Cytomegalovirus Reactivation in Drug Induced Hypersensitivity Syndrome

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Abstract

Drug induced hypersensitivity syndrome has been reported to a variety of drugs. Reactivation of herpes viruses is associated with relapse of symptoms even as late as five weeks after stopping the inciting drug. We report here a case of drug hypersensitivity with CMV reactivation which was treated successfully.

A 42 year old lady presented with a generalised erythematous rash over her entire body and oral mucosal involvement since 20 days, watery diarrhoea for 5 days and a day of fever prior to presentation. Her past history was remarkable for asymmetrical joint pains involving large and small joints with no swelling or stiffness for 18 months which had worsened over the last 2 months. She was diagnosed to have rheumatoid arthritis elsewhere and had been initiated on leflunomide 10 mg twice daily, salazopyrine 1 gm twice daily and prednisolone 10 mg twice daily 22 days prior to the onset of the rash. On examination she was afebrile, pulse was 88 beats per minute and regular, blood pressure was 110/80 mmHg. She had cheilitis with glossitis and a diffuse erythematous papular rash with desquamation over the face, trunk and extremities associated with purpuric macules over legs and feet. There were no tender, swollen joints and range of movement across all joints was normal. Schober’s and Faber’s test were negative. Rest of the systemic examination was normal. Laboratory investigations at admission are given below (Table 1).

A diagnosis of drug induced hypersensitivity syndrome secondary to leflunomide or salazopyrine was made. The drugs were withdrawn and she was treated with dexamethasone 6 mg thrice daily along with activated charcoal 50 mg every 6 hours to enhance elimination of the drug and fluticasone ointment for local application on body. During therapy with activated charcoal she developed loose stools and after excluding infective causes, activated charcoal was replaced with cholestyramine 8 gm thrice daily. Her skin lesions and serum transaminases improved so dexamethasone was tapered to 4 mg twice a day and she was discharged. However, within a week she again developed a recurrence of the erythroderma, a ‘scratch dermatitis’ and transaminases that had normalised showed a rise (AST 45; ALT 138). She was readmitted for management. Since ‘scratch dermatitis’ in a drug hypersensitivity syndrome could suggest viral reactivation with cytomegalovirus (CMV), she was tested for the same. Her CMV IgM antibody was positive and CMV PCR showed 6506 copies/ml in blood. Skin biopsy from one of the lesions showed pigment incontinence and mild perivascular chronic inflammation but did not show cytomegalic cells with inclusions. She was initiated on intravenous ganciclovir 300 mg twice a day which she received for 3 weeks along with intravenous immunoglobulin at a dose of 400 mg/kg over 5 days and oral steroids were increased to 75 mg/day. On this treatment, the hepatitis resolved and CMV PCR reduced to 21 copies/ml. The erythroderma responded more slowly. She was discharged a month later on oral prednisolone 45 mg once daily. At that time she was symptomatically better, had mild generalised erythema with scaling but the...
infiltration had resolved. On follow up 6 weeks after discharge, she had complete resolution of skin lesions and liver enzymes had normalised. The steroids were tapered and stopped 4 months after initiation of treatment (Figure 1).

Drug induced hypersensitivity syndrome (DIHS) can occur with several drugs such as anticonvulsants, dapsone, allopurinol, minocycline, salazosulphapyrazine and mexiletine.1 Leflunomide has also been reported to cause drug hypersensitivity syndrome.2 Leflunomide is an immunomodulatory drug used in the treatment of rheumatoid arthritis. It is converted to its active metabolite A771726 which has a half-life of 2 weeks. Various cutaneous adverse reactions like toxic epidermal necrolysis, Steven-Johnson’s syndrome, erythema multiforme and erythroderma are also reported with this drug.3 The incidence of leflunomide induced cutaneous adverse reactions is reported to be around 7-12% in various studies.4,5 To our knowledge this is the first report of cytomegalovirus reactivation in the setting of probable leflunomide induced drug hypersensitivity syndrome.

The clinical features of this syndrome apart from a drug rash are haematologic abnormalities like eosinophilia, presence of atypical lymphocytes, elevated liver enzymes, lymphadenopathy, interstitial nephritis, interstitial pneumonia or carditis and fever. The disease is known to flare-up even long after the withdrawal of the offending drug. These flares are caused by reactivation of certain viruses, commonly human herpes virus -6 (HHV-6). Therefore the new proposed diagnostic criteria for the diagnosis of DIHS includes human herpes virus -6 (HHV-6) reactivation for diagnosis.6 Other virus reactivations caused by herpes viruses such as Epstein Barr virus, cytomegalovirus and human herpes virus 7 (HHV-7) are also implicated in the relapse of symptoms after discontinuation of the causative drug.7 HHV 6 reactivation typically occurs 2-4 weeks after the onset of the syndrome, EBV reactivation between 3-5 weeks after onset of symptoms and CMV between 4-5 weeks.8 Cutaneous CMV disease is suspected in the presence of scratch dermatitis and erythematous rashes.9 The patient may also develop a leucopenia, thrombocytopenia or a decrease in serum globulin levels. Unexplained slight fever and lumbar pain may herald the development of gastro-intestinal disease due to CMV. CMV gastro-intestinal disease may present as bleeding gastric ulcers or an enterocolitis. CMV disease is confirmed by biopsy of the skin or gastro-intestinal lesions. This will show cytomegalic cells with characteristic “owl eye” inclusions. Also CMV antigenaemia can be detected in peripheral blood. Such patients should be treated with ganciclovir. CMV cutaneous disease arises both from reactivation of a local latent virus or auto-inoculation in periorificial areas by faecal, urinary or salivary shedding of CMV.9 Therefore the skin lesions may be present anywhere in the body and must be carefully looked for. A high index of suspicion for CMV reactivation is required and biopsies of appropriate lesions along with CMV antigen testing should be done in order to institute timely and appropriate therapy to prevent life-threatening complications of CMV disease like a massive gastro-intestinal bleed or an enterocolitis.

In our experience, patients who have developed DIHS following use of leflunomide present with severe disease and worsen to develop a haemophagocytic syndrome followed by death (unpublished data). We cannot state with certainty that the rash in this patient was due to leflunomide alone as the patient was also on salazopyrine and the association between salazopyrine induced drug hypersensitivity and cytomegalovirus reactivation is well reported.9,10 However, this patient improved after withdrawal of both drugs and treatment with systemic steroids,
ganciclovir and immunoglobulin.

In conclusion when a patient on treatment for a drug induced hypersensitivity syndrome presents with a flare up of disease including a “scratch dermatitis” and worsening hepatitis, CMV reactivation should be evaluated for. Timely treatment with gancyclovir can prevent serious complications due to CMV reactivation.

References


