Mycoplasma pneumoniae-induced pneumonia with Stevens-Johnson syndrome of acute atypical course

Magdalena Walicka[1], Magdalena Majsterek[2], Adriana Rakowska[2], Monika Słowińska[2], Justyna Sicińska[2], Beata Góralska[2], Marta Ptasińska[1], Lidia Rudnicka[2,3], Ewa Marcinowska-Suchowierska[1]

[1] Clinic of Family Medicine and Internal Diseases at the Medical Centre for Postgraduate Education (CKMP), Warsaw, Poland

[2] Clinic of Dermatology at MSWiA Central Clinical Hospital, Warsaw, Poland

[3] Polish Academy of Sciences, Warsaw, Poland

Abstract: We present a case of Stevens-Johnson syndrome of acute clinical course with massive occupation of the mucus membranes of the respiratory system, oral cavity, genitals and conjunctiva in a patient with pneumonia. A probable etiological factor was infection with *Mycoplasma pneumoniae*, however clarithromycin could be another potential inducing factor.

Key words: mucosa, *Mycoplasma pneumoniae*, pneumonia, Stevens-Johnson syndrome

INTRODUCTION

Stevens-Johnson syndrome (SJS) is an acute reaction of the skin and mucosa related to the oversensitivity to medications or brought on by infection. SJS belongs to the same group of diseases as erythema multiforme, toxic epidermal necrolysis (TEN) and SJS/TEN overlapping syndrome, although the relationship between these remains a subject of controversy. Occurrence of SJS is 1–7 cases per million people annually [1], and the mortality rate is about 5% [2].

Erythematous or erythematous-cystic skin changes, frequently "target" or "atypical target" diffused pictures are characteristic for Stevens-Johnson syndrome, but are generally observed on less than 10% of the skin surface. Cystic, ulcerative and hemorrhagic lesions of mucosa (conjunctivas, respiratory system, digestive system, genitourinary system) and general symptoms (fever, malaise) are also observed. Changes within the mucosa of respiratory or digestive system are observed in 10–30% of SJS cases [3]. Organ changes manifested by the increased activity of aminotransferases, pancreatic enzymes or traits of glomerulonephritis may also occur [1]. In adult patients the disease is mainly a post-medication reaction, in children it is usually incurred by infection. Over 100 medications responsible for SJS formation are described in the literature. These medications are sulphonamides, anticonvulsants, antibiotics (cephalosporins, macrolides, chloramphenicol, doxycycline, ciprofloxacin), non-steroid anti-inflammatory drugs, hydrocortisone sodium salt and allopurinol [2]. The following infectious factors are considered: herpex simplex virus, *Adenoviruses, Enteroviruses*, hepatitis B virus, *Enterobacter*, *Mycobacterium tuberculosis, Mycoplasma pneumoniae, Streptococcus pneumoniae, Treponema pallidum, Yersinia enterocolitica, Histoplasma capsulatum, Coccidioides immitis*, from among which, according to some authors, *Mycoplasma pneumoniae* is the most frequent factor. Development of full-symptomatic form of SJS is usually observed in the course of this infection. However, "atypical SJS" can occur, characterised by a total or partial absence of skin changes with strongly evident mucosa changes [3-5].

Here we present a case of SJS of an atypical, severe course in a patient with a diagnosed *M. pneumoniae* infection.

CASE REPORT

A 28-year-old male patient with history of atopy (seasonal allergic rhinitis and episode of dyspnoea in childhood), with a negative history of other diseases, developed such symptoms as headache and sore throat about 12 days before hospitalization. A fever of over 38°C and a cough appeared 2 days later. In spite of 7-day ambulatory therapy with amoxicillin with clavulanic acid (625 mg/8 h), the ailments did not resolve. Treatment with clarithromycin was implemented (500 mg/12 h). Ulcerative changes within the mucosa of the oral cavity and an intensification of the sore throat joined the maintaining symptoms of infection. In the performed chest X-ray picture, parenchymal densities in the perihilar region of the lower left lobe and peripheral densities in lower areas of both lungs were found. In the laboratory tests, increased C-reactive protein (CRP) concentration (247.9 mg/l) with normal leukocytes count ($6.6 \times 10^3/mm^3$) were observed.

