CLINICAL REPORT

Severe Pneumonia Caused by Combined Infection with *Pneumocystis carinii*, Parainfluenza Virus Type 3, Cytomegalovirus and *Aspergillus fumigatus* in a Patient with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse cutaneous reactions to drugs. We report here the first case of severe pneumonia caused by an unusual combined infection with *Pneumocystis carinii (jiroveci)*, parainfluenza virus type 3, cytomegalovirus and *Aspergillus fumigatus* in a 63-year-old female patient with allopurinol-induced SJS/TEN overlap syndrome. Following treatment with high-dose systemic corticosteroids and intravenous immunoglobulin for SJS/TEN, her mucocutaneous lesions improved and she was due to be discharged. However, 15 days after cessation of corticosteroids, she developed pneumonia. Bronchoalveolar lavage revealed that the cause of infection was *Pneumocystis carinii (jiroveci)*, parainfluenza virus type 3, cytomegalovirus and *Aspergillus*. These findings indicate that patients with SJS/TEN, particularly those treated with systemic corticosteroids, may be susceptible to infection with combinations of pathological agents resulting from damage to the bronchial epithelia. *Key words: Stevens-Johnson syndrome; toxic epidermal necrolysis; corticosteroid; pneumonia; infection.*

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse cutaneous reactions, most commonly triggered by drugs (1). The pathology consists of immunologically mediated idiosyncratic reactions (2). Although there is a lack of consensus regarding whether SJS and TEN represent different severities of the same condition or separate disorders, they are distinguished mainly by severity and percentage of body surface involved. SJS is the less severe condition, in which skin sloughing is limited to less than 10% of the body surface. TEN involves sloughing of more than 30% of the body surface area, and SJS/TEN overlap syndrome describes patients with involvement of greater than 10%, but less than 30% of the body surface area (3).

Although withdrawal of the offending drug is critical, the optimal treatment approach is not yet known. Corticosteroids are generally recommended for SJS (4), and intravenous immunoglobulins (IVIGs) for TEN (5), although the use of corticosteroids is controversial and there have been no randomized controlled trials. Some data support the use of corticosteroids only in the early phase of the condition, because of their decreasing effect on epidermal loss (4, 6–8), but others disapprove of the use of corticosteroids because they lead to increased infection and gastrointestinal bleeding (9, 10).

We describe here a patient with SJS/TEN overlap syndrome who had been treated with systemic corticosteroids and IVIG, and who subsequently developed severe interstitial pneumonia caused by a combination of infectious agents after her skin lesions had improved.

CASE REPORT

A 63-year-old woman visited our allergy clinic with a mucocutaneous macular skin rash with bulla. She had a history of surgery and anti-tuberculosis treatment for intestinal tuberculosis 30 years previously, and she was a hepatitis C virus carrier. Three months earlier, she had an acute myocardial infarction and underwent percutaneous coronary intervention, followed by treatment with 100 mg/day aspirin. One month prior to coming to our clinic, she had been diagnosed with essential thrombocytosis and 14 days prior to coming to our clinic she was prescribed anagrelide 1 mg/day and allopurinol 200 mg/day by a haematologist. Seven days later, she developed an erythematous skin rash on both legs, which later spread throughout her body. She subsequently developed ocular, oral and genital mucosa erosions as well as slough of skin bulla on

approximately 20% of her body surface area, and the erosions were progressing. Seropurulent conjunctivitis was also present bilaterally (Fig. 1).

She appeared to be acutely ill, but her mental state was alert. Her initial vital signs were blood pressure 120/66 mmHg, heart rate 69 beats/min, respiration rate 18/min and body temperature 37.4°C. Laboratory results on admission revealed a white blood cell count (WBC) count of 10,200/mm³ (neutrophils 91%, lymphocytes 6 %); a platelet count of 160,000 /mm³; an erythrocyte sedimentation rate (ESR) of 26 mm/h; a serum C-reactive protein concentration of 10.4 mg/dl; serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations of 97 U/l and 107 U/l, respectively; a blood urea nitrogen (BUN) concentration of 28 mg/dl; a serum creatinine concentration of 1.4 mg/dl; serum sodium and potassium concentrations of 130 mEq/l and 5.5 mEq/l, respectively; a total protein serum concentration of 6.2 g/dl (normal 6–8 g/dl); and a serum albumin concentration of 3.4 g/dl (normal 3.3–5.2 g/dl). Urine analyses were normal.

