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Case report

Rash, disseminated intravascular coagulation and legionella: Episode 10 and a rewind into the past

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A B S T R A C T

Legionella pneumophila is the most common cause of legionellosis and is one of the organisms causing atypical pneumonia. We report the presentation of disseminated intravascular coagulation (DIC) and skin rash in a single case of severe *Legionella pneumonia*. The unique clinical presentation of a diffuse rash diagnosed as purpura fulminans and the unpredictable variations encountered during the diagnostic work-up of the case make this write-up crucial. This article synthesizes all reported cases of *L. pneumonia* associated with cutaneous manifestations as well as cases presenting with DIC. Furthermore, this manuscript illustrates the correlation between cutaneous and coagulopathic manifestations, and morbidity and mortality from *L. pneumonia*.

Introduction

Cutaneous manifestations in Legionellosis are very uncommon. They may present as maculopapular, erythematous, or petechial skin lesions [1]. About 9 cases thus far have been reported describing a rash associated with Legionella infection. A clear mechanism for the rash was not evident in the majority of them. Another uncommon, but well-described phenomenon associated with *Legionella pneumophila* and *Legionella longbeachae*, is disseminated intravascular coagulation (DIC) [2]. Legionella urine antigen testing is the main diagnostic test utilized to detect *L. pneumophila*. However, it has about a 25–30% false negative rate [3]; awareness about this is lacking and a failure to cover for organisms like legionella early during the illness may lead to uncontrolled endotoxin-related phenomena such as DIC. We hereby elucidate a complicated case of *L. pneumophila* accompanied by a clinically visible rash as well as coagulopathy culminating in respiratory failure and shock. We have also extracted data from various reference sources including PUBMED, EMBASE, MEDLINE and Ovid, to provide a consolidated view of all reported cases of legionella associated with cutaneous manifestations and DIC.

Case presentation

A 44-year-old male with a past medical history of hyperlipidemia was brought to the ER with a one-week history of cough, body aches, fever, fatigue and a red maculopapular rash on the inner thighs. At presentation, he was in respiratory failure, underwent emergent endotracheal intubation and mechanical ventilation and was admitted to the medical ICU. Initial chest X-ray and CT scan revealed right middle and lower lobe pneumonia (See Figs. 1 and 2). Labs tests showed leukopenia (WBC 1.6x10E+09/L) and thrombocytopenia (platelet count 94,000). He was started on broad-spectrum antibiotics including vancomycin, ciprofloxacin, metronidazole, and doxycycline. Twenty-four hours into hospitalization, the patient's rash became more confluent, with dark necrotic-appearing areas (see Fig. 3), and spread to involve the arms, legs, trunk, tip of the nose and left ear along with acral cyanosis. Due to concern for infective endocarditis, a trans-thoracic echocardiogram was performed that was reported as negative for any vegetation. Serological testing including viral studies, Lyme antibody (Ab), and Rickettsia Ab were negative. Routine blood, urine, and sputum cultures were also negative. Although the initial Legionella urinary antigen testing was reported negative, subsequent repeat analysis in the ICU was positive. In the ICU, the initial serology titers for legionella serogroup 1 were positive at 1:64 and subsequently 1:1024 during the first week. His antibiotics were then adjusted to include ceftriaxone, doxycycline, and moxifloxacin. Simultaneously, work-up for his rash was undertaken and a biopsy was

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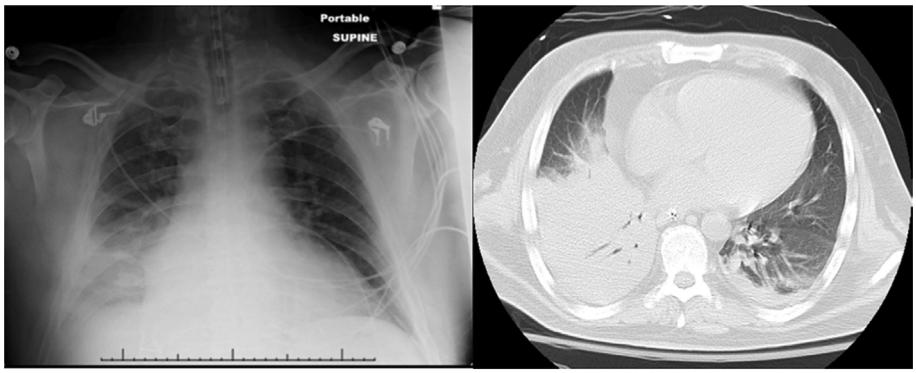

