

CLINICAL REPORT

Legionnaires' Disease Associated with Macular Rash: Two Cases

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Legionnaires' disease is an acute bacterial infection, generally sustained by *Legionella pneumophila*, which involves primarily the lower respiratory tract, although it is often associated with multi-systemic extrapulmonary manifestations. Afflicted patients may sometimes have gastrointestinal symptoms, liver function abnormalities, renal failure or central nervous system complications, while cutaneous manifestations are very uncommon and may include erythematous, maculopapular or petechial skin lesions. Pathogenesis of skin involvement in the setting of Legionnaires' disease is still uncertain, but may involve toxic or immunological mechanisms. Two exceptional cases of *Legionella* pneumonia complicated by diffuse, macular rash in two adult women are described, in association with severe peripheral polyneuropathy and flaccid quadriplegia in one case. Key words: *Legionella pneumophila*; pneumonia; rash; macular lesions; urinary antigen test.

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Legionnaires' disease is an acute, pulmonary, potentially fatal infection caused by the gram-negative bacilli of the *Legionellaceae* family. Legionnaires' disease usually occurs as a severe pneumonia associated with multi-systemic extrapulmonary manifestations. However, patients with *Legionella* infection may have mild symptoms (such as fever, asthenia and muscle aches, known as Pontiac fever), or a completely silent illness.

Any species of the *Legionellaceae* family may cause this form of pneumonia in both normal and immunocompromised hosts, but the most frequently pathogenic species is *Legionella pneumophila*, which accounts for about 90% of all human infections. Ubiquitous in aquatic environments, the gram-negative *Legionella* organism is a facultative, intracellular parasite of freshwater protozoa, such as the amoebae. The prevailing mode of transmission is probably by direct inhalation of aerosols that come from a water source

(including air-conditioning cooling towers, water mains, showers and swimming-pools), contaminated with *Legionella* bacteria (1, 2).

Legionellosis may be diagnosed as an outbreak after persons have breathed mists that come from a water source contaminated by *Legionella*, but it often occurs as a single, isolated case not associated with any recognized cluster of cases (1–3).

People of any age may get Legionnaires' disease, but it most often affects middle-aged and older persons, particularly cigarette smokers. Patients with an impaired immune defence, especially when the deficiency involves the cell-mediated immunity (HIV infection, corticosteroid therapy, myeloma, acute or chronic lymphocytic leukaemia, lymphoma), may be at increased risk. Other associated conditions include solid malignancies, renal failure, alcoholism and diabetes (4, 5).

Extrapulmonary involvement is sometimes observed in subjects with legionellosis, including gastrointestinal symptoms (vomiting, diarrhoea), liver test alterations (elevated serum transaminase or bilirubin levels), renal failure (oliguria, proteinuria, haematuria, increased serum creatinine concentrations) or neurological disorders (encephalopathy, encephalitis, cranial nerve or peripheral paralysis). However, cutaneous manifestations are very rarely reported, and only six cases of skin rash complicating *Legionella* pneumonia have been described to date, to the best of our knowledge (3, 4, 6).

Two exceptional cases of diffuse, macular skin rash in two middle-aged women with Legionnaires' disease are described here.

CASE REPORTS

Case 1. A 48-year-old Caucasian woman was hospitalized owing to persisting hyperpyrexia, chills, asthenia, anorexia and dry cough for about 3 days, followed by a diffuse, erythematous, non-pruriginous rash involving chest, abdomen and limbs (Fig. 1).

Physical examination at the time of admission showed peripheral cyanosis, tachypnoea, dyspnoea and elevated body temperature (39°C). Pulmonary auscultation revealed a respiratory silence at the basis of the right lung and diffuse, bilateral rales at the upper lobes. Diffuse, rounded, red-coloured macular lesions, painless and not pruriginous, approximately 3–6 mm in



Fig. 1. Diffuse, erythematous, non-pruriginous rash involving chest, abdomen and limbs in Case 1.

diameter, were found on the chest, back, abdomen and legs. The laboratory work-up demonstrated severe hypoxia (arterial oxygen pressure, 48 mmHg; arterial oxygen saturation, 84%), with remarkable leukocytosis and neutrophilia (white blood cell count, 25740 mm^{-3} ; absolute neutrophil count, 24970 mm^{-3}), hyponatraemia (133 mEq l^{-1}), and increased plasma levels of transaminases (alanine aminotransferase, 56 U l^{-1}) and lactic dehydrogenase (664 U l^{-1}), in association with an elevated erythrocyte sedimentation rate (67 mm h^{-1}).

Chest X-ray and contrast-enhanced CT scan disclosed bilateral, diffuse, alveolar pulmonary infiltrates, associated with moderate pleural effusion at the right lung bases. Cultures of urine, sputum and broncho-alveolar lavage were negative, while blood cultures proved positive for *Staphylococcus aureus*. Sputum and broncho-alveolar lavage fluid were also cultured for *Legionella* on BCYE agar. A search for autoantibodies and serology for *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Chlamydia psittaci*, *C. pneumoniae*, *L. pneumophila* and human immunodeficiency virus (HIV) were negative.

Antimicrobial chemotherapy was immediately started with intravenous amoxicillin-clavulanate (2.2 g three times daily), ciprofloxacin (500 mg twice daily), in association with methylprednisolone (20 mg three times daily).

One week later, the antimicrobial regimen was changed owing to persisting hyperpyrexia and respiratory distress syndrome, and amoxicillin-clavulanate was replaced with intravenous imipenem (500 mg three times daily), while macular rash completely disappeared 2 days after the admission. At the same time, urinary

antigen testing (by immunoenzymatic assay) for *L. pneumophila* was requested.

