Redni broj članka: 813

ISSN 1331-2820 (Tisak)
ISSN 1848-7769 (Online)

A 76-year old man with Legionnaires' disease and rash: a case report

76-godišnji bolesnik s legionarskom bolesti i osipom: prikaz bolesnika

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Key words
Legionella pneumophila
petechial rash
pneumonia

Ključne riječi
Legionella pneumophila
petehijalni osip
pneumonija

Primljeno: 2017–04–14
Received: 2017–04–14
Prihvaćeno: 2017–06–15
Accepted: 2017–06–15

Case report

Legionella pneumophila is an important cause of atypical community – acquired pneumonia. Legionnaires' disease usually manifests with high-grade fever and nonproductive cough, while the presence of diarrhoea, neurologic symptoms, hyponatremia and failure to respond to beta-lactam antibiotics can provide clues to diagnosis of Legionnaires's disease. Cutaneous lesions in Legionnaires' disease are very rare – a rash associated with the clinical manifestation of Legionella infection was described and evaluated in 10 cases according to literature. Herein we present a 76-year-old patient treated at the University Hospital for Infectious Diseases in Zagreb, Croatia because of Legionnaires' disease and a petechial rash.

Prikaz bolesnika

Legionella pneumophila je važan uzročnik atipične domicilne pneumonije. Legionarska bolest najčešće se manifestira febrilitetom i suhim kašljem, a prisutnost dijareje, neuroloških manifestacija poput smetenosti, hiponatremije te neuspjeha terapije betalaktamskim antibioticima može uputiti na dijagnozu legionarske bolesti. Kožne manifestacije legionarske bolesti su izuzetno rijetke te je do sada opisano 10 takvih slučajeva u literaturi. U ovom smo radu prikazali 76-godišnjeg bolesnika s legionarskom bolesti koji je hospitaliziran u Klinici za infektivne bolesti zbog legionarske bolesti praćene petehijalnim osipom.

Introduction

Legionella species are one of the most common pathogens causing community-acquired pneumonia (CAP), accounting for approximately 4 percent of cases of CAP [1] in Europe. The *Legionella* spp. are small gram-negative bacilli with fastidious growth requirements, and while there are at least 60 different species of Legionella identified, *Legionella pneumophila*, particularly serogroup 1 is the causative agent for most disease cases. As legioneallae are usually connected to an aquatic environment, water is a major reservoir for this pathogen. Main sources of infection include either natural freshwater environments, or more commonly human-made water systems: plumbing of large buildings (consisting of water heaters, storage tanks, and pipes), humidifiers, air conditioning systems, cooling towers, decorative fountains, showers or hot tubs. Factors known to enhance colonization include warm temperatures (25 to 42 °C), stagnation, and scale and sediment. Legionella is transmitted via inhalation of aerosolized water containing the bacteria, and only a single episode of possible person-to-person transmission of Legionnaires' disease has been reported so far [2]. The systemic form of the disease including severe pneumonia and infection involving other systems is frequently termed Legionnaires' disease by its first identification in 1977 [3]. Cutaneous lesions in Legionnaires' disease are very rare – a rash associated with the clinical manifestation of *Legionella* infection was described and evaluated in 10 cases according to literature [4]. Herein we present a patient treated at the University Hospital for Infectious Diseases in Zagreb because of Legionnaires' disease and a petechial rash.

Clinical Presentation

A 76-year-old man was admitted to the University Hospital for Infectious Diseases in Zagreb, Croatia in October 2016 because of fever, rash and cough. Current illness had started seven days prior to admission with fever up to 39 °C with shaking chills. From the second day of illness the patient noticed diffuse rash on his lower legs which had spread to the hands, and on the fifth day of illness he noticed occasional dry cough and had few loose stools. He was prescribed with amoxicillin-clavulanic acid which he was taking for three days without improvement.

His past medical history was significant for hypertension, gastritis and anaemia. He had a melanoma operation 10 years ago (without metastases) and was treated for brucellosis 30 years ago. He was taking nebivolol for his hypertension. The patient was a smoker (50 packs/year) and reported moderate alcohol consumption (one glass of wine daily). He lived in Argentina, in rural area near Buenos Aires and worked as a veterinarian (cows, horses). He denied any sick contacts. He was travelling abroad on his vacation and arrived to Europe 14 days prior to his present illness. Prior to coming to Zagreb, he travelled through Italy, Slovenia, Adriatic coast and Bosnia and Herzegovina.

