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Case Report

A Case of Refractory Adult-Onset Still's Disease with High Serum Interleukin-18 Levels Treated with Monitoring of Serum Levels of Cyclosporine

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Abstract We report the case of a 31-year-old woman who developed adult-onset Still's disease (AOSD) with a high level of serum interleukin (IL)-18. Although treated with high dose steroids, she suffered repeated remissions and her condition deteriorated. After we administered oral cyclosporine A (CsA), 200 mg/d, monitoring C2 and trough levels, her symptoms improved significantly. We decreased the dose of methylprednisolone slowly without noting a relapse. The use of CsA accompanied by C2 and trough level monitoring should be considered for refractory AOSD patients with high levels of serum IL-18.

Key Words : Adult onset Still's disease, Interleukin-18, Cyclosporine

Introduction

Adult-onset Still's disease (AOSD) is an idiopathic systemic inflammatory disease characterized by remittent fever, arthralgia, liver dysfunction and lymphadenomegaly. AOSD is usually treated with non-steroidal anti-inflammatory drugs, steroids and other immunosuppressive agents. However, the disease often becomes resistant to treatment. Recent studies suggest that serum interleukin (IL)-18 levels reflect the disease activity of AOSD[1)2)], and, indeed, AOSD with high serum IL-18 levels is often steroid-resistant[3)].

Cyclosporine A (CsA), a calcineurin inhibitor, is used in combination with monitoring peak and trough serum concentrations to prevent organ rejection in kidney transplant patients. Although CsA is one option for steroid-resistant AOSD, adequate plasma concentrations of CsA for AOSD have not been defined.

We report herein a case of AOSD with high serum IL-18 levels, which was successfully treated by monitoring 2-hour blood concentrations of CsA (C2) and its trough levels.

Case report

A 31-year-old woman was referred to our hospital with pyrexia, conjunctival injection and cervical lymphadenomegaly in early July 2009. Her body temperature had increased to 38-39℃ in the 2 weeks before her admission. A physical examination on admission repoted a 41-kg adult female, 154 cm tall, who presented, with erythema of the face, trunk, and arms (Fig. 1) ; cervical lympadenomegaly ; throat redness ; and tonsillar hypertrophy. Hepatosplenomegaly, arthralgia, and swollen fingers were not apparent. The results of the laboratory tests were as follows : white blood cell count of 9,400/μl (neutrophils 84.4 %, lymphocytes 8.9%, monocytes 2.9%, eosinophils 0.8%, basophils 0.4%) ; hemoglobin, 12.8 g/dl ; platelet, 128,000/μl ; C-reactive protein (CRP), 5.44

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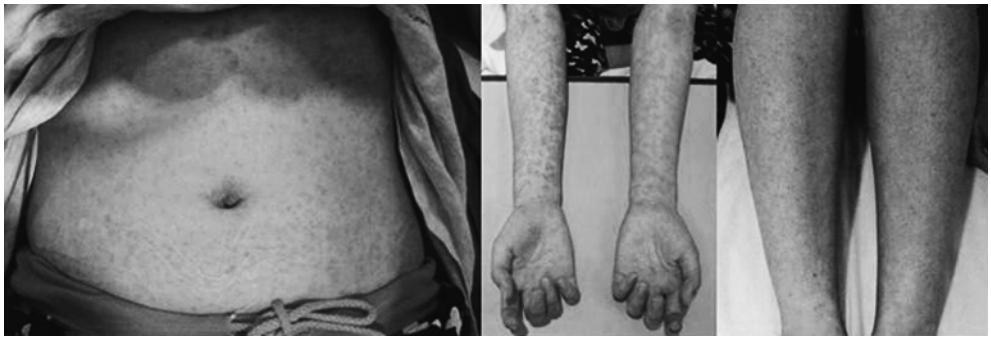