Correspondence to:
Magdalena Walicka, MD, Klinika Medycyny Rodzinnej i Chorób Wewnętrznych CMKP, SPSK im. Prof. W. Orłowskiego, ul. Czerniakowska 231, 00-416 Warsaw, Poland, phone: +48-22-628-69-50, fax: +48-22-622-79-81, e-mail: m_walicka@wp.pl
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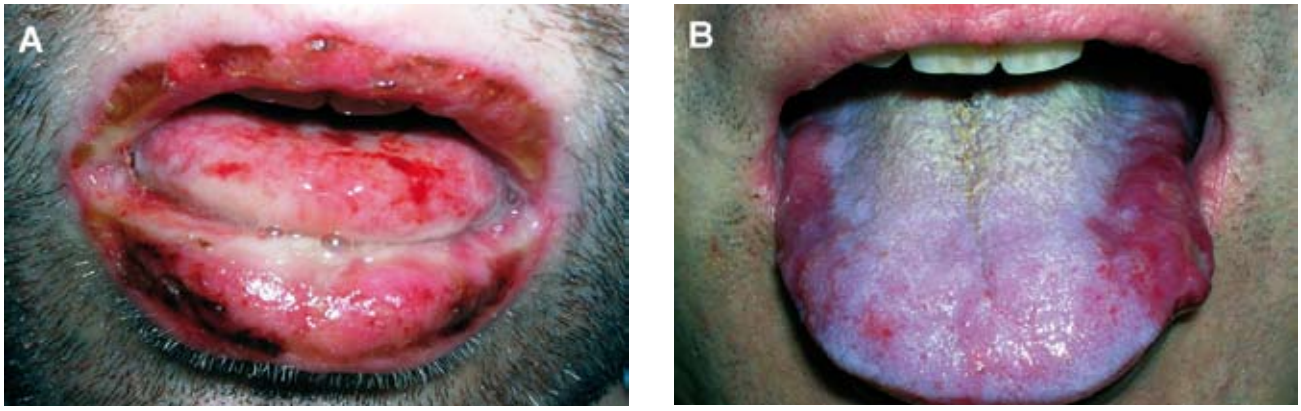

Figure. A. Maximal mouth opening in the first days of the disease. Massive necrolysis within the mucosa of oral cavity and necrolysis of lips. **B.** Residual mucosal changes after 2 weeks of treatment

On admission to the Clinic of Family Medicine and Internal Diseases at CMKP the patient's general condition was poor; auscultation rales and crepitations were found on the lungs, to a greater degree over the right side. Subconjunctival hemorrhage, traits of purulent conjunctivitis, cystic changes and hemorrhagic crusts on the lips and mucosa of the oral cavity were observed. Accompanying skin changes were not observed. Laboratory tests revealed the following results: normal count of 9 thousand leukocytes (in smear: rejuvenation of granulocytes, relative lymphopenia), increased CRP concentration 243 mg/l, increased erythrocyte sedimentation rate (ESR) 94 mm/h, increased transaminases activity (alanine transferase [ALT] 190 IU/l, asparagine transferase [AST] 97 IU/l), γ-glutamyl transpeptidase (GGTP; 686 IU/l) and lactate dehydrogenase (1189 IU/l), in urin analysis: leukocyturia (10–15 in the field of vision) and erythrocyturia (6–10 in the field of vision, fresh and partially lixiviated). An ultrasound examination of the abdomen cavity did not reveal any abnormalities. Treatment with clarithromycin (500 mg/12 h orally) was continued, ceftriaxone (2 g/24 h *i.v.)*, fluconasole (100 mg/24 h orally), acyclovir (4000 mg/24 h in divided doses orally), drops and ointment with antibiotic to the conjunctival sac for local use were added.

In the next 3 days of hospitalization patient's general condition worsened. Traits of bronchospasm and massive secretion retention in the airways, requiring the use of bronchodilators (salbutamol a 2.5 mg in nebulisation) were observed. Ulcerative and hemorrhagic lesions on the conjunctiva and mucosa of the oral cavity were exacerbated, erythematous-cystic changes on the mucosa of genitals appeared. Massive changes within the mucosa of the oral cavity and throat made oral nutrition impossible. In the laboratory tests increase of CRP concentration (301 mg/l) was observed. A control chest X-ray was performed (5 days after the last examination), in which parenchymal densities had maintained. A sputum smear was negative.