Fig. 1. ICU admission chest X-ray: consolidation at right base; perihilar pulmonary congestion. CT chest: right middle lobe and right lower lobe pneumonia.

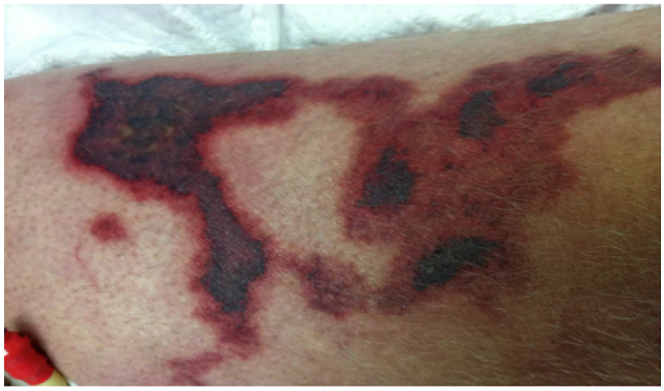

Fig. 2. Image of skin findings: diffuse maculopapular rash with dark necrotic-appearing areas.

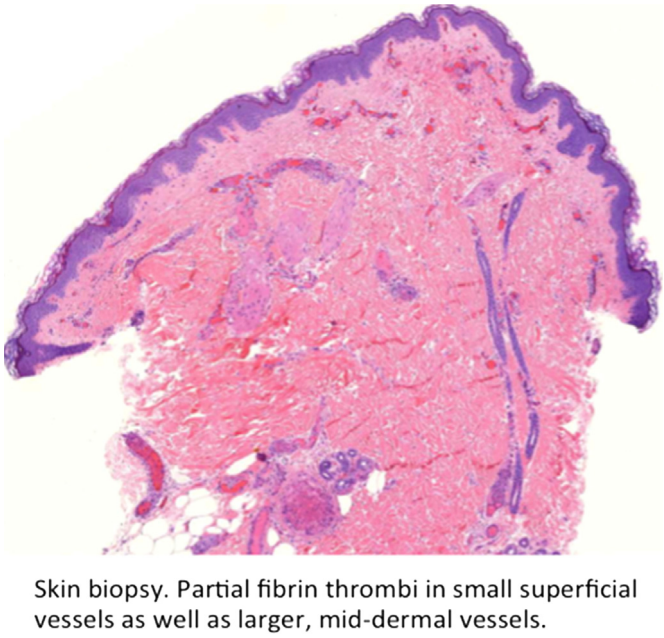

Fig. 3. Skin biopsy histopathology: partial fibrin thrombi in small, superficial vessels as wells as larger mid-dermal vessels.

obtained from his right thigh. Histopathology revealed partial fibrin thrombi in small, superficial vessels as well as larger mid-dermal vessels and fibrinoid degeneration of the vessel walls, overall consistent with a coagulopathy (see Fig 4). The differential diagnosis included DIC, thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT), and anti-phospholipid antibody syndrome. Subsequent work-up revealed a negative HIT panel. Thrombocytopenia with a normal creatinine was not consistent with TTP. He was finally diagnosed with DIC secondary to *Legionella pneumonia* based on elevated fibrin split products (FDP) and decreased fibrinogen levels. Under appropriate antibiotic coverage, his clinical status improved. The diffuse rash cleared, and the leukopenia as well as thrombocytopenia resolved. He was extubated later during the ICU course and was discharged home within 2 weeks.

