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Case Report

Adult-Onset Still's Disease with Pericardial Effusion and Bilateral Pleural Effusion

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Abstract

Adult-Onset-Still's-Disease is a rare, chronic systemic autoimmune disease of unknown aetiology. It characteristically presents with a triad of fever, arthritis and evanescent rash in the presence of other systemic manifestations. This report describes the case of a 61-year-old gentleman, known case of schizophrenia and learning disability who while on the rehabilitation ward following a hip fracture deteriorated to the point of becoming bed-bound. He had cyclical fevers for a number of months in the absence of arthralgias or the typical rash. History taking was difficult due to the learning disability and speech problems, which were pre-existent. He had bilateral pleural effusions and pericardial effusion in the presence of grossly elevated C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and ferritin. He was diagnosed as having Adult-Onset-Still's-Disease after excluding infective causes, connective tissue diseases and haematological malignancies, according to the Yamaguchi-criteria. The patient was started on Prednisolone, which resulted in normalisation of the CRP and ESR. The pleural effusions resolved and the patient improved clinically and psychologically. He was able to mobilise again. In this case, we describe the polycyclic systemic variant of the disease. Treatment with steroids lead to resolution of symptoms. Disease-modifying-agents should be considered as maintenance therapy for the condition.

Keywords: Still's disease; Pericarditis; Cyclical fever; Autoimmune; Arthritis; Rash

Introduction

Adult-Onset Still's Disease (AOSD) is a rare, chronic systemic autoimmune disease of unknown aetiology with an estimated prevalence of 1 - 24 cases in a million people and an incidence of 0.14 – 0.40 cases per 100,000 people [1] with a female to male ratio of 2.1 [2]. It has a bimodal distribution commonly affecting people between 15-25 years and those between 36 – 46 years although cases in the elderly have also been reported [3,4].

It classically presents with a triad of fever, arthritis and a rash in the presence of other systemic manifestations. It is a diagnosis of exclusion once infective, autoimmune and malignant causes have been excluded. Multiple systems are usually affected and patients present with a number of medical complaints. Timely diagnosis and appropriate treatment with biologic drugs such as tumour necrosis factor alpha agents or interleukin antagonists and disease modifying anti-rheumatic drugs can lead to a favourable prognosis [5]. We present a case of a patient with severe communication difficulties that restricted history taking and who presented with longstanding fevers yet no other symptoms. He was successfully treated with steroids and steroid sparing agents.

Case Presentation

A 61-year-old Caucasian gentleman who was known to suffer from schizophrenia, learning disability, atrial flutter, congestive heart failure and epilepsy on a rehabilitation ward for a humeral fracture, was noted to have recurrent episodes of high fever which had been present for months. He had been treated with antibiotics on a number of occasions targeting a lower respiratory tract infection despite no symptoms or obvious consolidations on the chest X-Ray at the general hospital prior to being transferred to the rehabilitation hospital. There the patient was treated for suspected infective endocarditis in view of vegetation seen on transthoracic Echocardiogram (ECHO) which then resulted negative on a trans-oesophageal ECHO.

The fevers resolved for two months but then started once again in a cyclical pattern and lasted for over 2 months while the patient was at the rehabilitation hospital. During this time, the patient was noted to deteriorate significantly, becoming bed-bound with occasional tantrums. The patient denied symptoms such as myalgias, sore throat, headache, back pain, dysuria, blurred vision, oral ulceration, eye pain or arthralgias throughout this time, although history taking was limited and difficult due to the learning disability. He had no recent history of travelling and did not have contact with any animals prior to admission for rehabilitation, other than his pet dog. Review of body systems was negative. The patient was on sodium valproate, carbamezapine, phenytoin, digoxin, bumetanide and olanzapine. He was allergic to ceftazidime and gentamycin. He had no significant family history. On physical examination the patient had temperatures of 39 degrees Celcius with a blood

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pressure of 102/74mmHg and tachycardia of 120 beats/minute. The chest, cardiovascular, abdominal and neurological examinations were all normal on assessment. He had a small healing sacral sore. On one occasion, a non-puritic maculopapular rash over the sternum with Koebner effect was noted which resolved over an hour. The patient denied any tenderness of the joints and no lymph nodes were palpable. There was no evidence of synovitis.

