Secondary cutaneous leukocytoclastic vasculitis associated with Mycoplasma pneumoniae: a case report and literature review

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ABSTRACT

Background: *Mycoplasma pneumoniae* (*M. pneumoniae*) is one of the most common causes of atypical pneumonia in pediatric and adult populations worldwide. It can also affect many other organs including neurological, cardiac, hematologic, gastrointestinal, renal, osteoarticular, ocular, and cutaneous involvement. *Mycoplasma pneumoniae*-related cutaneous vasculitis is an infrequent manifestation. Several cases of secondary cutaneous leukocytoclastic vasculitis (LCV) associated with *M. pneumoniae* have been publicly reported in both English and foreign languages.

Case Presentation: This report details the case of a 44-year-old Thai male presented with high-grade fever accompanied by generalized erythematous papules, patches, and some pustules for 3 days with no chest symptoms. He was treated with ceftriaxone, doxycycline, and clindamycin for 5 days without clinical improvement. However, histopathological and direct immunofluorescence tests later confirmed a diagnosis of LCV. Serological tests showed positivity for *M. pneumoniae*. The regimen was then changed to azithromycin 500 mg daily for 5 days and the lesions showed remarked improvement without scarring.

Conclusion: The importance of recognizing and addressing the atypical presentations of *M. pneumoniae* in febrile patients with cutaneous vasculitis is imperative to guide targeted treatment decisions, thus facilitating rapid clinical improvement.

Keywords: Case report, *M. pneumoniae*-associated vasculitis, cutaneous leukocytoclastic vasculitis, *Mycoplasma pneumoniae* infection, atypical bacterial infection, secondary vasculitis, extrapulmonary manifestations.

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Background

Mycoplasma pneumoniae is a type of bacterial pathogen whose primary manifestation is typically respiratory symptoms. It can also affect almost many other organs or systems [1]. Extrapulmonary manifestations include neurological, cardiac, hematologic, gastrointestinal, renal, osteoarticular, ocular, and cutaneous involvement. However, cutaneous vasculitis is very rare and has been reported in some cases. This report presents a 44-year-old male affected with leukocytoclastic vasculitis (LCV) due to *M. pneumoniae* infection without pulmonary manifestation.

Case Presentation

A 44-year-old Thai man came to the outpatient clinic with a chief complaint of a 3-day history of high-grade fever accompanied by generalized erythematous papules and patches on trunk, back, and all extremities. He developed deteriorating myalgia and subsequently began taking ibuprofen 400 mg three times a day after the appearance of rashes, without improvement. The patient has a preexisting medical condition of hemoglobin (Hb) H disease and is currently taking folic acid supplements. He has not had cough, dyspnea, photosensitivity rashes, alopecia, prolonged fever, or arthralgia.

On physical examination, he had a temperature of 39.5°C, with generalized erythematous papules and patches with some non-blanchable painful erythematous patches on trunk and all extremities (Figure 1a–d). Some pustules were found on both ankles (Figure 1e–f). He also had mild erosions on hard palate without lip erosion. No targetoid lesions were detected. Other systemic examinations were otherwise unremarkable.

Laboratory findings revealed a white blood cell count of 20.35 10^9/L with neutrophil predominance (neutrophils 17.83 10^9/L), Hb 7.2 g/dL, hematocrit (Hct) 26.2% (baseline Hb 8.2 g/dL, Hct 31.3%), alanine transaminase 51 U/L, total bilirubin 66.53 µmol/L, and direct bilirubin 5.81 µmol/L. Urinalysis showed white blood cells 10-20/HP, and RBC 10-20/HP without the presence of

