The cause of fever and pulmonary infiltrate: a difficult etiological diagnosis

Bahjat Barakat,[1] Raffaele Pezzilli[2]

[1]Emergency Department, [2]Department of Digestive System, Sant'Orsola-Malpighi Hospital, University of Bologna, Italy

Abstract

Adult-onset Still's disease is a rare condition that typically presents itself with intermittent fever, arthralgia and salmon colored rash. The involvement of the in lung is less common and very rare. Diagnosis is relatively difficult because of the presence of non-specific symptoms and the lack of serological markers specific to the disease. We report the case of a patient having a pulmonary infiltrate/infiltration compatible with pneumonia, cutaneous/skin rash and persistence of fever with multiple admissions to the Emergency Room due to the failure of treatment with antibiotics. After an appropriate work-up, a diagnosis of adult-onset Still's disease was made.

Introduction

Adult-onset Still's disease is a rare condition that typically presents itself with intermittent fever, arthralgia and salmon colored rash.[1] Diagnosis is difficult due to the presence of non specific symptoms, inflammatory processes and the lack of serological markers specific to the disease.[2] The presence of a pulmonary infiltrate, compatible with pneumonia, a skin rash and persistence of fever represent one of the reasons for admission to the Emergency Department, especially after previous empirical treatments with antibiotics have failed to resolve the pathological picture.[3] Thus, we believe that it is important to report a case of lung involvement in a patient with adult-onset Still's disease misdiagnosed as lung infection; our diagnosis is based on Yamaguchi's criteria.[2]

Case Report

Due to the appearance of high temperature (39.4°C) and sore throat, a 59 year- old male was examined by his general practitioner, who prescribed antibiotics and paracetamol for six days without obtaining any clinical benefit. For this reason the man was admitted to hospital. The patient was febrile (39.8°C), his arterial blood pressure was 130/75 mmHg, his heart rate 78 beats per minute, O_2 saturation 98%. The physical examination was unremarkable except for a harsh vesicular murmur and the chest x-ray showed an accentuation of interstitial plot at the right lower lobe (Figure 1). His pharynx exploration excluded the presence of infection. Laboratory examination revealed leukocitosis (WCC 17.49 10^9L, with a prevalence of neutrophils 89.4%), C-reactive protein (CRP) was abnormally high (28.6 mg/dL; normal reference limit <0.50); hepatic and renal functions, coagulation parameters and serum electrolytes were all normal. He was treated with intravenous amoxycilline and paracetamol for six days and was then discharged from the hospital. Two days later there was no improvement in the symptoms and a salmon colored rash and pain in the right knee had appeared. For this reason he was again referred to our Emergency Department. On physical examination, the patient's temperature was 39.7°C, heart rate was 120 beats per minutes, arterial blood pressure was 160/90 mmHg, respiratory frequency was 18 breaths/minute, harsh vesicular murmur persisted but the rest was unremarkable. Laboratory examination revealed elevated leukocytes (WCC 22.22 10^9L, with a prevalence of neutrophils 80.0%), CRP 23.1 mg/dL (upper normal limit 0.8 mg/dL); hepatic and renal functions, coagulation parameters and serum electrolytes were normal. The patient underwent CT of the chest which showed lower right lobe infiltration (Figure 2). A non-itchy patch of about 5cm in diameter salmon-pink in color on the right leg was present (Figure 3) and an ultrasonographic examination of the right leg showed no soft tissue alterations (Figure 4). The patient was initially treated with intravenous levofloxacin, piperacillin and tazobactan. At the same time, a urine analysis for *Legionella pneumophila*, pneumococcus, anti Chlamydia antibodies, mycoplasma, a serologic test for both A and B influenza viruses, parainfluenza virus, Epstein- Barr virus, Borrelia Burgdoferi, Rickettsia Conori, Coxiella Burneti, cytomegalovirus and Klebsiella pneumonia were all negative. In addition, a Quantiferon test, HIV serology and multiple urine and blood cultures were negative as were also a throat swab for Streptococcus pyogenes and a nasal swab for Staphylococcus. Due to the persistence of symptoms, the appearance of both diffuse rash and arthralgia, the persistence of increased levels of CRP and protein electrophoresis showing hypogammaglobulinemia (464 mg/dL), the patient underwent flexible bronchoscopy with lavage and bronchial brush the results of which were negative for malignant cells, mycobacteria, and repiratory virus; in addition echocardiography showed no alterations such as endocarditis vegetations. Ketoprophene for arthralgia was initiated after which the patient's symptoms rapidly improved. Serum rhemautologic tests (rheumatoid factor, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-citrullinated protein antibodies) were all negative. Still's disease was suspected, antibiotics were interrupted and a serum ferritin assay was carried out which was very high (3219 ng/mL; reference values 11-306 ng/mL). According to Yamaguchi's criteria (Table 1), a diagnosis of adult-onset Still's disease was made. Therapy with steroids (methylprednisolone at a dosage of 50 mg for 10 days and progressively tapered) was performed with subsequent rapid disappearance of the symptoms, normalization of inflammatory mediators and pulmonary involvement. The patient was then discharged with a diagnosis of adult-onset Still's disease with lung involvement at presentation.