Discussion

Legionnaire's disease was discovered in 1976 after an outbreak of pneumonia at an American Legion convention in Philadelphia. The causative organism was later isolated as *L. pneumophila*, an aerobic gram-negative rod. Legionellosis comprises of two syndromes, Legionnaire's disease and Pontiac fever. Legionnaire's disease refers to severe pneumonia that can be associated with multi-system disease [4]. Pontiac fever is an acute, self-limited, febrile illness sparing the lungs. About 64 serogroups of *L. pneumophila* have been identified but serogroup 1 is responsible for 70–90 percent of cases. It is transmitted by the aspiration of water contaminated with Legionella and not by person-to-person contact. This can originate from humidifiers, air conditioning, showers, respiratory therapy equipment, etc. Normally, mucociliary action helps clear Legionella in the upper respiratory tract. Organisms that reach the alveoli are consumed by macrophages, multiply within these cells until rupture, and then infect other macrophages. Legionella causes an acute fibropurulent pneumonia with alveolitis and bronchiolitis [5]. It can later affect other organs of the body like the kidneys, liver, brain, and spleen. Symptoms are non-specific including fever, fatigue, headache, confusion, and lethargy [6]. The causative organism, clinic-radiological dissociation, absence of lobar pneumonia in the early phase and paucity of symptoms seen in bacterial pneumonias make it definable as an atypical pneumonia. The mortality rate in Legionnaire's disease is 5–80% depending on certain risk factors like age, underlying

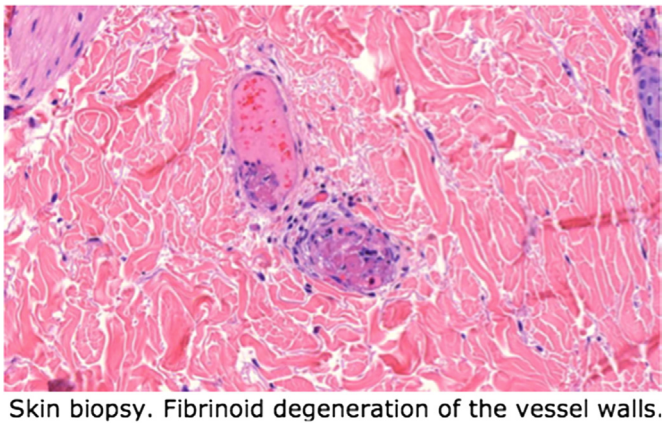

Fig. 4. Skin biopsy histopathology: fibrinoid degeneration of the vessel walls.

chronic disease, nosocomial infection, and time of initiation of therapy. Treatment should be initiated within eight hours or mortality increases [7]. Thus, early clinical suspicion is important.

Cutaneous manifestations including maculopapular, erythematous, or petechial skin lesions have been reported in about 9 cases of Legionella infection: 2 women with diffuse maculopapular rash who presented with fever, chills, asthenia and dry cough [1]; a man with encephalopathy, lymphadenopathy and petechial rash during an outbreak of Legionnaires' disease in Port Elizabeth [8]; a man with painful, non-pruritic, macular, erythematous rash limited to pretibial surfaces of both legs [9]; an immunosuppressed man with a maculopapular rash with secondary hemorrhage [10]; two men with macular rash and acute renal failure [11]; a pediatric case with erythema multiforme [12] and a 65 yr old man with a pruritic rash who signed out against medical advice and was brought back to the hospital in a critical condition before dying [13]. See Table 1. Our case represents extensive skin involvement associated with severe Legionella infection. The rash was maculopapular and limited to the inner thighs initially but later spread to other parts of the body with cyanosis of the toes; the rash was described as “purpura fulminans”. The preceding case reports have pointed out that the pathogenesis of the skin involvement may be directly related to a toxin released by the organism or related to an immune response of the host to the organism. [1] [8–13], On the other hand, the rash described in this case had an initial maculopapular phase followed by a purpuric picture. The biopsy finding of partial fibrin thrombi in superficial vessels as well as larger mid-dermal vessels and fibrinoid degeneration of the vessel walls suggests DIC as the underlying pathophysiology behind the purpuric phase of the rash. It may be reasonable to think that the maculopapular rash may be an early manifestation of circulating legionella endotoxins, which when goes uncontrolled becomes purpuric due to concomitant endotoxin-related DIC. Calza et al. mention two men with Pontiac fever as having had a papular rash referring to a report from Spitalny et al. Review of literature suggests that those 2 cases of Pontiac fever were recorded alongside 72 reports of whirlpool spa-related pseudomonal illness with rash, but were not associated with rash themselves [14,15].