Table 1. Basic laboratory parameters on hospital admission
Tablica 1. Osnovni laboratorijski nalazi pri primitku u bolnicu

Laboratory findings on hospital admission/day 7 of the disease			Reference range
Complete Blood Count	Erythrocytes	4.35	4.43 - 5.88 x 10^{12}/L
	Haemoglobin	134	129-166 g/L
	Haematocrit	0.408	0.390 - 0.487 L/L
	MCV	93.8	76.5 - 92.1 fL
	Platelets	291	178-420 x10^{9}/L
Differential	White Blood Cells	31.7	4.4 - 11.6 x 10^{9}/L
	Neutrophils	94.3	34-69%
	Lymphocytes	2.2	19-52%
	Monocytes	0.6	5-13%
	Eozinophils	0.2	0-9%
	Basophils	2.7	0-3%
CRP	420.5		<5.0 mg/L
Biochemistry	Glucose	7.4	4.4-6.4 mmol/L
	Urea	15.9	2.8-8.3 mmol/L
	Creatinine	153	79-125 umol/L
Electrolytes	Sodium	140	137-146 mmol/L
	Potassium	3.7	3.9-5.1 mmol/L
	Chloride	96	97-108 mmol/L
Hepatogram	Bilirubin	20	3-20 umol/L
	AST	124	11-38 U/L
	ALT	96	12-48 U/L
	GGT	12	11-55 U/L
	LDH	624	<241 U/L
Coagulation parameters	Fibrinogen	7.6	1.8 – 3.5 g/L
	APPT	28.7	23-36 s
	D-dimers	4.41	<0.5 µg/mL
	PT	50%	<70%
Protein electrophoresis	Total protein	49	66-81 g/L
	Albumin	18 (37%)	39.5-58.6 g/L 59.8-72.4 %

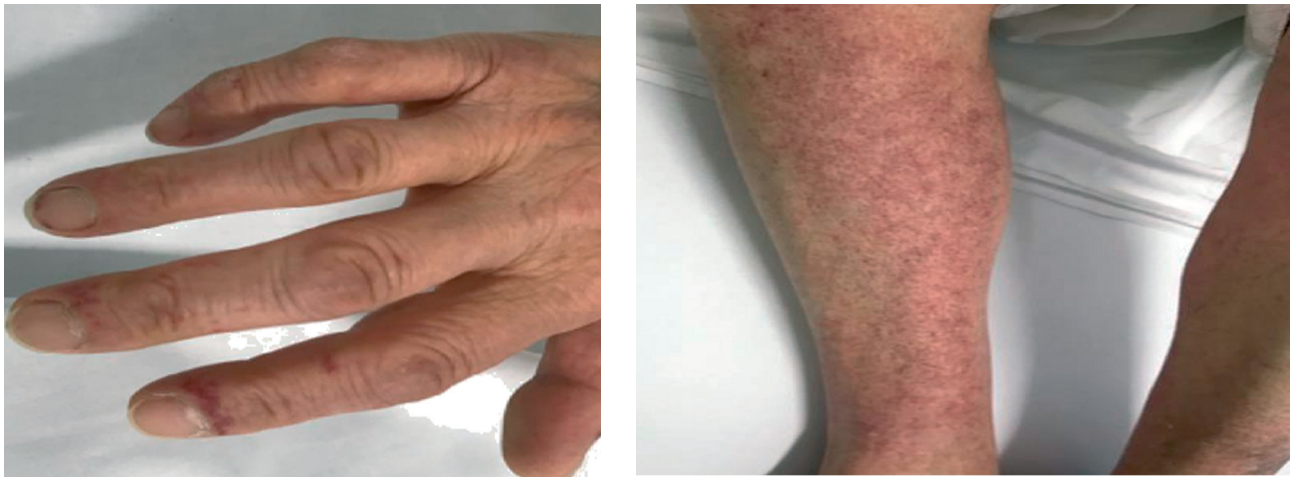

Figure 1. Petechial changes on the fingers and shins
Slika 1. Petehijalne promjene na prstima i potkoljenicama