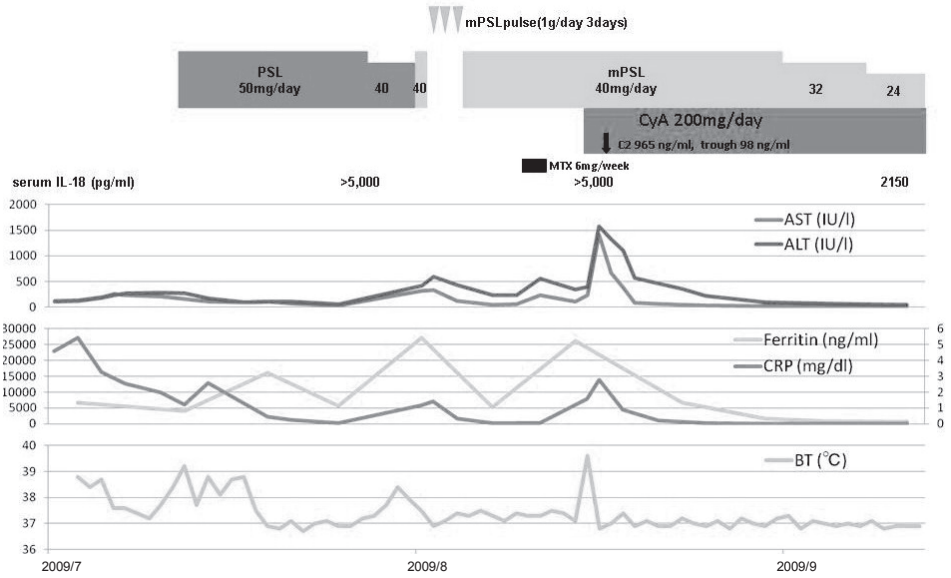
Fig. 1 Erythema of the face, trunk and arms on admission

mg/dl ; erythrocyte sedimentation rate, 44 mm/h ; prothrombin time, 13.2 seconds ; international normalized ratio, 1.03 ; activated partial thromboplastin time, 30.2 s ; CH50, 72 U/ml ; C3, 143 mg/dl ; C4, 42 mg/dl ; blood urea nitrogen, 7 mg/dl ; serum creatinine, 0.5 mg/dl ; Na 139 mEq/L ; K, 3.6 mEq/l ; Cl, 104 mEq/l ; lactate dehydrogenase, 722 IU/l ; aspartate aminotransferase, 137 IU/l ; alanine aminotranseferase, 127 IU/l ; ferritin, 6,770.3 ng/ml ; soluble interleukin-2 receptor (sIL-2R), 2,380 U/ml ; serum IL-6, 4.2 pg/ml ; IL-12, < 7.8 pg/ml ; IL-18, > 5,000 pg/ml ; and interferon-γ, 0.4 IU/ml. Antinuclear antibody (ANA) was × 40 (speckled pattern), while other autoantibodies (anti-Sm, anti-ribonucleoprotein, anti-cardiolipin IgG, anti-double-stranded DNA, and anti-SS-A) were not detected. Tests for both protein and occult blood in urine were negative. Microscopic examination of urine sediment revealed no red or white blood cells, nor were cellular casts found in urine. Blood, urine and throat lavage tests for bacterial or viral infection were negative.

We established the diagnosis of AOSD based on the presence of pyrexia, skin rash, sore throat, lymphadenomegaly, leukocytosis, liver dysfunction, and the lack of rheumatoid factor and negative antinuclear antibody. The clinical findings met three of the four major criteria and four of the four minor criteria for AOSD classification proposed by Yamaguchi et al.[4] Following administration of 50 mg/d of prednisolone (PSL), the patient's symptoms immediately improved ; however, after the dosage of PSL was decreased to 40 mg/d, the pyrexia and systemic diffuse erythema reappeared. Suspecting an allergic reaction to the PSL, we substituted methylprednisolone (mPSL) 32 mg/d for the PSL 40mg/d, but the patient's symptoms did not improve. We started steroid pulse therapy and increased the dose of mPSL to 40 mg/d. We administered methotrexate (MTX) 6 mg/w, but immediately suspended because of severe liver dysfunction. We then administered oral CsA 200 mg/d. CsA before breakfast and supper and observed a C2 of 965 ng/ml with a trough level of 98 ng/ml. Both pyrexia and skin eruption diminished significantly, and the CRP, transaminase and ferritin levels normalized. We gradually decreased the dose of mPSL without observing any relapse. Before the patient's discharge from our hospital, her serum IL-18 level had decreased to 2,150 pg/ml (Fig. 2).

Discussion

AOSD is a systemic inflammatory disease that presents with remittent fever, skin eruption, and arthralgia. The diagnostic criteria for AOSD proposed by Yamaguchi in 1992[4] are widely accepted. IL-18 is a macrophage-derived cytokine that induces interferon-γ production by Th1 lymphocytes and is thought to contribute to the development of AOSD[3]. Recent studies that have reported high levels of serum IL-18 in patients with AOSD suggest that IL-18, like serum ferritin, reflects the disease activity of AOSD[1)2)]. Chen et al. reported that serum



Abbreviations:PSL, prednisolone; mPSL,methylprednisolone; CsA, cyclosporineA; MTX, methotrexate; IL-18, interleukin-18; CRP, C-reactive protein.

