Adult-onset Still’s disease in a patient over 80 years old successfully treated with low-dose methotrexate therapy

MIWA KURASAWA1, KAZUHIKO KOTANI2, GOTARO KURASAWA1, KOBUYUKI SHIDA3, SHIGEKI YAMADA4, TOSHIHIKO TAGO5

1 Department of Internal Medicine, Nishiagatsuma Welfare Hospital, Naganohara, Japan
2 Division of Health Administration and Promotion, Faculty of Medicine, Tottori University, Yonago, Japan
3 Department of Orthopaedics, Nishiagatsuma Welfare Hospital, Naganohara, Japan
4 Department of Pathology, Omiya Medical Centre, Jichi Medical University, Omiya, Japan
5 Department of Surgery, Nishiagatsuma Welfare Hospital, Naganohara, Japan

Address correspondence to: M. Kurasawa. Tel: (+81)-279-83-7111 Fax: (+81)-279-83-8032. Email: miwa-kr@zero.ad.jp

Abstract

We report on an 83-year-old Japanese woman with adult-onset Still’s disease (AOSD), with marked hypercytokinemia (serum levels of ferritin (Fer) and interleukin (IL)-18 were markedly high). On seeing older patients with fever of unknown origin (FUO), particularly Asians, AOSD should be considered. Reduced doses of oral prednisolone following intravenous methylprednisolone (mPSL) therapy caused a flare-up of AOSD and led to Pneumocystis carinii (jeroveci) pneumonia. Low-dose methotrexate (MTX) therapy was administered as a steroid-sparing agent with good response. Our case suggests that in very elderly people, as in younger patients, MTX is useful for controlling AOSD with marked hypercytokinemia, and avoiding corticosteroid-induced adverse effects.

Keywords: adult-onset Still’s disease, super-old patients, Japanese, hypercytokinemia, pulse methylprednisolone, low-dose methotrexate, elderly

Introduction

Adult-onset Still’s disease (AOSD) is rare and has a bimodal age distribution in all ethnic groups with peaks at 15–25 and 36–46 years of age [1]. Onset in older people is very rare, and it has been described only occasionally in Japan, Europe and the USA [2–9]. Patients of Asian origin tend to be older for reasons that are not clear, and more than half of the reported cases older than 70 are Japanese [2, 3, 6–8]. Even in Japan, however, very few cases of initial onset of AOSD in old patients have been reported [6]. We describe an AOSD patient aged over 80 years with marked hypercytokinemia (HCK) and was administered methylprednisolone (mPSL) pulse therapy with methotrexate (MTX), who we believe is the oldest reported case treated with MTX.

Case presentation

An 83-year-old Japanese female complaining of appetite loss, sore throat, quotidian fever (max 39°C, peak in the
late afternoon), and polyarthralgia for several days, was admitted. She had an evanescent maculopapular rash on her right lower leg, which disappeared as the fever abated. The white blood cell (WBC) count was elevated to 14,300/µl (max 43,800). The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 22 mm/h (max 48) and 10.5 mg/dl (max 18.7), respectively. The liver function test scores were elevated: AST = 672 IU/l, ALT = 368 IU/l, and LDH = 911 mg/dl. The serum ferritin (Fer) and interleukin (IL)-18 were 10,340 ng/ml and 125,000 pg/ml, respectively. Serum was negative for anti-nuclear antibodies/rheumatoid factor, and no lymphadenopathy or hepatosplenomegaly was seen. Images of the Joints were normal. Blood, sputum and urine cultures grew no bacteria. There was no serological evidence of infection with either cytomegalovirus or Epstein-Barr virus. Therefore, we diagnosed AOSD according to the Yamaguchi criteria [10]. Following therapy with acetaminophen and loxoprofen, prednisolone (PSL) therapy (20 mg/day) was started, with a poor response. High-dose oral PSL (60 mg/day) plus intravenous mPSL (500 mg/day) pulse therapy improved her clinical symptoms and laboratory findings slightly, particularly, the values of the liver function tests. Nine weeks after admission, when the PSL was tapered to 30 mg/day, *Pneumocystis carinii* pneumonia developed, for which trimethoprim-sulfamethoxazole therapy was effective. Her AOSD flared-up with an increased ferritin level (1,397 ng/ml) during the slow tapering of PSL. We used oral MTX in a single weekly dose of 6 mg. (In Japan, MTX is available as a 2-mg tablet, and 6 mg weekly can be given as an initial dosage.) During the MTX therapy, no other additional drugs were used. After 2 months, all signs and symptoms had improved and the blood inflammation indexes, such as the WBC, ESR, CRP, Fer and IL-18 had normalised.

**Discussion**

AOSD in very old people is difficult to diagnose unless suspected, because it is generally considered a disorder of youth. However, when older patients with a fever of unknown origin (FUO) have a rash, AOSD should be suspected, because a rash, as seen in our case, is a valuable diagnostic sign [10]. Because the rash in AOSD often appears over the trunk or extremities, the area where the rash appeared in our case was somewhat atypical, but we still suspected AOSD on the basis of the features of the rash, such as its disappearance with the reduction in fever [10]. This is the first case of a patient aged over 80 years with AOSD receiving MTX therapy. Five additional cases in patients over 80 have been reported: two were treated with oral PSL plus mPSL therapy [6, 7] and one each with oral PSL only [3], non-steroidal anti-inflammatory drugs (NSAIDs) [8] and intravenous immunoglobulin plus NSAIDs [9]. Although MTX is not usually used for the super-old, we chose it for three reasons. First, MTX is more popular with Japanese physicians than other immunomodulating drugs (e.g. cyclophosphamide, azathioprine, cyclosporine, intravenous immunoglobulin, anakinra, or infliximab). In particular, MTX therapy is established in rheumatoid disorders, which have a pathophysiology similar to that of AOSD. Second, although low-dose MTX can lead to opportunistic infections, as can PSL, we wanted the corticosteroid-sparing effects of MTX [11], because our case recurred at a reduced PSL and had the adverse effects of long-term PSL, such as immunosuppression (i.e. *P. carinii* pneumonia). Third, although Fer is an evident marker of the disease activity [12], as in our case, it was the marked HCK evident as high IL-18 levels that attracted our attention rather than hyperferritinaemia. It has been reported that the mean serum IL-18 in AOSD is 1243.4 pg/dl [13], but our patient had very high levels. We postulate that the remarkable HCK reflected the disease activity better than routine inflammatory markers, such as ESR and CRP. The good outcome with MTX in our case suggests that marked HCK is a sign of PSL resistance, which should lead physicians to switch to MTX. In the future, the role of HCK in AOSD disease activity and therapy should be studied.

In summary, we report a super-old AOSD patient with HCK treated with MTX. AOSD should not be overlooked in older patients with FUO, particularly Asians. In older people, MTX might be useful for controlling HCK and for avoiding relapse and corticosteroid-induced adverse effects.

**Key points**

- AOSD could appear even in patients over 80 years with FUO.
- Our AOSD patient (83 years) was successfully treated not with corticosteroid but with methotrexate (MTX). This case is perhaps the oldest patient treated with MTX, and the resistance of corticosteroid may be due to marked hypercytokinaemia (HCK).
- In patients over 80 years with AOSD and HCK, MTX might be useful for controlling the disease status and avoiding relapse of the disease and corticosteroid-induced adverse effects.

**Conflicts of interest**

None

**References**

M. Kurasawa et al.


Received 30 April 2006; accepted in revised form 1 September 2006