Stevens-Johnson syndrome was diagnosed on the basis of the clinical picture. The antibiotics were discontinued due to the possibility of their intensifying SJS symptoms, and the patient was transferred to the Clinic of Dermatology at CSK MSWiA. On admission to the Clinic of Dermatology, a cough with expectoration of huge amounts of sputum containing extensive fragments of desquamated epithelium was still present. Massive changes on the mucosa of oral cavity (Figure) and throat and discrete erythematous changes within the nail walls of the toes were observed. In the laboratory tests maintaining elevated parameters of inflammatory state (ESR 96 mm/h, CRP 257.8 mg/l, fibrinogen 745 mg/dl), hypertransaminasemia (AST 187 IU/l, ALT 195 IU/l) and increased γ-glutamyl transferase activity (GGTP 588 IU/l) were found. The sputum and urine smear were negative. The immunoenzymatic examination, performed three times, suggested an active *Mycoplasma pneumoniae* infection. Ciprofloxacin (400 mg every 12 hours in intravenous infusions) and cyclosporin A (3.3 mg/kg of body mass/day in divided doses every 12 hours, in intravenous infusions), intravenous fluids (10% glucose solution, 0.9% NaCl, PWE), nebulisation with fenoterol and ipratropium bromide were included in the therapy. Werapamil (2.5 mg *i.v.*) was immediately administered for the increased of blood pressure. Mucosa of the oral cavity was aseptically cleared; Trascodent, 2% chloramphenicol and nystatin were externally applied. A massage of the conjunctival recesses was performed and 1% chloramphenicol in eye ointment, dexpanthenol + poliacrylic acid, natri hyaluronas and hydroxypropyl were locally used. Changes within the acorn were treated with Trascodent, 2% chloramphenicol and clotrimazole in cream.

After 4 days of therapy his clinical state improved, enabling an implementation of a fluid diet. Food administration began with the fluid diet (Nutridrink®), and when the state of the oral cavity mucosa improved, this diet was enriched with mixed products, balanced with regard to caloricity and protein content in comparison to the normal diet. Several days later there was an almost complete regression of mucosal changes and cough, and a normalisation of inflammatory state parameters and liver enzymes were observed. Parenteral cyclosporin A preparation was replaced with oral preparation in the initial dose of 6.6 mg/kg of body mass/24 h.

Enoxaparin (60 mg/24 h *s.c.)* was administered to maintain hyperfibrinogenemia and elevated concentration of D-dimers. In the control chest X-ray, densities in the left lower lobe were found which might have responded to descending changes after the pneumonia. Antibiotic therapy was modified, including the preparation of doxycycline and dosage of cyclosporin A was gradually reduced to 2.2 mg/kg of body mass/24 h. Blood cyclosporin concentration was monitored.

Beside the transitionally elevated values of blood pressure in the first days of the therapy with cyclosporin, which normalized after the use of werapamil and insignificantly elevated creatinine concentration (to 1.41 mg/dl), advese effects of the therapy were not observed.

After 20 days of therapy the patient was generally in good condition, without active inflammatory changes, with almost completed reepithelization of the previously pathologically changed mucosa, and was discharged from the hospital. Continuation of the remaining dosages of cyclosporin A (200 mg/24 h), doxycycline (200 mg/24 h), fluconasole (100 mg/24 h), enoxaparin (60 mg/24 h subcutaneously) and ambroxol (0.06 g/24 h) and fenoterol (4×0.2 mg) was recommended. During the ambulatory treatment, medication doses were gradually decreased and finally discontinued 8 weeks after the first symptoms of the disease. During the post-discharge 8-month ambulatory treatment, no significant late complications were observed.