We diagnosed the patient with SJS/TEN overlap syndrome induced by allopurinol, because her skin sloughing was approximately 20% of body surface area. She was administered systemic corticosteroid (180 mg/day intravenous (i.v.) methylprednisolone for 2 days, thereafter tapered slowly for 21 consecutive days; i.v. methylprednisolone 120 mg/day for 7 days, 80 mg/day for 2 days, 60 mg/day for 2 days, 30 mg/day for 5 days, 20 mg/day for 2 days and 10 mg/days for last 3

days) and IVIG (1 g/kg for 3 days), as well as supportive treatment, including massive skin dressing, wound care, total parenteral nutrition and adequate hydration. She was not administered prophylactic antibiotics. Her mucocutaneous lesions improved gradually, and she was due to be discharged.

On hospital day 38 (15 days after cessation of corticosteroids), she experienced fever (38.2°C), dry cough and dyspnoea. A chest X-ray and high-resolution computed tomography assessments showed multifocal patch consolidations with ground-glass opacity in both lungs (Fig. 2).

Owing to the rapid progression of her respiratory distress, she was endotracheally intubated and started on empirical antibiotics (imipenem, ciprofloxacin, vancomycin and trimethoprim/sulphamethoxazole) and transferred to the intensive care unit (ICU). The next day, she underwent bronchoalveolar lavage (BAL). Bronchoscopy showed diffuse hyperaemia and focal ulcers. After 48 h, her BAL fluid was positive for parainfluenza virus type 3 (PIV3) and *Pneumocystis carinii* (*jiroveci*) pneumonia (PCP) by direct antigen tests. Subsequent shell viral culture of the BAL fluid was positive for PIV3 and cytomegalovirus (CMV), and a fungus culture of the BAL fluid was positive for *Aspergillus fumigatus*. However, bacterial cultures of the BAL fluid were all negative, including for *Mycobacterium tuberculosis*. We diagnosed this patient as having interstitial pneumonia caused by combined infection with PCP, PIV3, CMV and *Aspergillus*. She was administered trimethoprim/

Fig. 1. Severe bullous mucocutaneous lesions on (A) the face and (B) extremities. (C) Exfoliated skin on the back. (D) Seropurulent conjunctivitis with pseudomembrane.

Fig. 2. (A) Chest X-ray on hospital day 1, showing scars caused by tuberculosis. (B) Chest X-ray and (C) high-resolution computed tomography on hospital day 38 showing multifocal patch consolidations with ground-glass opacity in both lungs.

sulphamethoxazole, voriconazole, ganciclovir and oral ribavirin.

She was subsequently treated with clindamycin and primaquine for 17 days (anti-PCP medication was changed from trimethoprim/sulphamethoxazole, because the consolidation of the lung on her chest X-ray was aggravated and a follow-up PCP assay (direct antigen test) in BAL fluid was still positive despite undergoing trimethoprim/sulphamethoxazole therapy for a week), oral ribavirin for 7 days, ganciclovir for 15 days, and voriconazole for 8 days. Serial BAL assays were negative for all organisms. She was improved and transferred to the general ward, although she still had ventilator-associated pneumonia caused by *Acinetobacter baumannii*. At present, she is undergoing respiratory rehabilitation treatment.

DISCUSSION

SJS/TEN is classically a clinical condition, thought to be due to a hypersensitivity complex affecting the skin and mucous membranes (11). SJS and TEN occur in patients of all ages, all races, and both sexes, with an incidence ranging from 0.4 to 1.2 per million and 1.2–6 per million person-years, respectively. Most cases of SJS/TEN are drug-induced, with fewer than 5% of patients reporting no drug use. In patients with no drug use, SJS/TEN is induced by chemicals, mycoplasma pneumonia, viral infections, and immunization. Drug-induced SJS/TEN typically begins 1–3 weeks after the initiation of therapy, but occurs more rapidly upon re-challenge (1). Antibiotics (sulphonamides), anti-epileptics (carbamazepine, phenobarbital) and non-steroidal anti-inflammatory drugs (piroxicam) were reported to be the leading causes of SJS/TEN (12), but a recent study reported that allopurinol is a more common cause of SJS/TEN than these drugs (13). Considering its frequency, allopurinol is a culprit drug in this patient.

Current theories regarding the immunological cause of SJS/TEN suggest that CD8+ cytotoxic T cells trigger keratinocyte apoptosis via perforin, granulysin and the interaction of CD95 (fas) with fas ligand, but our current understanding is far from complete (11).

Although withdrawal of the offending drug is critical, and supportive care is the main treatment of SJS/TEN, the optimal treatment approach is unclear (1). In

general, supportive treatments including massive skin dressing/wound care with sterile technique in a burn care unit, maintaining a warm temperature, no use of prophylactic antibiotics, total parenteral nutrition and adequate hydration are similar to those of burn victims, but there are some differences (14). At first, fluid replacement and nutritional support does not need to be as aggressive as for burns of the same extent, due to the smaller amount of wound exudation (15–17). Secondly, mucosal vulnerability is another factor for consideration in the care of SJS/TEN (which may be present in inhalation burn patients). Mucosal damage in the airways and gastrointestinal tract could induce life-threatening bleeding complications (such as haemoptysis or ulcer bleeding); therefore, coagulation factors and blood counts should be normalized within normal ranges, and the transfusion of red cells, platelets and plasma products should be considered when needed. Any manipulation, such as nasogastric tube insertion or laryngoscopy for endotracheal intubation, should be performed very carefully, with careful consideration of the risk of bleeding (14, 16). Finally, frequent ophthalmological intervention is required to prevent visual dysfunction in SJS/TEN (14).