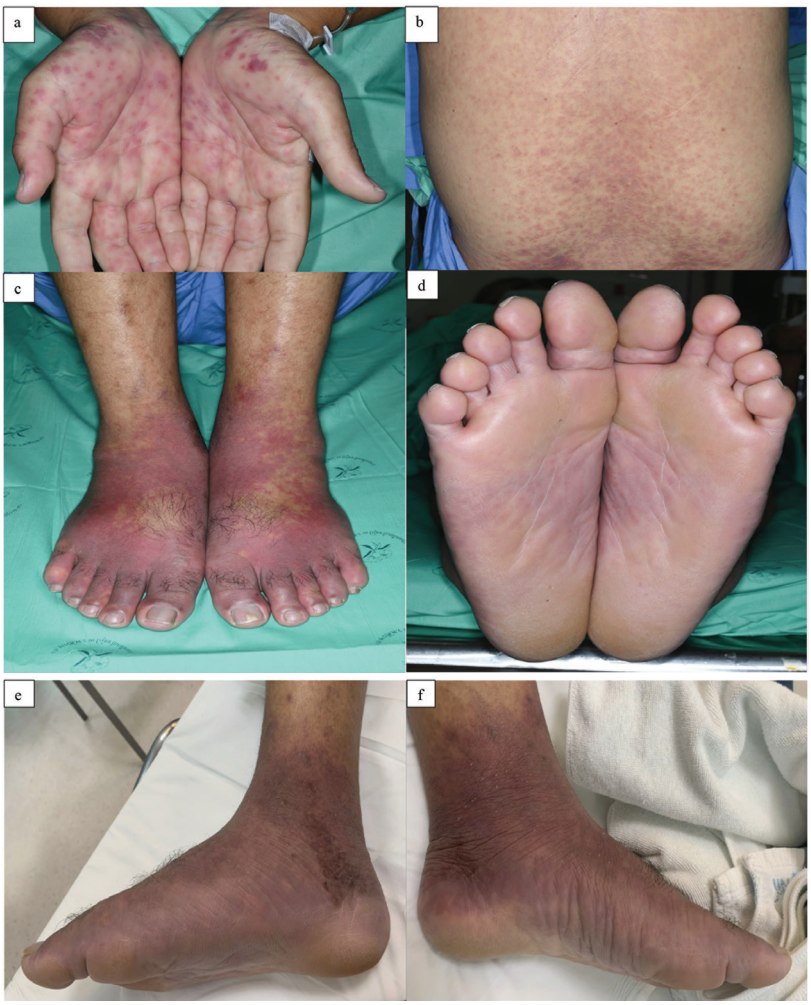

Figure 1. *The clinical presentations showed generalized erythematous papules and patches with some non-blanchable painful erythematous patches on trunk and all extremities (a-d). Some pustules on was found on both ankles (e,f).*

dysmorphic erythrocytes. Serological tests were negative for antinuclear antibodies, anti-streptolysin O, anti-DNase B, antimyeloperoxidase, antiproteinase 3 as well as antibodies to Zika virus, *Leptospira*, human herpes virus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, hepatitis B virus, and hepatitis C virus. Complement 3 (C3) and 4 (C4) levels were normal. Furthermore, the respiratory viruses panel for RNA/DNA detection was negative, including all adenovirus, human metapneumovirus, enterovirus, RSV (types A, B), influenza viruses (A and B), parainfluenza viruses, coronavirus, human rhinovirus, human bocavirus likewise other bacteria: *Bordetella parapertussis*, *Bordetella pertussis*, *Chlamydophila pneumoniae*, *Hemophilus influenza*, *Legionella pneumophila*, and *Streptococcus pneumoniae*. *Mycoplasma pneumoniae* antibody titers by agglutination with a gelatin particle agglutination (PA) test kit (SERODIA-MYCO II (Serodia test), Fujirebio Inc. Japan; with the manufacturer's cutoff set at ≥1:40) were positive on the titer of 1:80. Hemoculture, urine culture, and pus from the right foot were all negative for organisms. A chest radiograph did not show any sign of active pulmonary disease.

Histopathological examination of the left thigh revealed superficial neutrophilic perivascular infiltration with endothelial swelling. There were scattered extravasated erythrocytes (Figure 2a). The direct immunofluorescence (DIF) study demonstrated focal granular deposition of C3 along the dermo-epidermal junction (DEJ) and superficial blood vessels (Figure 2b). These findings are compatible with LCV.

