DOI: 10.3315/jdcr.2010.1043

Journal of Dermatological Case Reports

Stevens-Jonhson syndrome associated with cytomegalovirus infection in a child with ependymoma

Maria João Cruz[1], *Alberto Mota*[1,2], *Teresa Baudrier*[1], *Maria João Gil-da-Costa*[3], *Filomena Azevedo*[1]

1. Department of Dermatology and Venereology, Hospital de São João, Porto, Portugal.
2. Faculty of Medicine, University of Porto, Portugal.
3. Department of Pediatric Hematoncology, Hospital de São João, Porto, Portugal.

Corresponding author:

Maria João Cruz

Department of Dermatology and Venereology, Hospital São João

Alameda Prof. Hernani Monteiro, 4202-451 Porto, Portugal

E-mail: *mjmc@live.com.pt*

Key words:

child, cytomegalovirus, ganciclovir, intravenous immunoglobulin, perianal, Stevens-Johnson syndrome

Abstract

Background: Stevens-Johnson syndrome is an uncommon, acute life-threatening disease characterized by extensive epidermal sloughing and mucositis. In childhood, as in adulthood, this condition is mostly related to drugs, in particular antibiotics. Only a few cases reported were firmly attributed to infectious agents, mainly Mycoplasma pneumonia but the causative role of infectious microorganisms seems particularly relevant in pediatric patients. The seriousness of this condition imposes a prompt recognition and the early withdrawal of the potential causative drugs or the institution of directed measures against infectious agents (depending on the suspected etiology), as well as a supportive and more specific therapy. Some treatments claim to halt the progression of skin detachment, but remain of unproven benefit due to the lack of prospective, well controlled, randomized clinical trials.

Main Observations: We report a case of a 2-year-old boy admitted in our hospital for the treatment of an ependymoma of the posterior fossa, who developed a Stevens-Johnson syndrome associated most probably with a cytomegalovirus infection. He was successfully treated with high dose intravenous immunoglobulin and gancyclovir.

Conclusion: To the best of our knowledge, this is the first case of SJS associated with CMV infection.

Introduction

In 1922 Stevens and Johnson were the first to describe the features of what is known as the Stevens-Johnson syndrome (SJS)[1]. They described two children with fever, conjunctivitis, stomatitis and skin lesions. It is a disorder with a low incidence (1 to 6 per million persons-year) but carries a significant mortality rate (approximately 5%)[2]. Nowadays is considered to be part of a spectrum characterized by severe acute mucocutaneous bullous disease, most commonly drug-induced, which includes not only SJS but also SJS/Toxic Epidermal Necrolysis (TEN) overlap and pure TEN, according to features such as the affected body surface area with skin detachment[3].

We describe a case of a 2-year-old boy admitted to our hospital for the treatment of an internal malignancy, who developed a SJS associated with cytomegalovirus (CMV) infection.

Case report

A 2-year-old boy was admitted at the Department of Pediatric Hematoncology for the management of a non-excisable ependymoma of the posterior fossa. The patient was under predisolone (1mg/kg/day) to reduce the intracranial edema. Seven days after admission the patient developed eyelids edema, conjunctival injection, oral mucositis and perianal painful erosions (Fig. 1 AB). Two days later erythematous macular lesions were noted on the ears, trunk and hands and the perianal erosions evolved to ulcers.

Laboratory evaluation showed a very mild elevation of C-reactive protein (9.4 mg/dL), WBC 12.420/mm^3, with 78.3% polymorphonuclear leukocytes; hemoglobin 10.8 g/dL; platelet count 417.000/mm^3, and erythrocyte sedimentation rate 12 mm/h. Urine, blood and sputum cultures were sterile. Chest radiograph was unremarkable. The detection of antibodies against epidermal-basement-membrane

