A case of immune reconstitution syndrome: adult-onset Still's disease in a patient with HIV infection

Sir, A 22-yr-old homosexual man presented systemically unwell in March 2006, was diagnosed with HIV infection [baseline CD4 32 cells/mm³ (7%), viral load 589 708 copies] and commenced on highly active anti-retroviral therapy (HAART) with abacavir, lamivudine and ritonavir/lopinavir. Twelve days later, the patient presented with new symptoms of sore throat, fever, rigors, myalgia, asymmetrical large joint arthralgia and morning stiffness. He reported diarrhoea since starting anti-retroviral therapy, but denied ocular or genital symptoms. He had no relevant past medical, family or travel history. Examination revealed effusions of the middle ankle and right elbow and a pale pink maculo-papular rash on his chest. During his admission, the patient experienced a dramatic improvement in his left ankle and right elbow and a pale pink maculo-papular rash on his chest. Examination revealed effusions of the middle ankle and right elbow and a pale pink maculo-papular rash on his chest.

On the basis of three major (fever 39°C lasting >1 week; arthralgia lasting >2 weeks; typical rash) and two minor symptoms of AOSD, the patient was diagnosed with adult-onset Still's disease (AOSD) [1]. The therapeutic challenges posed by concurrent HIV infection and autoimmune/inflammatory disease suggests a favourable outcome following treatment, with the exception of a patient with SLE whose symptoms worsened during HAART [2]. In the context of HIV infection, the management of this patient with AOSD has proved complex. Glucocorticoids are potentiated by ritonavir and therefore conservative daily doses (prednisolone 20 mg) were used initially. The patient experienced a dramatic response within 1 week. However, the course of both the AOSD and HIV were unrelenting and refractory with episodic recurrence of rash, fevers, sweats, synovitis and elevated liver transaminases. While the liver dysregulation responded to increased prednisolone (35 mg), the CD4⁺ T-cell count deteriorated to 89 cells/mm³ and therefore tenofovir was added. Symptoms relapsed each time that tenofovir was added. Symptoms relapsed each time that tenofovir was added. Symptoms relapsed each time that tenofovir was added.

In our patient, the clinical presentation of acute AOSD within 12 days of commencing HAART is highly suggestive of IRIS [1]. There have been three previous case reports of AOSD in HIV but these occurred in the pre-HAART era and therefore could not implicate IRIS [7, 8]. In the context of HIV infection, the management of this patient with AOSD has proved complex. Glucocorticoids are potentiated by ritonavir and therefore conservative daily doses (prednisolone 20 mg) were used initially. The patient experienced a dramatic response within 1 week. However, the course of both the AOSD and HIV were unrelenting and refractory with episodic recurrence of rash, fevers, sweats, synovitis and elevated liver transaminases. While the liver dysregulation responded to increased prednisolone (35 mg), the CD4⁺ T-cell count deteriorated to 89 cells/mm³ and therefore tenofovir was added. Symptoms relapsed each time that tenofovir was added. Symptoms relapsed each time that tenofovir was added. Symptoms relapsed each time that tenofovir was added.

In the context of HIV infection, the management of this patient with AOSD has proved complex. Glucocorticoids are potentiated by ritonavir and therefore conservative daily doses (prednisolone 20 mg) were used initially. The patient experienced a dramatic response within 1 week. However, the course of both the AOSD and HIV were unrelenting and refractory with episodic recurrence of rash, fevers, sweats, synovitis and elevated liver transaminases. While the liver dysregulation responded to increased prednisolone (35 mg), the CD4⁺ T-cell count deteriorated to 89 cells/mm³ and therefore tenofovir was added. Symptoms relapsed each time that tenofovir was added. Symptoms relapsed each time that tenofovir was added. Symptoms relapsed each time that tenofovir was added.

In the context of IRIS, a recent review including nine cases of HIV-associated AOSD demonstrated that AOSD may be a reactive phenomenon triggered by infectious agents and have found elevated levels of IgM and IgG antibodies against viruses (mumps, parainfluenza, rubella, Coxsackie B4, echovirus 7, adenovirus, influenza A, herpes viruses, hepatitis B, parvovirus B19, EBV, CMV) and bacteria (Yersinia enterocolitica, Mycoplasma pneumoniae, Chlamydia pneumoniae, Brucella abortus, Borrelia burgdorferi) [2]. Infection alone is unlikely to be sufficient to trigger AOSD and it is likely that a predisposing genetic background is needed, but to date no specific genetic polymorphisms have been demonstrated.

Evidence is accumulating to suggest that AOSD is a T-cell-driven disease [3]. Immune dysregulation, including abnormalities of T-cell number and function is a major feature of HIV infection. Additionally, the commencement of HAART leads to a release of naïve T-cells (CD4⁺ and CD8⁺), increases the CD4⁺ to CD8⁺ ratio and cytokine levels and precipitates imbalance of the TH1/TH2 profile [4, 5]. In 10–40% of the patients [6], these changes can precipitate the onset or provoke the deterioration of infectious, malignant and autoimmune conditions, the phenomenon of ‘immune reconstitution inflammatory syndrome’ (IRIS). IRIS is thought to result from rapid, marked restoration of pathogen-specific immune responses (to infectious or non-infectious antigens) usually within the first 8 weeks of HAART [4]. Risk factors include low CD4 count, presence of latent infection and marked virological and immunological response to HAART [6]. Although IRIS was first described in relation to infections, such as tuberculosis or CMV, there is increasing recognition of autoimmune conditions including SLE, RA and ReA [6].

