Reactivation of cytomegalovirus in a patient with Stevens-Johnson syndrome/toxic epidermal necrolysis

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse cutaneous reactions to drugs. We describe a 19-year-old patient with SJS/TEN overlap syndrome who had been treated with antiepileptic drugs and subsequently developed severe interstitial pneumonia. A cytomegalovirus (CMV) infection was diagnosed by real-time PCR detection during bronchoalveolar lavage. If our observations are based on biological data, temporal relationship and clinical features, it is possible to infer that the reactivation of CMV with viral replication can predispose a person to SJS/TEN. In the light of the current literature, the probable association that links drug-induced SJS/TEN to the fulminant reactivation of CMV is discussed.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are variants of acute, rapidly progressive mucocutaneous reactions which differ only in the amount of body surface area (BSA) that is affected. SJS is the less severe condition, in which skin sloughing is limited to less than 10% of the BSA. With TEN, there is sloughing of more than 30% of the BSA. In the case of SJS/TEN overlap syndrome, patients have been described to have greater than 10%, but less than 30%, affected BSA. SJS/TEN is a life-threatening condition, where extensive detachment of the skin is characterised by full-thickness necrosis of the epidermis. Most cases of SJS/TEN are drug induced. In patients who have not taken drugs, SJS/TEN is induced by chemicals, Mycoplasma pneumoniae, immunisation and viral infections. We describe a patient with SJS/TEN overlap syndrome who had been treated with antiepileptic drugs and who developed severe interstitial pneumonia caused by cytomegalovirus (CMV) in parallel.

Case history

A 19-year-old Moroccan woman, with no history of a drug or food allergy, followed-up for a month for epilepsy, was treated with phenobarbital (100 mg/day) and valproate (1 000 mg/day) and was admitted for erythroderma. She had a fever of 39.8°C and dyspnoea.

On admission, the patient reported having experienced chills, a cough and rhinorrhea two days earlier. A rash developed on her face days after starting epilepsy treatment and rapidly progressed to her trunk, limbs, neck and chest over the next four days. Subsequently, the facial rash evolved into pustules. She had multiple erosions on the mouth and vulva and her conjunctiva was inflamed. Nikolsky’s sign was positive. The total extent of the erythematous rash was 35% BSA. Histological investigation of the damaged skin revealed evidence of a drug eruption (extensive epidermal necrosis, focal subepidermal necrotic blisters, melanin incontinence and moderate perivascular lymphocytic infiltrate in the absence of eosinophils, neutrophils and viral inclusions). Direct immune fluorescence staining was performed [immunoglobulin M (IgM), immunoglobulin G (IgG), immunoglobulin A (IgA)] and complement component 3. No immunoglobulin or complement deposition in the epidermis or the epidermal-dermal zone was detected. The diagnosis of SJS/TEN, caused by antiepileptic drugs, was made.

Laboratory testing revealed anaemia, eosinophilia, increased inflammatory markers and a white blood cell count of 10x10^9/µl. A chest X-ray showed multifocal patch consolidations with ground-glass opacity in both lungs. No bacterial pathogen was isolated in the respiratory tract, urine and blood. Viral serology (human immunodeficiency virus and hepatitis B and C) was negative. Real-time PCT detection (R-gene® kits) during bronchoalveolar lavage (BAL) revealed and confirmed (by cell culture of the MRC-5 cells) that the cause of the respiratory symptom was CMV. Prior serology data showed that this patient had had a primary CMV infection at the age of six years, which could explain the current reactivation. Real-time PCR in the blood showed fulminant viraemia with 459 copies/ml (a threshold of 350).

The antiepileptic drugs were withdrawn and anticoagulant therapy, parenteral analgesia, eye drops and antiseptic mouth
therapy were initiated. Ganciclovir intravenously (10 mg/kg/day) was started. Oxygen therapy was initiated with parenteral nutrition and adequate hydration. Six days after starting antiviral therapy, the patient’s serial BAL assays were negative. Skin lesions began to heal without the introduction of corticosteroids. The patient had improved and was transferred to the general ward. She was prescribed ganciclovir for a further two weeks.

Discussion

SJS and TEN are severe adverse cutaneous drug reactions that predominantly involve the skin and mucous membranes. The diagnosis relies on clinical symptoms and histological features. Treatment with corticosteroids is recommended, but is not necessarily effective. Several drugs can induce SJS/TEN, and M. pneumoniae and herpesvirus infections are believed to be associated with these conditions. The aetiology is unknown in many SJS/TEN cases.

This case demonstrates a possible link between CMV replication and SJS or TEN. The patient developed SJS/TEN in parallel with pneumonia caused by CMV reactivation several days after initiation of an antiepileptic drug. There have been rare cases in which viral reactivation was accompanied by flu-like symptoms. It is possible that the duration of reactivation was the six days before the patient’s admission. The temporal relationship and the clinical features strongly suggest that CMV with viral replication predisposes to SJS/TEN.

Without a full understanding of the underlying mechanisms that were involved, it is difficult to establish a direct causal link between CMV and drug hypersensitivity. However, a relationship between viral infections and the simultaneous or subsequent development of drug rashes has been observed in a number of clinical situations. The full cascade of events that lead from viral infections to the development of a drug allergy in humans remains poorly understood. An ampicillin rash during infectious mononucleosis, and an increased risk of developing drug rashes in acquired immune deficiency syndrome, are well-known examples of such a relationship. The herpesvirus family is the most likely to significantly influence immune responses. This is because herpesviruses can induce and maintain a potent memory T-cell response. This property arises from their ubiquitous prevalence in human populations and the capacity to grow in lymphoid cells. Specific viral infections had been shown to increase CD95 (Fas) or Fas-ligand expression and increased sensitivity to Fas/Fas ligand-dependent apoptosis. Treatment strategies for SJS and TEN, when these conditions are associated with CMV, include treatment with ganciclovir, avoidance of possible offending drugs and abstention from systemic steroids. The possible mechanism is the interaction of CMV with some of the enzymes that detoxify the offending drugs. This causes the deposition of toxic and immunogenic metabolites on the epidermis.

The hypothesis is whether or not TEN is linked to fulminant CMV infection, and also whether or not CMV triggers an interaction between cytotoxic T lymphocytes, natural killer cells and keratinocytes. Further observational studies are warranted.

Conclusion

This case illustrates that possible CMV interstitial pneumonia, secondary to CMV reactivation, may possibly predispose a patient to SJS/TEN. Furthermore, flu-like symptoms that manifest prior to the appearance of a rash may be prodromal symptoms which could then progress to SJS/TEN. This might be indicative of a CMV reactivation, and consequently, CMV-related pneumonia. Pneumonia that is associated with SJS/TEN may be secondary to alveolar sloughing, therefore not all pneumonia that occurs in parallel with SJS/TEN is indicative of CMV reactivation. The implications for clinical practice are that SJS/TEN is an adverse condition that is caused by drugs and that patients at risk of developing SJS/TEN could be identified by measuring their CMV loads during the first few days after onset, even if the CMV IgM and IgG levels are negative.

Conflict of interest

We declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

References