Unusual presentation of more common disease/injury

Adult-onset Still's disease revealed by perimyocarditis and a concomitant reactivation of an EBV infection

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Summary

We describe a 17-year-old patient presenting perimyocarditis as the initial manifestation of the adult-onset Still's disease. Corticotherapy was rapidly successful but induced major acute hepatitis in relation with Epstein-Barr virus reactivation. After 1 year, even if the global outcome is favourable, a slightly lowered ejection fraction still persists. Former case reports and differential diagnosis with reactive haemophagocytic syndrome would be discussed.

BACKGROUND

Juvenile arthritis (Still's disease) was not considered as an adult disease until 1971, when Bywaters¹ distinguished an adult variant of the same (adult-onset Still's disease, AOSD). Its incidence is estimated at 0.16/100 000 in France,² with a median age of 25 years at the onset.³ It may be present as a severe polysystemic disease⁴⁻⁸ with a very heterogeneous clinical presentation. As there is no specific marker,⁶⁻⁹ the diagnosis is based on the Yamaguchi criteria,¹⁰ reviewed by Fautrel *et al*,¹¹ who added hyperferritinaemia as a major criteria (table 1).

AOSD-like juvenile arthritis may occur as a single episode or recurrent disease or else undergo a chronic evolution similar to rheumatoid arthritis.¹²⁻¹³ Severe widespread polyarthritis is common in AOSD and represents the main prognostic factor of a chronic outcome.¹⁴ Heart involvement and particularly myocarditis may be considered as one of the causes of death due to AOSD.⁶

CASE PRESENTATION

A 17-year-old Caucasian male patient was admitted with a 3-day history of fever, headache, arthralgia, myalgia, mild diarrhoea, sore throat and chest pain with a slight respiratory discomfort.

His medical history had been marked by an influenza-like syndrome 3 months before. He had travelled to Mexico 6 months back and there had been no animal contact. Physical examination revealed fever (39 °C), tachycardia (102/min), blood pressure at 120/85 mm Hg, arterial oxygen saturation at 98% and some small cervical adenopathies. Heart, chest and abdominal examinations were normal as well as those of joints, chest wall and dorsal spines.

INVESTIGATIONS

Biological assessment revealed haemoglobin, 14.5 g/dl; white cell count, $13.2 \times 10^3/\text{mm}^3$ (polynuclear neutrophils, 84%; lymphocytes, 8.5% with presence of activated

lymphocytes); platelets, $206 \times 10^3/\text{mm}^3$ erythrocyte sedimentation rate 50 mm/h, C reactive protein 239 mg/l. Creatinine, natremia, kalemia, calcemia, alanine and aspartate aminotransferase, proteinemia were normal, lactate dehydrogenase 1.4 times the normal upper value.

Chest x-rays showed a mild bilateral interstitial syndrome and pericardial friction revealed perimyocarditis with a low ejection fraction of only 40% on echocardiography. A complementary examination by an MRI confirmed a low ejection fraction and showed slight pericardial effusion but no specific signs of myocarditis. Troponine level increased to 0.67 ng/ml and N-terminal B-type natriuretic peptide (pro-BNP) to 2500 pg/ml.

TREATMENT

The patient was transferred to the cardiological intensive care station, where a treatment associating diuretics, angiotensin inhibitors and aspirine were administered. Three days after admission to the hospital, roseola-like eruptions occurred on the trunk and lower limbs (figure 1). Biological screening of autoimmune diseases as well as haemocultures, viral and bacterial serologies (hepatitis A, B, C, HIV, CMV, *Parvovirus B 19*, *Borrelia*, *Bartonella*, *Brucella*, *Yersinia*, *Herpes Virus*) proved to be negative or revealed an acquired immunity, with the exception of Epstein-Barr virus (EBV) serology, positive for anti-VCA IgG, anti-VCA IgM and EBNA.

At this time, an extremely high level of ferritinaemia at 62 750 µg/l with a 14% glycolysated fraction, slightly increased triglycerides at 2.1 g/l, and persisting fever were reminiscent of reactive haemophagocytic syndrome (RHS). Treatment with high-dose intravenous immunoglobulins was started, but was discontinued after the first dose of 1 g/kg owing to the poor tolerance.

OUTCOME AND FOLLOW-UP

However, skin eruption, absence of cytopaenia or medullary signs of RHS, as well as persistence of arthro-myalgia

Figure 1 Skin eruptions of adult-onset Still's disease (AOSD).

were rather suggestive of adult Still's disease. Thus, a treatment with prednisone at 1 mg/kg made it possible to obtain apyrexia and disappearance of arthralgia and chest pain within a few days. The ejection fraction of the left ventricle was normalised at 65% after 1 week of treatment.