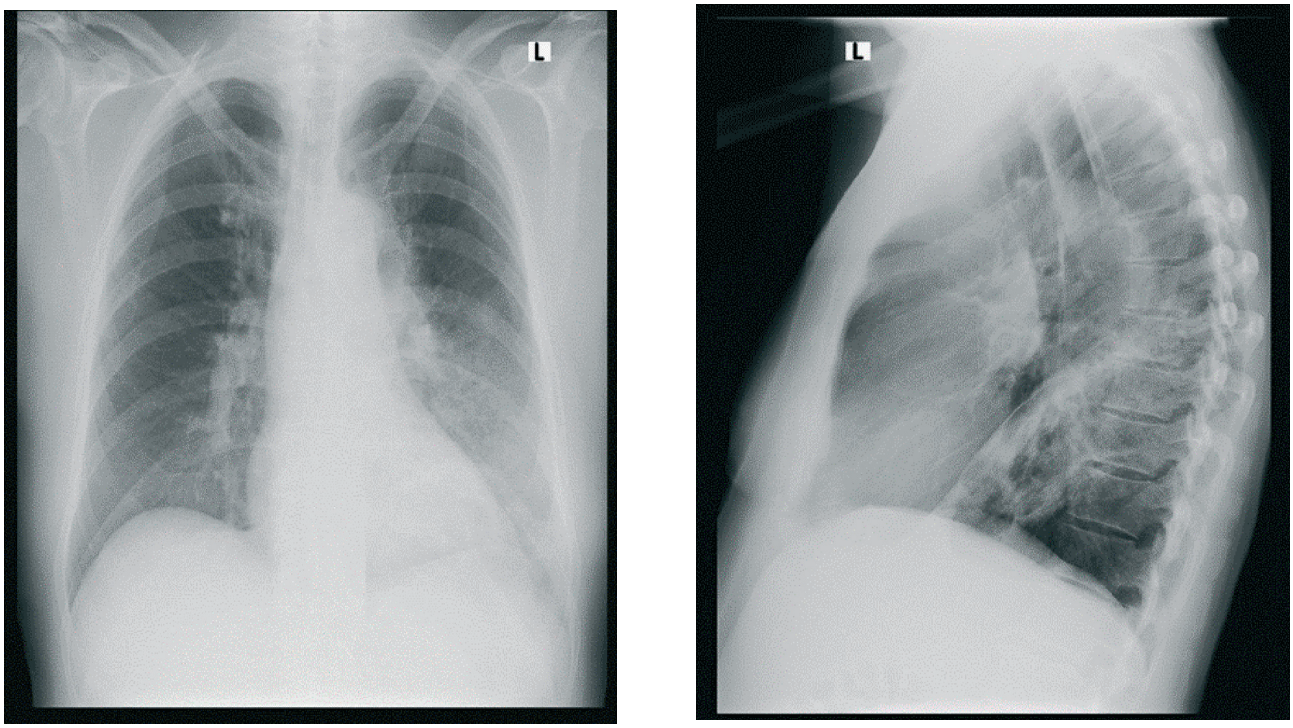

Figure 2. Chest X-ray on hospital admission. Large infiltrate in the left lower lung with incipient pleural effusion
Slika 2. Radiogram prsnog koša pri primitku u bolnicu. Veliki infiltrat donjeg lijevog pluća s manjim pleuralnim izljevom

He was seen in the emergency room of the University Hospital for Infectious Diseases on the seventh day of his present illness. On examination he was alert, oriented, dehydrated with malaise. His vital parameters were as follows: BP 110/75 mmHg, pulse 86/min, RR 26/min, O2 sat 93%, tympanic temperature 38.8 °C, GCS 15. Physical examination was significant for petechiae and ecchymoses on the nose, fingers on the arms and legs, and shins, and crackles were heard in the base of the left lung. Remainder of the physical examination was unremarkable.

Laboratory results taken after the examination are presented in Table 1, and his chest X-ray is presented in Figure 2 (alveolar infiltrate in the left lower lung with incipient pleural effusion).

The patient was admitted to hospital on the same day because of clinical suspicion of sepsis and bacterial pneu-