Discussion

Adult-onset Still's disease is a rare disease of unknown origin which presents itself with high spiking fever usually associated with diffuse artharlgia, initially localized skin rash which then becomes diffuse

Correspondence: Raffaele Pezzilli, Department of Digestive Diseases and Internal Medicine, Sant'Orsola-Malpighi Hospital, Bologna, Italy.
Tel: +39.0516364148 - Fax: +39.0516364148.
E-mail: raffaele.pezzilli@aosp.bo.it

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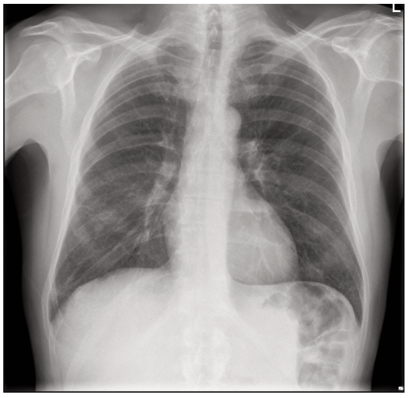

Figure 1. Chest x-ray showing an accentuation of interstitial plot at the right lower lobe.

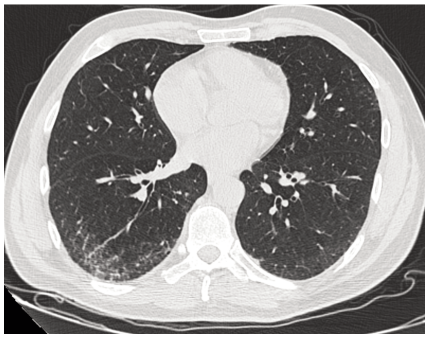

Figure 2. Computed tomography scan of the chest showing lower right lobe infiltration.

and rarely involves the lung with a radiological picture compatible with pneumonia.[2] There are no markers for this disease and according to Yamaguchi's criteria, the diagnosis should be established after excluding infections, malignancies and autoimmune disease.[4] Yamaguchi's criteria are based on clinical and laboratory parameters; in our case all four major criteria were present; in addition, two of the minor criteria such as sore throat and negative tests for antinuclear antibodies and rheumatoid factor were also present.

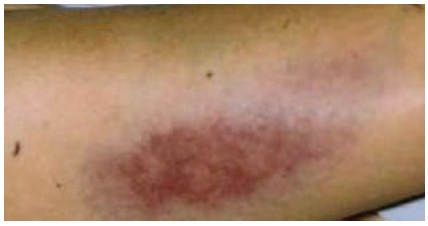

Figure 3. Non-itchy patch of about 5 cm in diameter, salmon-pink in color localized in the right leg.

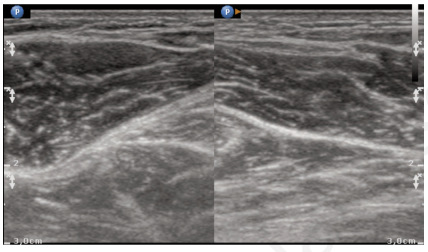

Figure 4. Ultrasonographic examination of the right leg showed no alterations to soft tissue.

An unusual finding of adult-onset Still's disease present in our case and which delayed a definitive diagnosis was the presence of pulmonary infiltrate compatible with pneumonia.[5]

We might conclude that pulmonary involvement in the form of interstitial pneumonia can be the initial presentation of adult-onset Still's disease that responds quickly to steroid treatment. Thus, after exclusion of common infective, malignant and inflammatory etiologies, in the case of non resolving pneumonia, a suspicion of adult-onset Still's disease should be made. Finally, even if Yamaguchi's criteria are not present, some authors report that high levels of serum ferritin are useful for indicating disease activity and abnormally high serum ferritin concentrations are present in over 90% of cases.[6] This protein assay is present in Fautrel's more recent criteria for diagnosing adult onset Still's disease (Table 2).[7] However, there are no comparative studies assessing Yamaguchi's and Fautrel's criteria, even if Yamaguchi's criteria have 93% sensitivity and Fautrel's criteria have about 81% sensitivity.[8]

Table 1. Yamaguchi's criteria for the diagnosis of adult-onset Still's disease.[4]

Criteria Major	Minor	Exclusion
Fever >39°C, lasting 1 week or longer	Sore throat	Infections
Arthralgia or arthritis, lasting 2 weeks or longer	Recent development of significant lymphadenopathy	Malignancies (mainly malignant lymphoma)
Typical rash	Hepatomegaly or splenomegaly	Other rheumatic disease (mainly systemic vasculitides)
Leukocytosis >10,000/mm^3 with >80% polymorphonuclear cells	Abnormal liver function tests	Negative tests for antinuclear antibody and rheumatoid factor (IgM)

Five or more criteria are required, of which two or more must be major.

Table 2. Fautrel's criteria for the diagnosis of adult-onset Still's disease.[7]

Criteria Major	Minor
Spiking fever ≥39°C	Maculopapular rash
Arthralgia	Leukocytosis ≥10,000/mm^3
Transient erythema	
Pharyngitis	
Polymorphonuclear cells ≥80%	
Glycosylated ferritin ≤20%	

Four or more major criteria are required, or 3 major and 2 minor criteria.

Conclusions

The answer to the question of whether adult-onset Still's disease with pulmonary involvement is of interest for physicians working in the Emergency Department is *yes it is*, because it is not rare for patients to be admitted to hospital for non response to antibiotics or persistent fever in times of global pandemic flu and in several cases different admissions by a patient from one clinic to another may make it difficult to establish diagnosis of this disease.

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