both cases.

Although the clinical course of AOSD may be self-limiting or chronic, it is most often one of recurrent nature with periods of acute relapses and frequently spontaneous remissions [14]. The course of the disease observed in both patients, characterised by remissions and relapses was therefore typical of AOSD.

The management of AOSD most often involves NSAIDs or glucocorticosteroids with immunosuppressant drugs or even biologicals being used in more severe cases [36, 37]. Therapeutic effects in the two presented cases were achieved with low-dose prednisone, gradually tapered off. No recurrences were observed during the several months of follow-up.

Conclusions

Exudative pericarditis is a disease of diverse aetiologies. One of the rare causes of this pathology in young adults, especially if fulminant general symptoms are present, may be Still’s disease. However, before this diagnosis is established, other causes that might be responsible for the patient’s symptoms must be ruled out, such as infections. The diagnostic criteria developed by various authors, mainly based on clinical manifestations and laboratory findings, including serum ferritin levels, may be helpful in the differential diagnosis.

References