The patient had a number of blood cultures which were all negative, including samples for mycology. Multiple urine samples were negative as was a wound swab from the sacral sore. C-Reactive Protein (CRP) was elevated at 400mg/L (Normal 0-5mg/L), erythrocyte sedimentation rate (ESR) at 120 mm/hr (normal 12-16mm/hr) with ferritin levels of 380ug/L (normal 22-328). The patient had a slight leukocytosis with a white cell count of 12.05 (normal up to 11.4 x109/l) with neutrophilic predominance of more than 80% (10.52 (normal range up to 7.2 x109/l)), a normocytic anaemia and thrombocytosis. Liver function tests were minimally deranged with a gamma-glutamyltransferase of 254 U/l (normal 8-61 U/l), alkaline phosphatase of 86 U/l (normal 40 -129 U/l) and alanine transaminase of 15 U/l (within normal limits). Hepatitis screen, HIV and autoimmune screen were all negative. Antinuclear antibodies, double stranded-DNA, extractable nuclear antigen and rheumatoid factor antibodies were negative pointing against a diagnosis of Rheumatoid arthritis or systemic lupus erythomatosum. Galactomannan antigen test was also negative. Anti-epileptic drug levels were all within range. Serum protein electrophoresis and serum albumin were within normal limits.

The patient received intravenous co-amoxiclav for 10 days followed by 10 days of piperacillin - tazobactam and 4 days of meropenem and teicoplanin yet he remained febrile and with raised inflammatory markers. A computed topography of the thorax, abdomen and pelvis showed small bibasal consolidations associated with pleural effusions and a large pericardial effusion yet no signs of lymphadenopathy or alternate pathology such as tuberculosis as shown in Figure 1. The case was discussed with respiratory physicians in view of the bilateral pleural effusions. Pleural fluid analysis was not performed as the risks of thoracocentesis were believed to outweigh the benefits given that the patient was poorly compliant and in frail condition at the time.

A trans-oesophageal echocardiogram was performed which excluded infective endocarditis. Echocardiogram showed normal left ventricular dimensions with normal systolic function, in the presence of mild mitral regurgitation. A moderate pericardial effusion was also noted. A pericardial tap was not deemed necessary at the time as the effusion was not causing any symptoms or haemodynamic compromise. The patient was started on colchicine to no effect and was thus discontinued after a number of weeks. This was started since Familial Mediterranean Fever was one of the differential diagnoses being considered and lack of response to colchicine refuted this diagnosis. Haematological conditions including leukaemia and lymphomas were excluded on the basis of absence of laboratory and physical findings. The infectious disease specialists were consulted and Coxiella burnetti antigen was taken and was found to be negative. No further tests to exclude tuberculosis were deemed necessary by the infectious disease specialists at the time given the patient's history and lack of suggestive features on imaging, absence of haemoptysis, sputum production and shortness of breath which was not in keeping with mycobacterial infection.

A tentative diagnosis of polycyclic systemic variant of adult-onset Still's disease was made according to Yamaguchi criteria. The patient was given 7 doses of intravenous hydrocortisone (100mg three times a day regimen) followed by 30mg prednisolone daily. The patient improved clinically and remained afebrile while on steroids. CRP decreased to 29 and the ESR to 80. Chest X-ray taken after 7 days of steroids showed resolution of the pleural effusions and consolidations. The patient improved clinically and was able to mobilise. Psychological improvement was also noted. Since the patient required high doses of steroids to keep the inflammatory markers under control (60mg/ day), Methotrexate was then introduced as a steroid-sparing agent at a dose of 7.5mg/ week. Normalisation of inflammatory markers was noted by this time. The patient continued improving and over time managed to regain dependence in activities of daily living.

Discussion

Adult Onset Still's disease (AOSD) is an uncommon autoimmune condition. The classical clinical presentation is with a rash, arthralgia and high fevers. The fever is usually high spiking and occurs most often in the evening with temperatures returning to normal in the mornings. During the febrile episodes, patients might get pharyngitis, something which our patient never complained of. Febrile episodes are commonly accompanied by a salmon-coloured maculopapular skin rash that usually occurs on the trunk or the extremities [6]. In up to a third of cases, the rash might exhibit Koebner's phenomenon if it occurs on sites of cutaneous injury secondary to trauma or pressure [7] such as was noted in our patient. Skin biopsy of the rash shows a nonspecific perivascular inflammation with immunofluorescence showing C3 protein deposition [3]. Arthralgia is also correlated with the fever with the majority of patients experiencing migrating arthralgia early on in the disease which eventually settles with time.