Fig. 2 Clinical course.

IL-18 levels were associated with liver dysfunction, IL-6 levels were associated with skin symptoms, IL-8 levels were associated with arthritis in AOSD[5]. Kawaguchi et al. reported significantly higher serum IL-18 levels in steroid-resistant AOSD (similar to the present case), than in steroid-sensitive AOSD[3]. These reports suggest that steroid monotherapy may be insufficient and that additional immunosuppressive therapy should be considered in the treatment of AOSD with high serum IL-18 levels. While various immunosuppressive drugs, including CsA, tacrolimus[6], infliximab[7], etanercept[8], adalimumab[9], tocilizumab[10], and, γ-globulin[11], have been reported for the treatment of steroid-resistant AOSD, agreement is not unanimous. Mitamura et al. reported seven cases of AOSD resistant to steroids, cyclophosphamide, MTX, and leflunomide that were improved with CsA[12]. In this case, the sIL-2R levels were elevated, reflecting high T-cell activity. CsA which suppresses the activity of T cells, seemed to be the optimal treatment in this case. As far as we investigated, the dosages of CsA were controlled according to trough levels. Levy et al. reported that, the inhibitory effect of CsA on calcineurin activity is determined by the area under the concentration-time curve (AUC) 0-4 h. However, AUC 0-4 h values correlate well with C2 levels, not trough levels[13]. Mahalati et al. reported that an AUC 0-4 hr of 4,400 ng・h/ml reduced the incidence of acute rejection in kidney transplant recipients[14], suggesting that an adequate AUC 0-4 h value is necessary for inhibition of calcineurin activity. However, because the calculation of AUC 0-4 h requires repetitive blood sampling and dedicated software, C2 itself could be more conveniently monitored when adjusting dosages of CsA.

Since CsA is lipid -soluble, its oral absorption is affected by meal intake. When administered more than 15 min before a meal, the peak concentration of CsA is consistent with C1-C2[13]. According to the above-mentioned report by Mahalati et al.[14], a C2 value between 1,400 and 1,700ng/ml is required to maintain an AUC 0-4 h of 4,400 ng・h/ml. Pape et al. recommended maintaining C2 between 750 and 1,000ng/ml to prevent acute rejection in pediatric kidney transplant recipients[15]. To the best of our knowledge, no guidelines for the optimal concentration of CsA in the treatment of AOSD has been

determined. In our case, when we administered 200 mg/day of CsA, the resulting C2 of 965 ng/ml, brought about clinical improvements. Although relatively low, this C2 level of CsA, as well as the trough level, may be an effective concentration to achieve when treating AOSD.

Here, we report a case of refractory AOSD treated with CsA. Although monitoring the peak level of CsA has not been common in the treatment of AOSD, our experience that controlling the dose of CsA based on monitored levels of C2 and trough will benefit patients with steroid-resistant AOSD.

Conflict of interests The authors declare that they have no conflict of interests.

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（和文抄録）

血清 IL-18 高値を呈し，シクロスポリンが奏効した成人発症スチル病の 1 例

国立病院機構九州医療センター 膠原病内科・臨床研究センター

寶來吉朗，幸山敦子，宮村知也，平田明恵，中村真隆，
安藤　仁，高濱宗一郎，南　留美，山本政弘，末松栄一

症例は 31 歳，女性．2009 年 7 月より発熱，発疹，咽頭痛，頚部リンパ節腫脹が出現し当科紹介入院．入院時検査成績 CRP 5.44mg/dl，WBC 9,400/μl，AST 137IU/l，ALT 127IU/l，LDH 722IU/l，血清 IL-18 > 5,000/ml を認め成人発症スチル病（AOSD）と診断．プレドニゾロン（PSL）50mg/日投与を開始し症状は一旦軽快したが，PSL 減量に伴い再燃を認めた．難治性の AOSD と診断しステロイドパルス療法を施行後，シクロスポリン（CsA）200mg/日の投与を開始（血中濃度投与後２時間値 965ng/ml，トラフ値 98ng/ml）．以後症状は軽快し，コントロール良好である．血清 IL-18 高値を呈し，治療抵抗性の AOSD には C2 をモニタリングしたうえで，十分量の CsA を投与することが有効な治療法と考えられた．