Stevens-Johnson syndrome/erythema multiforme major and Chlamydia pneumoniae infection in young patients

Ana Filipa Duarte,1 Maria João Cruz,2 Elisabete Moreira,2 Teresa Baudrier,2 Alberto Mota,1 Filomena Azevedo2
1Hospital São João, EPE and Faculty of Medicine, Porto, Portugal; 2Hospital São João, EPE, Porto, Portugal

Abstract

Erythema multiforme major (EMM) is an acute, self-limited mucocutaneous disease characterized by the abrupt onset of symmetrical fixed red papules evolving to target lesions. It is triggered mainly by infections, such as herpes simplex virus (HSV) and Mycoplasma pneumoniae, or drugs. In instances of extensive skin lesions with “giant” atypical targets, centripetal distribution, prominent involvement of several mucous sites and fever, it may be difficult to distinguish from Stevens-Johnson syndrome (SJS), a rarer, life-threatening reaction which is mainly drug-induced.2

In 2002, 4 patients (aged 6-29 years) presented with erythema multiforme major (EMM), keratinocytes and inflammatory cell infiltration, compatible with atypical pneumonia. Skin biopsy specimen taken from the border of a lesion on the back, showed dermo-epidermal detachment, apoptotic keratinocytes and inflammatory cell infiltrate, compatible with SJS (Figure 2).

Serum IgG for C. pneumoniae was negative and IgM was 3.4 U/mL (normal < 0.5 U/mL) on admittance but turned frankly positive (36.7 U/mL) four weeks later. The remaining investigation showed mild leukocytosis with neutrophilia and an elevated reactive C protein. Blood and urine cultures were negative. Serologies to Herpes simplex, M. pneumoniae, Parovirus B19, Varicella zoster Virus (VZV), Hepatitis B and C, Varicella-Zoster Virus (VZV), and Legionella pneumophila antigen, were all negative.

Oral clarithromycin 500 mg twice a day for ten days and topical betamethasone twice a day for five days and once a day for a further five days. In the 3 cases, the eruption subsided gradually, with complete resolution in 2-4 weeks. A few months after convalescence, seroconversion was observed. IgM for Herpes simplex type 2 and C. pneumoniae became negative, but a positive IgG was detected in the case of patient #4.

Discussion

C. pneumoniae is a human Gram-negative pathogen responsible for 5-20% of community-acquired pneumonias in adults and children.3

Correspondence: Ana Filipa Duarte, Department of Dermatology and Venereology, Hospital São João, Alameda Professor Hernâni Monteiro 4200-319 Porto, Portugal.

E-mail: duarte.af30@gmail.com

Key words: Stevens-Johnson syndrome, erythema multiforme major, Chlamydia pneumoniae.

Received for publication: 27 December 2009. Revision received: 2 March 2010. Accepted for publication: 3 March 2010.

This work is licensed under a Creative Commons Attribution 3.0 License (by-nc 3.0).

©Copyright A.F. Duarte et al., 2010 Licensee PAGEPress, Italy Dermatology Reports 2010; 2:e6 doi:10.4081/dr.2010.e6

Case Reports

We report a 7-year-old boy with a rapidly progressive macular-papular exanthema evolving to atypical target lesions involving less than 10% of the body surface, oral mucosa erosions, conjunctivitis and fever (38°C) in less than 24 hours (Patient #1 - Figure 1). There was no history of drug intake in the past two months. Nikolsky sign was positive. Pulmonary auscultation was normal, but the X-ray revealed a bilateral interstitial infiltrate, compatible with atypical pneumonia. Skin biopsy specimen taken from the border of a lesion on the back, showed dermo-epidermal detachment, apoptotic keratinocytes and inflammatory cell infiltration, compatible with SJS (Figure 2).

Serum IgG for C. pneumoniae was negative and IgM was 3.4 U/mL (normal < 0.5 U/mL) on admittance but turned frankly positive (36.7 U/mL) four weeks later. The remaining investigation showed mild leukocytosis with neutrophilia and an elevated reactive C protein. Blood and urine cultures were negative. Serologies to Herpes simplex, M. pneumoniae, Parovirus B19, Varicella zoster Virus (VZV), Hepatitis B and C, Venereal Disease Research Laboratory (VDRL), T. pallidum Human Agglutination (TPHA) and urine Legionella pneumophila antigen, were all negative.

Oral clarithromycin 500 mg twice a day for ten days and topical betamethasone twice a day for five days and once a day for a further five days were prescribed with complete clinical resolution in ten days.

In addition 3 other cases of C. pneumoniae were demonstrated as co-infection in patients with EMM.

Case Reports

Patient #2, a 3-year-old girl (Figure 3) developed a confluent maculopapular exanthema evolving to target lesions, localized to the face, chest and limbs, associated with fever and conjunctival hyperemia. Serum IgM for both M. pneumoniae and C. pneumoniae was reactive by enzyme immunoassay and IgG was negative suggesting recent infection.