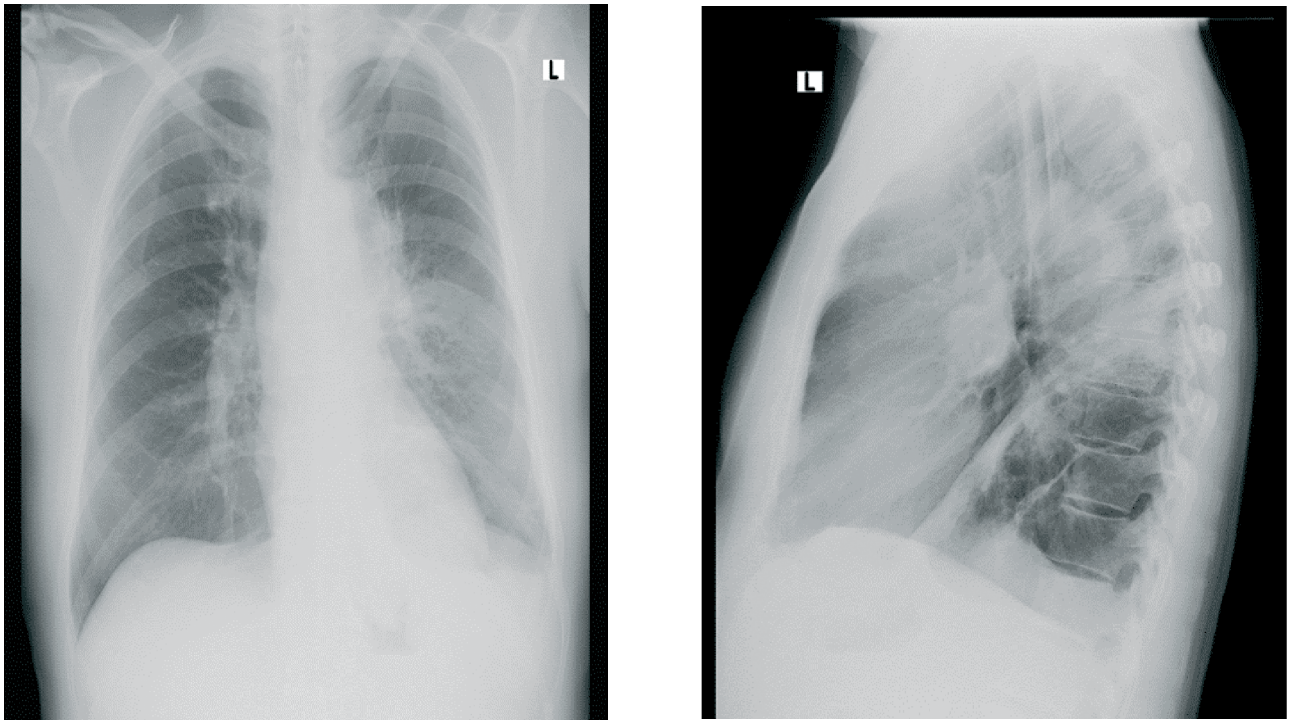

Figure 3. Chest X-ray after 10 days of treatment. Progression of the density of the left lobe infiltrate and a pleural effusion of the left lung base, measuring approx. 4.5 cm

Slika 3. Radiogram prsnog koša nakon 10 dana liječenja. Progresija gustoće infiltrata lijevog plućnog krila i pleuralni izljev lijeve plućne baze oko 4,5 cm

Table 2. Laboratory parameters on the 10th day of hospital treatment

Tablica 2. Laboratorijski parametri 10.-og dana bolničkog liječenja

Laboratory findings during hospitalization/day 16 of the disease			Reference range
Complete Blood Count	Erythrocytes	3.30	4.43 - 5.88 x 10^{12}/L
	Haemoglobin	101	129-166 g/L
	Haematocrit	0.408	0.390 - 0.487 L/L
	MCV	92.0	76.5 - 92.1 fL
	Platelets	396	178-420 x10^{9}/L
Differential	White Blood Cells	8.5	4.4 - 11.6 x 10^{9}/L
	Neutrophils	86.2	34-69%
	Lymphocytes	6.0	19-52%
	Monocytes	6.8	5-13%
	Eozinophils	0.5	0-9%
	Basophils	0.5	0-3%
CRP	96		<5.0 mg/L
Biochemistry	Glucose	4.6	4.4-6.4 mmol/L
	Urea	3.4	2.8-8.3 mmol/L
	Creatinine	90	79-125 umol/L
Electrolytes	Sodium	144	137-146 mmol/L
	Potassium	3.4	3.9-5.1 mmol/L
	Chloride	106	97-108 mmol/L

monia. Additional samples were taken for blood culture, urine culture, *Legionella pneumophila* serogroup 1 urinary antigen. He was started on empiric antimicrobial therapy with parenteral piperacillin-tazobactam and azithromycin, together with symptomatic therapy (fluids and oxygen supplementation). On the second day of hospital stay the results of *Legionella pneumophila* serogroup 1 urinary antigen came positive and antimicrobial therapy was continued with azithromycin; therapy with piperacilin-tazobactam was changed to ceftriaxone which was continued until blood culture results came out negative. Hospital stay was complicated with parapneumonic pleural effusion (Figure 3) which was treated conservatively and post-antimicrobial diarrhoea that was treated with vancomycin. The patient was febrile during the first five days, the rash slowly regressed during the first week of hospitalization. Follow-up laboratory results are shown in Table 2. The patient was discharged after ten days of hospitalization and he was feeling well two months after the discharge.