Treatment with corticosteroids, although effective in most other acute inflammatory disorders, is not necessarily effective. Although other anti-inflammatory, immunosuppressive agents, such as cyclosporine, cyclophosphamide, thalidomide, and IVIG, have been administered to arrest the underlying immunological mechanisms promoting SJS/TEN, their efficacy has not been demonstrated in controlled clinical trials (11, 18). Consequently, treatment strategies usually depend on the clinical experience of each treating physician.

Although some studies have suggested an association between administration of systemic corticosteroids and increased morbidity and mortality, particularly in patients with TEN who have received corticosteroids for prolonged periods (9, 10), many reports support the use of corticosteroids. For example, acute treatment with high-dose corticosteroids (160–240 mg/day) has resulted in marked improvements in patients with SJS, without complications (4, 6, 7). Administration of an initial high dose until symptom improvement, followed by slow tapering (up to few months) has been reported to avoid the possibility of a relapse, which may be observed after early tapering (19). In addition, the use of initial pulse therapy (i.v. methylprednisolone, 20 mg/kg/day for 3 days) for SJS/TEN has been suggested (20).

A review of 30 articles published between 1976 and 2004 reporting the use of systemic corticosteroids in the care of patients with SJS/TEN suggested a brief short course (≤ 7 days) of high-dose systemic corticosteroids (e.g. 1–2 mg/kg i.v. methylprednisolone) for the acute care of patients with SJS/TEN. If corticosteroid withdrawal worsens the disease, however, these agents should

be re-administered immediately, and subsequently tapered (21).

IVIG has also been reported to be effective in patients with SJS and TEN. Its use was based on findings, that keratinocytes usually express the Fas-receptor CD95; antibodies in pooled human IVIG were shown to block the Fas-mediated necrosis of keratinocytes *in vitro*. Thus, upregulation of Fas-ligand expression on keratinocytes was thought to be the critical trigger for keratinocyte destruction in TEN. Administration of IVIG to 10 patients resulted in reduced mortality and a rapid healing time (22). A retrospective study in China reported that combination therapy with corticosteroids and IVIG tended to reduce the mortality rate compared with corticosteroid monotherapy (23).

Our patient was treated with both systemic corticosteroids and IVIG (1 g/kg for 3 days) during the early acute period of SJS/TEN. She was started on i.v. methylprednisolone 180 mg/day for 2 days, tapered slowly over the next 21 days (total treatment time 23 days). However, 15 days after cessation of the corticosteroids, she developed pneumonia caused by a combination of nosocomial pathogens.

The mortality rate of patients with SJS is less than 5%, whereas the mortality rate of patients with TEN is approximately 30%. The most common cause of death is sepsis induced by skin infections, particularly involving *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* (24). More extensive epidermal detachment, increased age, increased blood urea nitrogen concentration, and visceral involvement indicate a poorer prognosis. The prognosis does not seem to be affected by the type or dose of the responsible drug or the presence of HIV infection (1).

Bronchial injury, as demonstrated by fibreoptic bronchoscopy, has been reported to be associated with a poor prognosis in patients with TEN, and patients with bronchial injury have been found to develop bacterial pneumonia, atelectasis and pulmonary oedema. These pathogens are the same as those involved in cutaneous infections (*S. aureus* and/or *P. aeruginosa*) (25). The pathogens in our patient were quite different from those previously reported. PCP, PIV3, CMV and *Aspergillus* are common pathogens in immunocompromised hosts, especially those with impaired cellular immunity (26). It is likely that, in our patient, SJS/TEN-induced respiratory barrier disruption combined with corticosteroid-induced impairment of cell-mediated immunity contributed to the severe combined infection. Also, her other morbidities, including cardiovascular disease, essential thrombocytosis, and hepatitis C virus infection, may have contributed to these combined infections.

To our knowledge, our patient with SJS/TEN is the first in whom severe pneumonia was caused by this combination of unusual pathogens. Although pneumonia has been reported in other SJS/TEN patients, the responsible

pathogens were ordinary bacteria, especially *S. aureus* and/or *P. aeruginosa* (25).

Our findings highlight the importance, in patients with SJS/TEN, of considering that bronchial epithelial damage may increase the possibility of a combination of unusual infections, particularly in patients who are elderly and have other morbidities, or who are receiving systemic corticosteroids.

The authors declare no conflict of interest.

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