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

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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 (1-6 cases per million) and life-threatening reaction which is mainly drug-induced.2

Case Reports

We report a 7-year-old boy with a rapidly progressive maculopapular 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 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, Human Immunodeficiency Virus (HIV), Hepatitis B and C, Venereal Disease Research Laboratory (VDRL), T. pallidum Human Agglutination (TPHA) and urine Legionella pneumoniae 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. Patient #4 took 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. In patients #2 and #3, IgM for C. pneumoniae and M. pneumoniae turned negative and IgG turned positive.

Discussion

C. pneumoniae is a human Gram-negative pathogen responsible for 5-20% of community-acquired pneumonias in adults and children.3
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. The seroprevalence progressively increases with age, reaching 50% of antibodies against C. pneumoniae in the adult and exceeding 80% in the elderly.

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. EM is often associated with HSV, type 1 in 50% of cases and less often with HSV, type 2. The second most reported agent is C. pneumoniae, occurring in about 5% of cases, but other agents may be implicated. In the cases of SJS, drugs are the most important etiologic 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. 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 prime 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.

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.

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 EMM,11 and one report of EMM associated to C. pneumoniae alone.4 No reports were found of EM 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.12,17,19 Patients presenting with SJS/EMM should be evaluated for active and latent HSV infection and appropriate serological testing for M. pneumoniae. 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.2 In the light of this, we think it is advisable to suspect those agents in patients with respiratory infection signs and SJS/EMM.

References
4. Hammerschlag MR. Chlamydia pneumoniae