Ten days after the admission, neurological examination showed a complete flaccid quadriplegia with areflexia and reduced sensation. Brain contrast-enhanced CT scan, electroencephalogram and cerebrospinal fluid examination did not show any significant abnormalities, while electromyography revealed a severe axonal sensorimotor polyneuropathy involving both arms and legs.

Eleven days after the hospitalization, the positive result of urinary antigen testing for *L. pneumophila* was received, and prompted administration of intravenous clarithromycin (500 mg twice daily), in association with imipenem and ciprofloxacin, for a further 28 days.

The patient became afebrile 2 days after the start of the latter antibiotic treatment. One week later, respiratory symptoms regressed and laboratory work-up did not show any abnormality, except for a persisting, moderate increase of erythrocyte sedimentation rate (38 mm h^{-1}). A chest X-ray revealed a remarkable reduction of pleural effusion and pulmonary infiltrates.

At the end of this 4-week antibiotic therapy, the chest X-ray disclosed a complete resolution of the pneumonia, the neurological symptoms had remarkably improved and serological tests for *L. pneumophila* (by indirect immunofluorescent assay) became positive, with a titre of 1:512.

Case 2. A 32-year-old Caucasian woman was hospitalized owing to intermittent fever, chills, asthenia, diarrhoea and dry cough for about 5 days.

Physical examination at the time of admission demonstrated tachypnoea, dyspnoea and elevated body temperature (38.2°C). Pulmonary auscultation revealed diffuse, bilateral rales at the upper lobes. The laboratory work-up demonstrated leukocytosis and neutrophilia (white blood cell count, 15650 mm^{-3} ; absolute neutrophil count, 13920 mm^{-3}), hyponatraemia (131 mEq l^{-1}) and increased plasma levels of transaminases (alanine aminotransferase, 48 U l^{-1}), in association with an elevated erythrocyte sedimentation rate (81 mm h^{-1}).

Chest X-ray disclosed bilateral, diffuse, alveolar pulmonary infiltrates. Culture of urine, sputum and broncho-alveolar lavage tested negative, as did several blood cultures. Sputum and broncho-alveolar lavage fluid were also cultured for *Legionella* on BCYE agar. A search for autoantibodies and serology for *M. pneumoniae*, *C. burnetii*, *C. psittaci*, *C. pneumoniae*, *L. pneumophila* and HIV, was negative.

Antimicrobial chemotherapy was immediately started with intravenous imipenem (1 g three times daily), teicoplanin (400 mg daily) and ciprofloxacin (500 mg twice daily), in association with methylprednisolone (20 mg twice daily).

Four days after the admission, widespread, erythematous, non-pruritic, rounding macular lesions,

4–6 mm in diameter, were observed on the chest and limb surfaces, and disappeared 24 h after their appearance. Skin rash did not seem to be related to a hypersensitivity reaction due to antimicrobial therapy, because of the absence of pruritus, normal plasma IgE level and eosinophil count.

Ten days later, the positive result of urinary antigen testing for *L. pneumophila* was received, and prompted substitution of intravenous imipenem and teicoplanin with clarithromycin (500 mg twice daily), in combination with ciprofloxacin, for a further 14 days.

The patient became afebrile and asymptomatic 3 days after the start of the latter antibiotic treatment. Two weeks later, laboratory work-up did not show any abnormality, and chest X-ray disclosed a complete resolution of the pneumonia; serological tests for *L. pneumophila* (by indirect immunofluorescent assay) became positive, with a titre of 1:1024.

DISCUSSION

Cutaneous involvement during Legionnaires' disease is very uncommon and, to the best of our knowledge, only six cases of skin rash associated with legionellosis have been reported previously: a woman with encephalopathy, lymphadenopathy and petechial rash during an outbreak of Legionnaires' disease in Port Elizabeth (7); a man with painful, non-pruritic, macular, erythematous rash limited to pretibial surfaces of both legs (8); two men with Pontiac fever and papular rash (9); and two men with macular rash and acute renal failure (10). Pathogenesis of cutaneous lesions during the course of legionellosis is still unknown: skin involvement may have been mediated by either a toxin elaborated by the organism, an immunological response of the host to the bacterium, or some other unidentified mechanism (9,10).

The most useful routine tests for diagnosis of Legionnaires' disease are urinary antigen detection and sputum or broncho-alveolar lavage culture. Serological studies performed by indirect immunofluorescent assay are also helpful for diagnosis when convalescent-phase antibody titres can be compared with acute-phase titres. However, they cannot be employed for clinical decision-making because of the low positive predictive value of commercially available acute-phase serological tests, and the slow antibody appearance. Therefore, failure of seroconversion is common for legionellosis, particularly when non-pneumophila species are involved, and seroconversion may also take much longer than 4 weeks (11, 12).

Macrolides and fluoroquinolones are currently considered the first choice drugs for the antimicrobial treatment of persons with Legionnaires' disease. Oral erythromycin, intravenous azithromycin, and oral or intravenous levofloxacin have been approved by the US

Food and Drug Administration as first-line antimicrobial therapy for this infection (13). However, clarithromycin and several fluoroquinolones (such as ciprofloxacin and moxifloxacin) are highly active against *Legionella* bacterium, and may provide an effective antibiotic treatment (14–16).

The actual skin lesions in our case were a widespread, non-pruritic, macular rash in both patients, associated with peripheral neuropathy in one case.

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