An uncommon, but well-described phenomenon associated with *L. pneumophila* and also a few other species under the genus Legionella including *L. longbeachae*, is disseminated intravascular coagulation (DIC). There are at least 9 case reports of DIC in legionella infection. See Table 2. All of them except for one were subclinical in the sense that there were no bleeding or clotting manifestations seen alongside the abnormal DIC panel including platelet count, fibrin split products, and fibrinogen levels. See Table 2. The case described above is the first of reports to have shown clinical evidence of DIC as skin rash. Miragliotta et al. studied and demonstrated the in vitro effect of various members of the genus Legionella including *L. longbeachae* on human peripheral mononuclear cells. All the strains tested induced the generation of strong procoagulant activity (tissue factor) when incubated for an extended period of time with pure mononuclear cell suspensions. The production of mononuclear cell procoagulant activity was also observed after the addition of bacteria to citrated whole blood. It was found that *Escherichia coli* 0111:B4 showed comparable effects, but *Staphylococcus aureus* was much less effective. These results indicate that the presence of an endotoxin-like substance in the external cell wall of legionellae could contribute to the induction of mononuclear cells [16]. In an article by Matsubara et al., a severe case of *Legionella micdadei* was accompanied by the presence of DIC. The team of physicians applied endotoxin-eliminating therapy using a polymyxin-B-column (PMX) and continuous hemofiltration (CHF). The patient recovered from critical shock after the start of PMX, which together with continuous hemofiltration alleviated his systemic complications. Although the exact nature of the molecules/agents responsible for fatal systemic complications in Legionnare's disease are not well documented, these findings suggested that some substances removable by PMX and CHF might play an important role in pathogenesis [17]. A case described by Takayanagi et al. was unique from the fact that legionella co-infection with influenza virus was associated with DIC [18]. It appears that only one of the above case reports with DIC (Oldenburger) had bleeding manifestations in the form of post-thoracotomy bleeding [19]. None of the cases with DIC had cutaneous manifestations nor did the ones with rash have DIC in the clinical course.

The clinical importance of cutaneous manifestations and its relevance to morbidity and mortality from legionella pneumonia is yet to be determined. Analysis of the above reported cases showed that 4 of 10 cases (40%) with rash were associated with mortality from *L. pneumonia* and its complications. Until more clarity is gained with regard to the ability to predict who gets DIC associated with legionellosis, it is important to monitor CBC during the first few days of illness to look for subclinical thrombocytopenia followed by coagulopathy profile and DIC panel later as directed by the clinical course. Skin biopsy for the rash associated with legionellosis may prove beneficial so as to help with the etiology.

As indicated above, about 80% of cases are from *L. pneumophila* serogroup 1. The 20% false negative rate that is seen with urinary legionella antigen testing stems from the above fact and this calls for empiric coverage despite a negative test. The fact that legionella urine antigen positivity can remain for days after initiating broad-spectrum antibiotics makes it handy in patients who receive empiric anti-Legionella therapy. Furthermore, it takes only an hour for the urine antigen result to arrive [25]. Cost-effectiveness of urine legionella antigen testing in a public health perspective remains to be shown compared to costs related to morbidity and mortality associated with poorly controlled legionella infection [26]. However, nipping the evil in the bud helps.