Patient #3, a 29-year-old man (Figure 4), presented with a maculopapular exanthema and target lesions, localized to the face, trunk and limbs, fever and conjunctival hyperemia.
It is a significant cause of both lower and upper acute respiratory illness, including atypical pneumonia, bronchitis, pharyngitis and sinusitis, but most cases are mild or asymptomatic. 3 The seroprevalence progressively increases with age, reaching 50% of antibodies against *C. pneumoniae* in the adult and exceeding 80% in the elderly. 3

The ethiopathology of SJS and EMM is poorly understood, but some mechanisms, like immune-mediated vascular injury, cell-mediated immune response and autoimmune mechanisms are possible. 3 EM is often associated with HSV, type 1 in 50% of cases and less often type 2. 4 The second most reported agent is *M. pneumoniae*, occurring in about 5% of cases, but other agents may be implicated. 4 In the cases of SJS, drugs are the most important etiological factors.

The most commonly used method for the diagnosis of *C. pneumoniae* is serology, which basically offers a retrospective study. In our 4 patients, a microimmunofluorescence test, which is considered as the “gold standard” of acute infections because of high sensitivity and specificity, was performed. 5 For acute infection the patient should show a 4-fold increase in the IgG titre, an IgG titre of over 1:512 or a positive IgM titre. On primary infection, the IgM response usually appears at least three weeks after the onset of illness and the IgG response at 6-8 weeks. Because of the relatively long window for serological response in a primary infection, the antibody response may be missed if convalescent sera are obtained too soon. In fact, in some cases of acute infection, three months were needed for antibodies to be detected. Although PCR holds promise as a fast diagnostic tool, there are no standardized PCR or other nucleic acid amplification tests for detection of *C. pneumoniae*. 6

Since no other predisposing factor was present, and serology confirmed acute infection, Patient #1 had SJS due to *C. pneumoniae* infection. The other 3 patients had serologies suggesting that *C. pneumoniae* was at least a co-responsible factor for EMM.

Despite the fact that its role in this skin disease has been rarely reported, our cases support the view that a patient co-infection with *C. pneumoniae* and either with *M. pneumoniae* or Herpes simplex, seems to trigger EMM. It is possible that the presence of more than one infectious agent that includes *C. pneumoniae* may predispose patients to a more probable and/or more severe cutaneous reaction.

Besides SJS/EMM, *C. pneumoniae* is also associated with other skin reactions, including erythema nodosum, and hypersensitivity and Sweet syndromes. 8

To the best of our knowledge, there has only been one report of 2 patients with *C. pneumoniae* and *M. pneumoniae* co-infection associated with EMM11, and one report of EMM associated to *C. pneumoniae* alone. 9 No reports were found of EMM associated to *C. pneumoniae* and Herpes simplex type 2 co-infection.

We believe that SJS/EMM associated with *C. pneumoniae* is underdiagnosed, because it has been rarely reported and physicians are not sufficiently aware to search for it.1223 Patients presenting with SJS/EMM should be evaluated for active and latent HSV infection and appropriate serological testing for *M. pneumoniae*. 6 However, other infectious causes should be considered. A normal chest X-ray does not exclude *M. pneumoniae* or *C. pneumoniae* infection, because the patient does not necessarily disclose pneumonia despite a relevant infection, besides the fact that atypical pneumonia without evident radiological image can be present. 8

In the light of this, we think it is advisable to suspect those agents in patients with signs of respiratory infection sign and SJS/EMM.

References

1. Léauté-Lambrèze C, Lamireau T, Chawki D, et al. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. Arch Dis Child 2000;83:347-52.
2. Lam N-S, Yang Y-H, Wang L-C, et al. Clinical characteristics of childhood erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in Taiwanese children. J Microbiol Immunol Infect 2004;37:366-70.
3. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years experience. Drugs Saf 2002;25:965
4. Hammerschlag MR. Chlamydia pneumoniae-

Figure 1. Patient #1: atypical target lesions and erosions.

Figure 2. Patient #1: H&E (x40) - interface spongiosis, individual necrotic keratinocytes and perivascular inflammatory cell infiltrate.

Figure 3. Patient #2: confluent maculopapular exanthema evolving to target lesions.

Figure 4. Patient #3: atypical target lesions.
ae and the lung. Eur Respir J 2000;16:1001-7.
5. Miyashita N. Chlamydia pneumoniae infections. Kekkaku 2006;81:581-8.
6. Hammerschlag MR. The intracellular life of chlamydiae. Semin Pediatr Infect Dis 2002;13:239-48.
7. Schalock PC, Dinulos JGH, Pace N, et al. Erythema multiforme due to Mycoplasma pneumoniae infection in two children. Pediatric Dermatology 2006;23:546-55.
8. Saada D, Velasco S, Vabres P, Guillet G. Érythème polymorphe majeur et infection à Chlamydia pneumoniae. Ann Dermatol Venereol 2006;33:1001-4.
9. Schalock PC, Brennick JB, Dinulos JGH. Mycoplasma pneumoniae infection associated with bullous erythema multiforme. J Am Acad Dermatol 2005;52:705-6.
10. Wang S. The microimmunofluoresence test for Chlamydia pneumonia infection: technique and interpretation. J Infect Dis 2000;181:5421-5.
11. Terada K, Hiraga Y, Mori R, et al. Double infection of Mycoplasma pneumoniae and Chlamydia pneumoniae in children. Kansenshogaku Zasshi 1996;70:1176-80.