Three days later, a systematic biological screening revealed major cytolysis (aspartate aminotransferase 40 times and alanine aminotransferase 57 times the normal upper value), cholestasis (γ glutamyl transferase 8.5 times, alkaline phosphatase 2.5 times) and moderate hyperbilirubinaemia. The EBV viral load was strongly positive at 28 000 copies/ml. A body CT scan and abdominal echography performed at this stage showed moderate hepatomegaly (19 cm) and splenomegaly, but no hepatobiliary lesion.

We came to the conclusion of EBV reactivation with hepatitis facilitated by corticotherapy. Prednisone doses were rapidly lowered to 0.5 mg/kg within 1 month, to 0.2 mg/kg a month later, then by 2.5 mg steps every 2 months for an overall treatment duration of 11 months.

Figure 2 Isolated nodule on heart MRI.

A second cardiac MRI examination revealed a nodular hypersignal on the lateral left ventricle wall, corresponding to a lesion of myocarditis (figure 2). Evolution was favourable, patient remaining in clinical and biological remission 1 year after the onset of his disease except for a persistent low EBV viral load at 950 copies/ml; nevertheless, recent echocardiography and cardiac MRI revealed a slightly widened left ventricle without any signs of inflammation and a slightly lowered ejection fraction at 52%.

DISCUSSION

Cardiac involvement occurs clinically in 10% of juvenile Still's disease, echocardiographic signs even in more than 30%.¹⁵ Pericarditis is widely predominant, myocarditis is found in only 1% of patients and endocarditis is anecdotic.¹⁶ Perimyocarditis may lead to chronic congestive heart failure.⁹

In AOSD, pericarditis is also known as one of the most frequent systemic manifestations,^{12 17–19} tamponade being potentially life-threatening,¹⁷ but only 14 cases of myocardial involvement are well documented in the literature in current languages (table 1); three other case reports have been published.^{20–22}

Cardiac MRI has been described in only one other case (besides our patient), revealing septal and apical subendocardial oedema without necrosis.¹⁸ In four patients, typical lesions of acute interstitial myocarditis were proven by biopsy and one other after autopsy. Nevertheless, many

Table 1 AOSD criteria

Yamaguchi criterion for adult Still's disease (5 including 2 major items required)		Fautrel criterion for adult Still's disease (4 major or 3 major and 2 minor items required)	
Major criterion	Minor criterion	Major criterion	Minor criterion
Temperature of $>39^{\circ}\text{C}$ for >1 week	Sore throat	Spiking fever $>39^{\circ}$	Maculopapulous erythema
WBC $>10\,000/\mu\text{l}$ with $>80\%$ of PNNs	Lymph node enlargement	Arthralgias	WBC $>10\,000/\mu\text{l}$
Typical skin rash	Splenomegaly	Transitory skin rash	
Arthralgias >2 weeks	Liver dysfunction (high AST/ALT)	Sore throat	
	Negative ANA, RF	PNN $>80\%$	
		Glycylated ferritinaemia $<20\%$	

AOSD, adult-onset Still's disease; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanin aminotransferase; RF, rheumatoid factor; ANA, antinuclear antibodies.

Table 2 Published cases of AOSD with myocarditis

	Age/ sex	Prior Still's disease/age	Pericardial effusion	EF (%)	Ferritinaemia	Biopsy/ MRI	Concomitant infection	Treatment	Evolution	Ref.
1	21/m	No	Yes	39	ND	Biopsy	No	C po	Remission	4
2	16/m	No	ND	ND	ND	No	mumps	NSAID	Remission	15
3	57/m	No	Yes	40	ND	Biopsy	No	C po	part. rem.	16
4	26/f	No	No	ND	ND	No	No	C po	Remission	9
5	24/m	No	Yes	ND	3765/15	No	No	C bolus/po	Remission	23
6	34/m	No	No	51	5994/17	No	No	C bolus/po	Remission	24
7	31/m	Yes/24 and 30	No	ND	ND	Biopsy	No	C po	Remission after relapse at 12 m	7
8	33/m	No	Yes	40	16000	MRI	No	C bolus/po	Remission	18
9	20/m	Yes/17	Yes	ND	5500	No	No	C po, IgIV	Remission*	8
10	33/m	No	Yes	ND	6000/10	No	No	C bolus/po, IgIV	Remission	25
11	39/m	No	N.D.	40	13000	Autopsy	No	C bolus/po	Death	6
12	35/f	No	Yes	35	14097	No	No	C bolus/?	Remission	26
13	34/m	Yes/child	No	ND	ND	Biopsy	No	C bolus/po	Remission†	27
14	16/m	Yes/child	No	ND	ND	No	No	C bolus/?	Remission†	27
15	17/m	No	No	40	63000/14	MRI	EBV	C po	Remission	Case report