DISCUSSION

M. pneumoniae causes an average of 15–20% of all cases of out-of-hospital pneumonia in the whole population, and over 50% of cases of pneumonia in closed environments (schools, dormitories etc.) [6]. The infection of airways caused by *M. pneumoniae* usually manifests itself in a sore throat, hoarseness, fever, shivers, cough, headaches, earache, rhinitis, muscular pain and general malaise [7]. *M. pneumoniae* disables ciliary movement of the respiratory endothelium (including the arrest) and causes necrosis of mucous cells. Epithelial detachment and exudative, bronchial and peribronchial inflammatory reaction may spread on the alveoli. Microscopically, it causes interstitial pneumonia, bronchitis and bronchiolitis [8]. In 25% of patients with *M. pneumoniae* infection, in various periods from the onset of the symptoms of airways infection, extrapulmonary complications may appear [7], owing to direct microorganism invasion and/or an autoimmunological response: encephalitis and meningoencephalitis, myelitis, polyneural inflammation, cranial nerve palsy, coma, confusion and secondary to encephalitis acute psychoses, arthritis, myocarditis and pericarditis, hemolytic anemia, diffused intravenous clot formation, acute glomerulonephritis, renal insufficiency, IgA nephropathy, nausea, vomiting and diarrhoea, cholestatic hepatitis and pancreatitis [6-8].

Dermatological complications, such as: non-specific inflammatory rashes, erythema nodosum, purpura, vascular purpura, leucoclastic vasculitis, Schoenlein-Henoch purpura, classic Stevens-Johnson syndrome and toxic epidermal necrolysis and mucositis are observed in 25% of patients with mycoplasmatic infection [7]. The most probable mechanism of mucosal change development is pathogenic action of the disease-induced specific antibodies against the specific mucosal antigens [5]. Prognosis in mycoplasmatic infection-related mucositis appears to be good. In the available literature, 15 cases of this disease were described so far. None of them ended with patient's death.

In the case presented, the diagnosis of *M. pneumoniae* infection was made on the basis of indirect premises, including immunoenzymatic tests. Other etiologic factors of Stevens-Johnson syndrome, such as medications like clarithromycin, should be also considered. However, infection introduces an atypical course of the disease, previously described by other authors [4,5], with massive changes in the mucosa of the oral cavity and minimal skin lesions.

In therapy of typical SJS (mainly in cases of drug etiology), besides the symptomatic treatment, glucocorticosteroid preparations and intravenous immunoglobulins (IVIG), separately or in conjugated therapy are used [1]. In mycoplasmatic infection-related mucositis the therapy was limited to symptomatic treatment and administration of antibiotics. In one case IVIG was administered with good results.

The decision to use cyclosporin A was made on the basis of positive experience with this medication in Lyell's syndrome (a disease with a similar or identical patomechanism) and in patients with Stevens-Johnson syndrome with dominating skin occupation. Apoptosis is a mechanism responsible for massive necrosis of keratinocytes in TEN. Tumor necrosis factor α (TNF-α) path and CD95 (Fas) system are involved in this process. Apoptosis of keratinocytes in TEN is induced by interactions of FasR cellular surface receptor (CD95R) with FasL ligand (CD95L). In patients with TEN an increased expression of both FasR and FasL on keratinocytes is observed. A potential mechanism of favourably activating cyclosporin A in TEN appears to involve suppressing the influence of this medication on the lymphocytes T activity. Cyclosporin A-dependent decrease of TNF-α secretion, observed in vitro and in vivo, suppressing the influence of the drug-dependent expression of FasR, decrease of mRNA for FasL, and suppressing the influence on drug-induced apoptosis were also described. Until now, the use of cyclosporin A was described in about 20 patients with Lyell's and Stevens-Johnson syndromes. In the majority of cases, sudden suppression of active lesions and reepithelization were observed, and the survival rate was 95% [9].

Cyclosporin A concentration in the patient's blood serum was 0.435–0.692 μg/ml. In hitherto published reports on the use of cyclosporin A in Lyell's syndrome, the authors do not refer to the problem of drug serum concentration monitoring. This is probably caused by the very short period of treatment and lower doses used in dermatology as compared to transplantology.

This is the first case of atypical Stevens-Johnson syndrome with massive occupation of only the mucosa in which cyclosporin A was administered. Suppression of the disease's development and complete reepithelization, with minimal advese effects, were obtained.

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