Conclusion

A false negative urine legionella antigen test is not uncommon. Therefore, empirical anti-legionella therapy should be continued pending repeat urinary antigen tests and/or serum legionella titers due to the increased mortality seen with delay in initiation of such therapy. Cutaneous involvement with Legionellosis is uncommon and may present in various forms and may be complicated by hemorrhage or the presence of purpura fulminans. The presence of rash in the appropriate setting of laboratory abnormalities

Table 1
Legionella and skin manifestations. ULA – urine legionella antigen test, SLT – serum legionella titers.

Author	Age/sex/ race/place	Pulmonary involvement	Extra-pulmonary involvement	Rash type	Proposed theory	Biopsy	Resolved before or after anti-legionella antibiotic	Mortality	Testing
Calza [1]	48/F/C/Italy	Bilateral diffuse infiltrates; effusions	Flaccid quadriplegia and hyponatremia	Diffuse, rounded, red macular rash, painless, non- pruritic, 3–6 mm, trunk and extremities. Appeared Day 4. Resolved Day 6.	Toxin-related or immunological phenomenon.	–	Before	No	ULA- Day 11. SLT 1:512 – week 4
Calza [1]	32/F/C/Italy	Bilateral diffuse infiltrates; effusions	Hyponatremia	Red, non-pruritic, round, macular lesions, Trunk and extremities. 4–6 mm in diameter. Appeared Day 9 Resolved day 10.	Toxin-related or immunological phenomenon	–	Before	No	ULA- Day 10 SLT 1: 1024 – week 4
Ziemer [10]	64/M/C/Germany	Bilateral lobular pneumonia	Cholecystitis	Rapidly extending macular and maculopapular, livid, partially haemorrhagic exanthem with a target-like appearance – trunk, head and neck, late spread to limbs. Focal blisters. Time frame- not reported	Viral exanthema or bacterial antigen associated inflammatory reaction.	Normal epidermis focal parakeratosis. Oedematous papillar dermis; subepidermal blister formation.; Sparse perivascular lymphocytic infiltrate with haemorrhage	No resolution; death	Yes	ELISA IgM >300 U/ml (range:<120)
Helms [9]	46/M/-/Iowa	Bilateral nodular infiltrates progressed to consolidation	–	Bilateral pretibial skin erythematous rash; painful to touch, Non-pruritic. Appeared Day 5 Resolved Day 11	Legionella or TATLOCK bacterium- associated pretibial rash.	–	After	No	SLT Day 6 1:128 and Day 19 > 1:2048
Randall [8]	38/M/-/S.Africa	None	Altered mentation, lymphadenopathy, Slight neck rigidity	Petechial rash all over body and palate.	Unsure etiology	–	After	No	SLT Day 16 1:256
Allen [11]	67/M/-/Kansas	Bilateral pulmonary infiltrates	Acute renal failure and secondary pyelonephritis due to unclear etiology.	Diffuse, erythematous, maculopapular rash developed- trunk and extremities.	Toxin or immunological response	Marked edema, recent hemorrhage, increased mast cells, lymphocytes, and histiocytes, but rare eosinophils and polymorphonuclear leukocytes.	After	Yes	Sputum- Direct Fluorescence antibody staining microscopy and culture
Allen [11]	69/M/-/Kansas	Right lower lobe infiltrate	Acute renal failure with acute tubular necrosis and hepatic failure	Diffuse, erythematous, maculopapular rash developed- trunk and extremities.	Toxin or immunological response	Focal mild chronic inflammation, edema, and recent hemorrhage. No evidence of eosinophilic infiltrate.	Resolution not reported; death.	Yes	Sputum- Direct Fluorescence antibody staining microscopy and culture
Andersen [12]	3/M/-/Norway	Bilateral patchy infiltrates.	Gastrointestinal symptoms and encephalopathy	Erythema multiforme Appeared Day 16 Resolved Day 25	Bacterial or viral exanthem	–	Antibiotic completed before rash appeared;	No	SLT- 1: 256 in week 4. IgM detected on admission.
Meyer [13]	62/M/-/ Los Angeles	Right middle lobe progressing to bilateral infiltrates.	None	Pruritic rash	Related to antibiotic administration or related to legionellosis.	Not reported	Not reported	Yes	Sputum gram stain

Table 2
Legionella and disseminated intravascular coagulation. Abbreviations: IFA – indirect fluorescent antibody test, ULA – urine legionella antigen, BAL – bronchoalveolar lavage, SLT – serum legionella titers, ECMO – extracorporeal membrane oxygenation.