AOSD, adult-onset Still's disease; ND, not defined. EF, left ventricular ejection fraction; ferritinaemia, $\mu\text{g/l}/\%$ of glycolysated fraction; treatment: C, corticosteroids; NSAID, non-steroidal anti-inflammatory drugs; IgIV, high-dose intravenous immunoglobulines.

*Under treatment with prednisone, methotrexate and etanercept.

†long-term treatment for arthritis but no cardiac relapse.

cases of undiagnosed AOSD myocarditis may evolve chronically to progressive heart failure.⁶ (table 2).

Cardiac outcome seemed to be favourable in most of the 15 patients (but follow-up with control of heart function was not available in the majority of cases). One patient died from refractory congestive heart failure in spite of a high-dose prednisone therapy, one got partial remission and a slight impairment of left ventricular function occurred in our patient.

Treatment of Still's disease is based on non-steroidal anti-inflammatory drugs (NSAIDs), but glucocorticoids are required in 90% of the AOSD patients.¹⁹ An additional immunosuppressive treatment is necessary in refractory AOSD or in tapering prednisone doses. Methotrexate is particularly employed in polyarthritis patterns; on the whole, overall response to antirheumatic drugs (including hydroxychloroquine, ciclosporine A, penicillamine, gold or azathioprine) is about 40% in refractory cases across studies.^{3 28} Other immunosuppressive or immunomodulating treatments such as high-dose intravenous gamma-globulin,²⁹ tumour necrosis factor (TNF)-blocking agents^{30 31} or anakinra (anti-IL-1)³² proved to be efficacious in refractory disease (resumed by Efthymiou *et al* 2006²⁸). Cardiac involvement initially needs high-dose corticotherapy, but intravenous bolus of corticoids or initial association with immunosuppressive drugs is not absolutely necessary. Only one of the reviewed patients was treated by NSAIDs,¹⁵ two others presented myocarditis under immunosuppressive treatment^{7 8} even if other causes were discussed.⁷

In our case, corticosteroid therapy was complicated by concomitant iatrogenic EBV reactivation with initial highly cytolytic hepatitis, even if cytolysis was probably of multifactorial origin (EBV, Still's disease, high-dose paracetamol). Low viral load still persists after 1 year, without any lymphoproliferation signs.

Only one other case of AOSD with concomitant viral infection (mumps) has been described;¹⁵ a high level of mycoplasma antibodies was found in another one.

DIFFERENTIAL DIAGNOSIS

Clinical presentation associated with highly elevated ferritinaemia and a very low glycolysated fraction was highly suggestive of AOSD in our patient. However, RHS, in relation with EBV infection, could have been compatible.

RHS may also be present in Still's disease as described in a few series.^{33–35} This association should be considered in the absence of hyperleucocytosis, or in case of thrombocytopaenia, lymphopaenia, hypertriglyceridaemia or coagulopathy.³⁴ Serum ferritine levels seem to be much higher in AOSD-related RHS than in AOSD alone.³⁵

Analysis of cytokines in AOSD shows particularly high levels of IL-18,^{36 37} secreted by activated macrophages. Mononuclear cells' activation by different pathological agents could be the first step in the pathogenesis of AOSD.^{28 37} Hypothesis of a nosological continuum between RHS and AOSD has been evoked.³⁸

In our case, the absence of cytopaenia or medullary signs of RHS and only slight hypertriglyceridaemia made the diagnosis of RHS without Still's disease unlikely, but hypothesis of an association in the presence of highly significant EBV viremia cannot be excluded formally.

Learning points

- ▶ Myopericarditis is a rare but certainly underdiagnosed complication of adult-onset Still's disease (AOSD) with potentially defavourable outcome, so careful cardiac supervision is mandatory in all AOSD cases.
- ▶ Diagnosis of AOSD remains difficult; highly elevated total and very low glycosylated ferritinaemia is a nearly distinctive marker.
- ▶ Reactive haemophagocytic syndrome (RHS) can be distinguished of AOSD by medullary haemophagocytosis and cytopaenia but may be associated to AOSD. Viral reactivation with high-dose corticotherapy has to be considered and needs a careful follow-up.

Competing interests None.

Patient consent Obtained.

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