Multiple systems might be involved giving rise to lymphadenopathy, hepatomegaly, splenomegaly and rarely might also give rise to cardiopulmonary complications. Pericarditis can occur in up to 3-37% of patients with AOSD [8] and up to 20% of those with pericarditis may develop a pericardial effusion [8] which might lead to cardiac tamponade and untimely death if not detected early on. In our case, the patient developed a pericardial effusion without having had evidence of pericarditis clinically or on electrocardiography. In up to 3% of cases patients might have myocarditis which could potentially lead to heart failure, atrioventricular block, and arrhythmias [4,9].

Various diagnostic criteria have been proposed to aid diagnosing AOSD, however, the Yamaguchi criteria are the most sensitive. According to these diagnostic criteria, the patient must have 5 of the proposed features, of which 2 must be major features. The major criteria include persistent high fevers (>39C), arthralgias or arthritis for two weeks, the presence of a non-pruritic rash and leukocytosis with granulocytosis. The minor criteria include sore throat, lymphadenopathy, hepatosplenomegaly, abnormal LFTs and negative ANA and RF [7]. In our case, the patient met three of the major criteria with fever, leukocytosis and the presence of rash, noted on one occasion. This occurred in the presence of negative ANA/ RF and abnormal liver function tests. Raised CRP and ESR together with elevated ferritin and thrombocytosis are not part of the Yamaguchi criteria yet are still common findings in patients with AOSD and can hence help direct the clinician to the diagnosis [7,10].

AOSD should be considered when other causes for pyrexia of unknown origin have been excluded. These include infec-

tions such as tuberculosis, infectious endocarditis, Human Immunodeficiency Virus (HIV) or infectious diseases such as Coxiella burnetti. Haematological conditions such as leukaemias, lymphomas as well as connective tissue diseases such as systemic lupus erythematosum or mixed connective tissue disease should also be excluded. Familial Mediterranean fever should be considered in the differential diagnosis, especially in patients presenting in the Mediterranean region. The fever in FMF however, does not exhibit a quotidian pattern, lasts for 1 to 3 days and typically responds to colchicine, albeit not always. The lack of past history of fevers and a familial distribution of fevers pointed towards an alternative diagnosis in this case. Another syndrome which presents with periodic fevers that needed to be excluded was TNF Receptor Associated Periodic Syndrome (TRAPS) which closely resembles the presentation of AOSD. In TRAPS, patients have fever that lasts 3 to 4 weeks on average with associated ocular manifestations [5], which were absent in this case. TRAPS, like FMF, usually presents in childhood and has a familial distribution.

AOSD may present in 3 main ways. The monocyclic / self-limiting pattern occurs when the patient experiences a single episode of systemic disease that can last for an undefined period of time prior to going into remission. The polycyclic systemic variant of the disease is what we describe in this case, where there are two or more episodes of systemic manifestations that are separated by a period where the patient is symptom-free lasting for about 2 months. This variant can present with systemic disease in the absence of arthralgias or myalgias [1]. In the chronic articular pattern, patients experience severe articular manifestations that can lead to joint destruction. The joints most commonly affected are the knees, ankles, wrists and elbows although disease can also involve the distal interphalangeal joints [7].

Treatment involves the use or corticosteroids regardless of presentation, with prednisolone being the most favoured. Disease modifying anti-rheumatic drugs such as azathioprine, methotrexate, cyclophosphamide and cyclosporine have also been used as maintenance therapy for AOSD [11,12]. Patients who have cardiac tamponade should receive therapeutic pericardial drainage. Mild pericardial effusions can however be managed using non-steroidal anti-inflammatory agents [12].

Conclusion

Adult-onset Still's disease remains a diagnostic dilemma for many clinicians as it characteristically presents with non-specific symptoms that can be attributed to a number of other pathologies. In patients who are unable to communicate effectively, this might present even more of a challenge. The disease might go undiagnosed for a number of months over which time complications such as pleural effusions and pericardial effusions might occur, increasing morbidity and mortality from the disease. Timely diagnosis will lead to a more favourable outcome and will help to improve the quality of life.

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