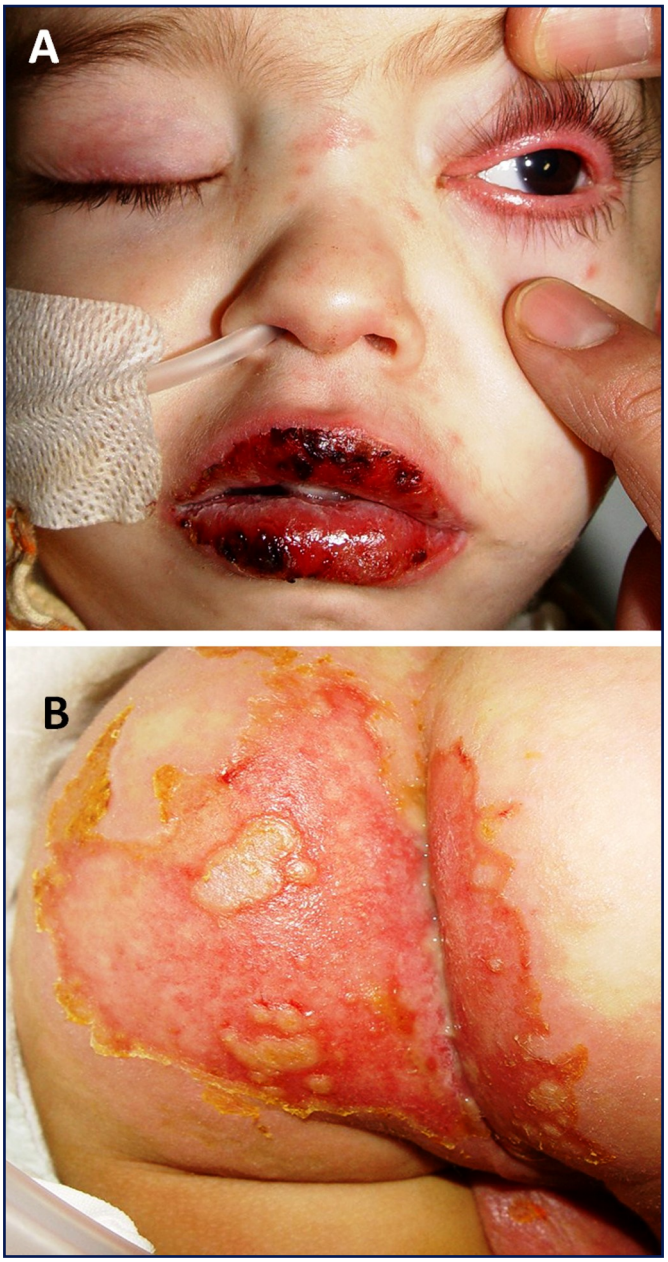

Figure 1

The patient developed eyelids edema, conjunctival injection (A), oral mucositis and perianal painful erosions. Two days later erythematous macular lesions were noted on the ears, trunk and hands and the perianal erosions evolved to ulcers (B).

and desmosomes was negative, as were the serological titters for Mycoplasma pneumonia, Chlamydia pneumoniae, Hepatitis B and C virus, HIV, Herpes simplex virus (HSV) 1 and 2, Varicella Zoster and Epstein Barr. However, Polimerase Chain Reaction (PCR) for DNA CMV was positive in the swab of ulcerated lesions. CMV IgG antibody titters were positive (191.4 AU/mL; normal range 0 to 15) with a normal IgM value. Two days later serological examination and PCR were both repeated disclosing an increased IgG anti-CMV titter (412.1 AU/mL) and confirming a PCR for DNA of CMV positive.

Punch biopsies were taken from lesional and perilesional skin. Histological examination showed epidermal acanthosis and vacuolar degeneration of the basal cell layer with intradermal apoptotic keratynocites. In the dermis, enlarged vascular endothelial cells accompanied by perivascular infiltration of lymphocytes and histiocytes were also noted (Fig. 2). Immunohistochemical analyses were negative including for CMV and HSV antigens, however, PCR was once again positive for DNA CMV in both skin biopsies.

Management was started with supportive measures and the dose of prednisolone was increased to 2mg/kg/day without significant response after 5 days. An ophthalmologist opinion was required and topical antibiotics and corticosteroids were prescribed. When histological examination confirmed the suspected diagnosis of SJS and PCR revealed CMV DNA in the cutaneous lesions, gancyclovir (10mg/kg/day for 21 days) and intravenous immunoglobulins (IVIg) (0.5g/kg/day for 3 days) were started and a significant improvement of the mucocutaneous attainment was observed after ten days. At two months of follow-up only a postinflammatory hyperpigmentation was noted and the patient could finally start the chemotherapy regimen proposed by the Department of Pediatric Hematoncology to treat the neoplasm.