In our patient, the clinical presentation of acute AOSD within 12 days of commencing HAART is highly suggestive of IRIS [1]. There have been three previous case reports of AOSD in HIV but these occurred in the pre-HAART era and therefore could not implicate IRIS [7, 8]. In the context of HIV infection, the management of this patient with AOSD has proved complex. Glucocorticoids are potentiated by ritonavir and therefore conservative daily doses (prednisolone 20 mg) were used initially. The patient experienced a dramatic response within 1 week. However, the course of both the AOSD and HIV were unrelenting and refractory with episodic recurrence of rash, fevers, sweats, synovitis and elevated liver transaminases. While the liver dysregulation responded to increased prednisolone (35 mg), the CD4⁺ T-cell count deteriorated to 89 cells/mm³ and therefore tenofovir was added. Symptoms relapsed each time that prednisolone was reduced <15 mg daily.

The therapeutic challenges posed by concurrent HIV infection and autoimmune/inflammatory disease have been described [6, 9]. In the context of IRIS, a recent review including nine cases of HIV-associated AOSD demonstrated that AOSD may be a reactive phenomenon triggered by infectious agents and have found elevated levels of IgM and IgG antibodies against viruses (mumps, parainfluenza, rubella, Coxsackie B4, echovirus 7, adenovirus, influenza A, herpes viruses, hepatitis B, parvovirus B19, EBV, CMV) and bacteria (Yersinia enterocolitica, Mycoplasma pneumoniae, Chlamydia pneumoniae, Brucella abortus, Borrelia burgdorferi) [2]. Infection alone is unlikely to be sufficient to trigger AOSD and it is likely that a predisposing genetic background is needed, but to date no specific genetic polymorphisms have been demonstrated.

Evidence is accumulating to suggest that AOSD is a T-cell-driven disease [3]. Immune dysregulation, including abnormalities of T-cell number and function is a major feature of HIV infection. Additionally, the commencement of HAART leads to a release of naïve T-cells (CD4⁺ and CD8⁺), increases the CD4⁺ to CD8⁺ ratio and cytokine levels and precipitates imbalance of the TH1/TH2 profile [4, 5]. In 10–40% of the patients [6], these changes can precipitate the onset or provoke the deterioration of infectious, malignant and autoimmune conditions, the phenomenon of ‘immune reconstitution inflammatory syndrome’ (IRIS). IRIS is thought to result from rapid, marked restoration of pathogen-specific immune responses (to infectious or non-infectious antigens) usually within the first 8 weeks of HAART [4]. Risk factors include low CD4 count, presence of latent infection and marked virological and immunological response to HAART [6]. Although IRIS was first described in relation to infections, such as tuberculosis or CMV, there is increasing recognition of autoimmune conditions including SLE, RA and ReA [6].

In our patient, the clinical presentation of acute AOSD within 12 days of commencing HAART is highly suggestive of IRIS [1]. There have been three previous case reports of AOSD in HIV but these occurred in the pre-HAART era and therefore could not implicate IRIS [7, 8].

In the context of HIV infection, the management of this patient with AOSD has proved complex. Glucocorticoids are potentiated by ritonavir and therefore conservative daily doses (prednisolone 20 mg) were used initially. The patient experienced a dramatic response within 1 week. However, the course of both the AOSD and HIV were unrelenting and refractory with episodic recurrence of rash, fevers, sweats, synovitis and elevated liver transaminases. While the liver dysregulation responded to increased prednisolone (35 mg), the CD4⁺ T-cell count deteriorated to 89 cells/mm³ and therefore tenofovir was added. Symptoms relapsed each time that prednisolone was reduced <15 mg daily.

The therapeutic challenges posed by concurrent HIV infection and autoimmune/inflammatory disease have been described [6, 9].
T cells and cytokines. The occurrence of this syndrome as part of IRIS may offer new insight into its pathogenesis.

<table>
<thead>
<tr>
<th>Rheumatology key message</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Autoimmune inflammatory rheumatic syndromes can occur in HIV infection.</td>
</tr>
</tbody>
</table>

Disclosure statement: The authors have declared no conflicts of interest.