Author	Age/sex/Race/Place	Microorganism	Pulmonary involvement	Extra-pulmonary involvement	DIC	Anti-legionella antibiotic use and resolution of DIC.	Other life-sustaining measures	Mortality	Testing
Olden-burger [19]	55/M/-/N.Dakota	*L. pneumophila* + *M. pneumoniae*	Right lower lobe, Left upper lobe and lingular consolidation	Vomiting, diarrhea	Post-thoracotomy bleeding; DIC panel positive	Condition worsened despite initiating on day 30.	Mechanical ventilation	Yes	Indirect fluorescence antibody (IFA) test 1:1024 on day 30
Yamauchi [21]	56/F/-/Japan	*L. pneumophila*	Pleural effusion and obscure pneumonic shadow with right basal crackles	Acute myocardial infarction, shock, hepato-splenomegaly.	DIC panel positive; no other clinical manifestation	Dramatic improvement after antibiotic transition	Vasopressors.	No	SLT 1:128 week 2. (clinical signs strongly suggestive of legionellosis).
Matsubara [17]	42/M/-/Japan	*L. micdadei*	Bilateral consolidation	Septic shock	DIC reported without other specifics	Worsened despite macrolides.	Vasopressors. Polymyxin-B column; Continuous hemofiltration.	No	SLT positive- titers not specified.
Gregory [23]	35/M/-/Tennessee	*L. pneumophila*	Right lower lobe infiltrate to panlobar.	Acute kidney injury, cardiac arrest	DIC panel positive; no hemorrhagic manifestation	Infiltrates cleared with antibiotic transition; resolution of DIC not reported.	Mechanical ventilation and hemodialysis.	Yes	IFA test with titers from 1:128 during week 2 to 1:1024.
Gregory [23]	65/M/-/Tennessee	*L. pneumophila*	Right upper lobe consolidation.	Encephalopathy	DIC panel positive; no hemorrhagic manifestation	Improved with extensive empiric antibiotic coverage	–	No	IFA test with titers from 1:32 to 1:1024 during convalescence.
Takayanagi [18]	–/–/–/–	*L. pneumophila*	Infiltrates complicated by aspergillus bronchitis.	Acute renal failure	DIC reported.	- (Japanese script)	–	–	–
McKinney [20]	66/M/-/Mexican cruise-California	*L. longbeachae*	Left lower lobe infiltrate progressed to bilateral infiltrates.	Heart block, cardiac arrest resuscitated.	DIC panel positive.	Improved after transition of antibiotics.	Mechanical ventilation	No	CYE agar culture grew legionella-like organism named as *L. longbeachae* thereafter.
Saijo [24]	56/M/-/Japan	*L. pneumophila*	Left multi-lobar consolidation	Acute liver and kidney injury, rhabdomyolysis.	DIC panel positive.	Improved after appropriate antibiotic.	Mechanical ventilation	No	ULA positive. BAL culture positive for serogroup 1.
Kassha [22]	58/F/C/United Kingdom	*L. pneumophila*	Bilateral infiltrates progressed to ARDS	Septic shock, Acute kidney injury	DIC reported without other specifics.	Empiric macrolide helped with steady improvement.	Mechanical ventilation, RRT, ECMO.	No	ULA and sputum microscopic exam- day 7.

suggestive of coagulopathy and worsening clinical status should raise suspicion for DIC. Few cases have been able to convincingly describe the pathogenesis of cutaneous manifestations in legionellosis. The above case may well be amongst the first few to report one. Further research may throw light on the implications of cutaneous phenomena on the clinical course of legionellosis and the factors predicting the development of DIC with legionellosis.

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