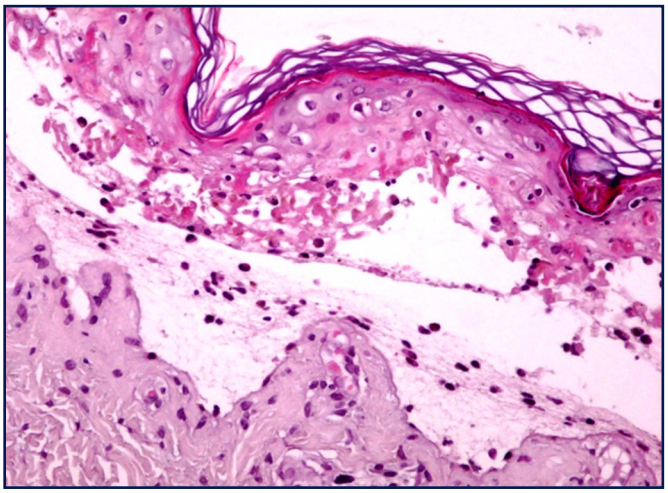

Figure 2

Histological examination showed epidermal acanthosis and vacuolar degeneration of the basal cell layer with intradermal apoptotic keratynocites. In the dermis, enlarged vascular endothelial cells accompanied by perivascular infiltration of lymphocytes and histiocytes were also noted.

Discussion

SJS and TEN are rare, potentially fatal, acute mucocutaneous conditions that commonly result from what seems an hypersensitivity reaction to systemic medication. More than 100 different drugs have been reported as possible causes. The most frequently implicated are antibiotics, aromatic anticonvulsivants, allopurinol and oxicams nonsteroid anti-inflammatory drugs[4]. The role of infectious agents in the development of SJS/TEN seems much less prominent than for erythema multiforme. However a few cases of SJS associated with Mycoplasma pneumoniae infection, viral diseases and vaccine immunization have been

reported and, interestingly, most of them in pediatric patients, as it occured in our case[5-7]. Although in our patient a precise causative event was not possible to establish, a relation to the CMV infection is highly plausible, which, to our knowledge, has been reported only once, but in the setting of erythema multiforme major not SJS as it occurred in our case.

CMV is a member of the herpesvirus family, sharing the common characteristics of a DNA genome capable of persisting in a latent state after primary infection8. Reactivation of latency can occur as a result of host-immune suppression and can lead to life-threatening CMV infection. This infection has recently become recognized as a significant contributor to morbidity and mortality in organ transplant recipients, in patients with AIDS and in patients receiving immunosuppressive therapy, including corticosteroid therapy, used in our patient. Systemic CMV infection is diagnosed by performing antigenaemia or DNAemia assay (PCR) on blood samples. Local infections, such those affecting single organ or apparatus, like the lungs and the gastrointestinal tract, are usually diagnosed by virus isolation from tissue biopsies or secretions, or by PCR[8]. CMV predominantly causes local (visceral) disease and the involvement of the skin is rare. However, the skin may be the initial site of CMV involvement and may provide the first clue to systemic infection. A wide spectrum of cutaneous lesions associated with CMV infection has been reported, including morbilliform eruptions, purpura, vesiculobullous lesions, nodules, papular eruptions, verrucous lesions and ulcerations[9,10], but to date no case of SJS has been related to this infectious agent. In our case a possible association between CMV and SJS is suggested by a temporal relationship. In addition, rising levels of anti-CMV IgG antibody titers in this patient, despite a normal IgM, strongly suggests acute infection. Furthermore, CMV DNA sequences were detected by PCR in fresh samples taken from skin lesions, which is, nowadays, the method with a higher sensitivity and specificity. Histological findings observed like enlarged vascular endothelial cells accompanied by perivascular infiltration of lymphocytes and histiocytes in the dermis are not pathognomonic, but are characteristic of CMV infection[8,9]. Although immunohistochemistry was negative for CMV, this is possible a false negative, due to its lower sensitivity in relation to PCR. Finally, the relatively rapid response to antiviral therapy combined with IVIG supports a dominant role for CMV infection in the pathogenesis of the skin disease. We propose that an immunological response to the virus reactivation that occurred prior to the skin eruption was the trigger to the development of SJS in this patient.