EDWINA LAWSON¹, KATHARINE BOND¹, DUNCAN CHURCHILL¹, KAREN WALKER-BONE²

¹Department of Genitourinary Medicine, Royal Sussex County Hospital, Brighton and ²Brighton and Sussex Medical School, Euan Keat Education Centre, Princess Royal Hospital, Haywards Heath, UK

Accepted 22 December 2008

Correspondence to: Karen Walker-Bone, Euan Keat Education Centre, Princess Royal Hospital, Lewes Road, Haywards Heath, West Sussex RH16 4EX, UK. E-mail: k.walker-bone@bsms.ac.uk


Rheumatology 2009;38:447–448
doi:10.1093/rheumatology/kep015
Advance Access publication 7 February 2009

A case of rituximab-induced interstitial pneumonitis observed in systemic lupus erythematosus

Sir, Rituximab (anti-CD20 mAb) depletes B lymphocytes and is widely used for the treatment of B-cell malignant lymphoma [1, 2]. The incidence of life-threatening side effects is very low, but there are some case reports of rituximab-induced interstitial pneumonitis (IP) in patients with haematological disorders [3]. We report the first case of rituximab-induced IP observed in SLE.

A 24-year-old woman was diagnosed as SLE based on the presence of malar rash, oral ulcers, leucopenia (1500/μl), thrombocytopenia (6.9 × 10³/μl), hypocomplementaemia (C3, 61 mg/dl; C4, 9 mg/dl), positive test for ANA (1:640), anti-Sm antibody (158 U/ml) and anti-dsDNA antibody (10 U/ml) and CNS involvement. MRI of the brain showed areas with high intensity by T₂-weighted image and low intensity by T₁-weighted image in the white matter bilaterally. She was treated with 1000 mg rituximab with pre-treatment of 125 mg methylprednisolone, because of lack of response to intravenous methylprednisolone pulse and 1 mg/kg/day oral prednisolone. Before rituximab administration, chest radiograph and CT was normal (Fig. 1A–C). After finishing infusion of rituximab, she developed dry cough, but breath sounds were normal with an oxygen saturation of 99% and normal chest X-ray. Four days after the administration, chest X-ray revealed interstitial opacities in the lung base bilaterally (Fig. 1D). Chest CT revealed diffuse ground-glass attenuation in non-specific areas of both lungs without any structural distortion (Fig. 1E and F). Congestive heart failure was excluded by normal study of ultrasound cardiology and normal level of serum brain natriuretic peptide. The case was diagnosed as rituximab-induced IP based on the bronchoalveolar lavages fluid examination (increased total cell count, 1.26 × 10⁸; increased lymphocytes, 68.9%; non-detection of cosinophils and neutrophils; low CD4/CD8 ratio, 0.19; negative PCR test for Pneumocystis jiroveci DNA and Mycobacterium DNA; and negative culture test for bacteria, fungus and Mycobacterium), negative examination for serum anti-Chlamydia antibody, CMV-antigenaemia and Legionella urinary antigen and ground-glass appearance on chest CT. She had no allergic history, and was not taking any medication. Treatment with 1 mg/kg/day of prednisolone was continued. Seven days after the diagnosis, dry cough subsided and chest X-ray and CT findings disappeared (Fig. 1G–I). Lupus-related symptoms, such as malar rash and oral ulcers disappeared, the numbers of leucocyte and platelet were increased to normal ranges, and titres of serum anti-Sm antibody and anti-dsDNA antibody were decreased. The dosage of prednisolone was tapered to 10 mg/day without any exacerbation.

Since several autoantibodies are presented in lupus patients and deposition of immune complex is shown in the affected organs, autoimmune B cells might be thought to have an important role for the pathogenesis of SLE. Rituximab has been used for the treatment of several autoimmune diseases, such as SLE [4, 5] and RA [6, 7]. So far, 16 cases with rituximab-induced IP have been reported and reviewed by Wagner et al [3]. In all cases, rituximab was used for haematological disorders, including 12 patients with malignant lymphoma, 3 with chronic lymphocytic leukaemia and 1 with immune thrombocytopenic purpura. Analysis of the available information showed that the patients were 65.5 ± 3.1 years old (mean ± s.e.m.), the number of cycles of rituximab infusion was 4.1 ± 0.7, all patients were treated with corticosteroids and 6 out of 16 patients died during the follow-up. Our patient was relatively young (27 years) and developed IP following the first dose of rituximab. Based on the PubMed database searches, this is the first report of an SLE patient who developed IP following initiation of rituximab therapy. Recently, rituximab-induced organizing pneumonia was reported in an RA patient [8]. Although it is rare, care should be taken with pulmonary complications when rituximab is prescribed not only for malignant lymphoma, but also for the other diseases, including SLE and RA.

For this patient, infusion of rituximab was performed according to the protocol of ongoing Phase II/III trial of SLE [9] and was well managed. Regarding the dosage of rituximab, twice infusion at 2 weeks interval of each 1000 mg rituximab was used in clinical trials of SLE [4, 5], ongoing trial [9] and also RA therapy [7] approved by the Food and Drug Administration in USA. In contrast, 4 weekly infusions of 375 mg/m² rituximab have been widely used in malignant lymphoma [2]. Therefore, an individual single dosage of rituximab is higher in SLE and RA, although total dosage is higher in lymphoma. This patient was treated with a single infusion of 1000 mg rituximab. Consequently, both individual and total dosage of rituximab may affect the development of IP. The etiology of rituximab-induced IP is unknown. It was reported that rituximab infusion was rapidly followed by activation of complement, B-lymphocyte cytolysis and lung damage.