Discussion

The pathogenesis of Legionnaires' disease is one of an intracellular infection – the organisms which reach the alveoli, after escaping the mucociliary clearance in the upper respiratory tract, multiply within the macrophages and later on infect other macrophages following the cell rupture. Legionella causes an intense alveolitis leading to different anatomical structure involvement such as lobar pneumonia, focal lobar pneumonia, bronchopneumonia, confluent bronchopneumonia, and lobular pneumonia [5]. As the organism can spread to affect other organ systems, there are multiple nonspecific symptoms at the beginning of disease – involving mostly fever, fatigue, headache, diarrhea, confusion, and lethargy [6] which, along with the absence of early radiological findings and the lack of symptoms present with the typical bacterial pneumonia, have traditionally classified legionellosis as an atypical pneumonia. The mortality rate in Legionnaire's disease varies from approximately 1 – 10 % [7] depending on the underlying host risk factors such as older age, tobacco and alcohol consumption, immunosuppression or presence of chronic comorbidities [7], but also on the delay of the appropriate antibiotic initiation and in-hospital acquisition [8].

Thus far, there have been 10 cases of cutaneous manifestations during legionella infection described in the literature [4] to the best of our knowledge. Skin involvement in Legionnaires' disease appears to have occurred either as immediate toxin-related rash or as a part of a host's immune response to the organism [4, 9]. In those cases rash was described as diffuse maculopapular (2 cases), petechial (1 case), a painful, non-pruritic, macular, erythematous rash limited to pretibial surfaces of both legs (1 case), a maculopapular rash with secondary hemorrhage in an immunosuppressed man (1 case), macular rash (2 cases), a pediatric case with erythema multiforme, a pruritic rash (1 case) and a case of an extensive purpura fulminans (1 case). In the last case report [4] the authors found fibrin thrombi in the superficial and larger mid-dermal vessels with fibrinoid degeneration of vessel walls suggesting disseminated intravascular coagulation (DIC) as the underlying pathophysiology of the purpura. The connection of legionella and blood clotting disturbances are also uncommon, but well-documented in previous case reports [10] including at least 9 cases of DIC associated with legionella infection, one of which required an endotoxin-eliminating therapy and continuous hemofiltration [11] for a successful treatment of critical shock. None of the above mentioned cases of DIC with legionellosis had a cutaneous presentation, apart from the patient described to have purpura fulminans along with severe pneumonia caused by Legionella and the elements of DIC (initial thrombocytopenia, elevated fibrin split products and decreased fibrinogen levels)[4].

The proposition of the pathogenesis of these events suggest that an initial response to circulating *Legionella* endotoxins may appear as a maculopapular rash which later in the course of the disease may become purpuric due to uncontrolled endotoxin-mediated development of DIC. The occurrence of skin manifestations regarding the course of the disease remains yet unclear, although 4 of 10 reported cases (40 %) with rash were associated with fatal outcome of Legionnaires' disease and its complications.

Our patient also had presented with a petechial form of the rash and peripheral ecchymoses but there were no apparent signs of DIC as thrombocyte count and fibrinogen levels were normal, however there were elevated fibrin split products and PT was prolonged at time of presentation which subsequently normalized. As the patient refused skin biopsy and due to the resolving trend of the rash within the first week of treatment, we could assume agreed the rash in this case was most probably endotoxin-mediated in the setting of severe pneumonia caused by *Legionella pneumophila*.

Conclusion

As the symptoms of the Legionnaires' disease in the early phase remain rather nonspecific, and the delay in appropriate antimicrobial initiation contributes to higher mortality risk, *Legionella* is an important community-acquired pathogen to be included in the differential diagnostic work-up of patients with community-acquired pneumonia. Cutaneous manifestations, as rare as they seem to appear in this setting, may contribute to further diagnostic delay and also may correlate with higher mortality.

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