At present SJS still lacks a specific therapeutic approach. Many treatment modalities have been proposed, some of which are clearly beneficial, some are more likely to be harmful and others are of greatest clinical interest but with unproven benefit. Nowadays, early withdrawal of the suspected offending drugs or the institution of anti-infectious medication, depending on the etiology, and meticulous supportive measures still constitute the cornerstone of treatment. Systemic drugs like corticosteroids, anti-tumour necrosis factor agents, thalidomide, cyclosporine, cyclophosphamide, N-acetylcysteine and other modalities such as plasmaferesis, have been tried along with supportive measures, but with variable results[10]. In 1998, on the basis of the identification of the mechanism of keratinocytes apoptosis in SJS and TEN, a therapy approach based on the use of IVIg was proposed with uniformly favorable results[10,11]. Nevertheless, the literature about this specific treatment is still dominated by uncontrolled trials, retrospective studies, case series and anecdotal reports. The need for a large, controlled, prospective, randomized trial that allows the establishment of effectiveness of this approach is evident, but the uncommon nature of this disease may postpone this goal. While the scientific community waits for these studies, the cumulative evidence of smaller trials, often uncontrolled studies and even sporadic case reports, as ours, can be compelling to reassure clinicians in treating this disease.

In conclusion, the interest of this report is not only to reinforce the effectiveness and safety of IVIg in the treatment of SJS but especially to alert to the possibility of other etiologies besides drugs, especially in pediatric patients. In fact, infectious microrganisms are not always considered as causative agents and because of that are easily missed. Careful monitoring of infection allows early diagnosis and timely initiation of anti-infectious treatment, which seems to represent important issues in the prognosis of these patients. To the best of our knowledge, this is the first case of SJS associated with CMV infection.

References

1. Stevens AM and Johnson FC. A new eruptive fever associated with stomatitis and ophtalmia. *Am J Dis Child.* 1922; 24: 526-533.
2. French LE and Prins C. Erythema Multiforme, Stevens-Johnson Syndrome and Toxic Epidremal Necrolysis. In: Bolognia JL, Jorizzo JL, Rapini RP (eds). Dermatology Vol.1, 2nd edition. Philadelphia, PA: Mosby, 2008; 287-299.
3. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergol Int.* 2006; 55: 9-16.
4. Valeyrie-Allanore L and Roujeau JC. Epidermal Necrolysis (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis). In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ (eds). Fitzpatrick's Dermatology in General Medicine Vol.1, 7th edition. McGraw-Hill, 2008; 349-55.
5. Walicka M, Majsterek M, Rakowska A, Słowińska M, Sicińska J, Góralska B, Ptasińska M, Rudnicka L, Marcinowska-Suchowierska E. Mycoplasma pneumoniae-induced pneumonia with Stevens-Johnson syndrome of acute atypical course. *Pol Arch Med Wewn.* 2008; 118: 449-453.
6. Mulvey JM, Padowitz A, Lindley-Jones M and Nickels R. Mycoplasma pneumoniae associated with Stevens Johnson syndrome. *Anaesth Intensive Care.* 2007; 35: 414-417.
7. Bay A, Akdeniz N, Calka O, Kösem M, Faik Oner A, et al. Primary varicella infection associated with Stevens-Johnson syndrome in a Turkish child. *J Dermatol.* 2005; 32: 745-750.

8. Ball R, Ball LK, Wise RP, Braun MM, Beeler JA, *et al*. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the vaccine adverse event reporting system. *Pediatr Infect Dis J*. 2001; 20: 219-223.

9. Drago F, Aragone MG, Lugani C and Rebora A. Cytomegalovirus infection in normal and immunocompromised humans. A review. *Dermatology*. 2000; 200: 189-195.

10. Choi YL, Kim JA, Jang KT, Kim DS, Kim WS, et al. Characteristics of cutaneous cytomegalovirus infection in non-acquired immune deficiency syndrome, immunocompromised patients. *Br J Dermatol*. 2006; 155: 977-982.

11. Stella M, Clemente A, Bollero D, Risso D, Dalmasso P. Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS): experience with high-dose intravenous immunoglobulins and topical conservative approach. A retrospective analysis. *Burns*. 2007; 33: 452-459.

12. Metry DW, Jung P and Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics*. 2003; 112: 1430-1436.