This patient was initially treated with empirical antibiotics by intravenous ceftriaxone 2 g daily, intravenous clindamycin 600 mg every 8 hours, and oral doxycycline 100 mg twice a day. The patient continued to undergo high temperature and appeared unwell. The regimen was then changed to azithromycin 500 mg daily for 5 days when serological tests showed positivity for *M. pneumoniae*. Additionally, LCV was managed with colchicine 0.6 mg daily and chloroquine 250 mg daily. The patient responded quickly to this treatment, with complete resolution of the skin lesions and no scarring.

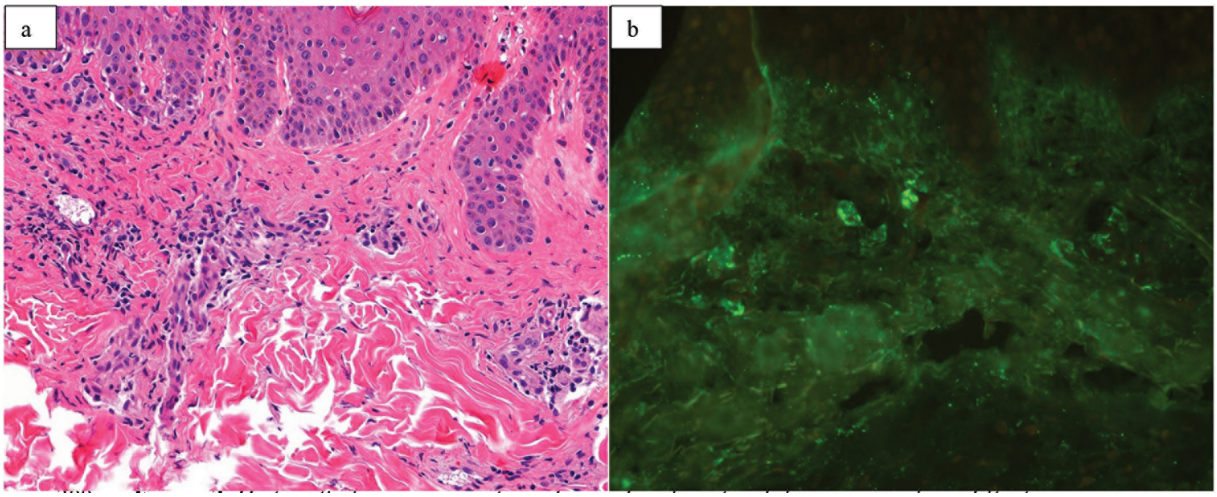

Figure 2. *Histopathologic examination of superficial neutrophilic perivascular infiltration with endothelial swelling with scattered extravasated erythrocytes. (Hematoxylin-eosin stain, original magnification x40) (a). DIF showed focally granular deposition of complement 3 along dermo-epidermal junction and superficial blood vessel (b).*

Discussion

Mycoplasma pneumoniae is distributed throughout the world, with epidemic peaks every 4 to 7 years [1], and affects primarily children and adolescents. *Mycoplasma pneumoniae* is a common cause of upper and lower respiratory infections. *Mycoplasma pneumoniae* accounts for approximately 40% of community-acquired pneumonia cases and is associated with extrapulmonary symptoms in up to 25% of cases [2]. Curiously, clinical pneumonia may not be present in cases where systemic or cutaneous reactions occur. Cutaneous manifestations are observed in 10%-25% of *M. pneumoniae* infections [3], most commonly presenting as exanthematous eruptions and vesicular rashes [4]. However, LCV remains underexplored due to the rarity of such cases. LCV is clinically characterized by non-blanchable erythematous maculopapular rashes mainly on the lower extremities and its histopathology showed neutrophilic perivascular infiltrate with fibrinoid necrosis. According to the existing literatures, 10 cases of *M. pneumoniae*-associated vasculitis have been shown in Table 1. Interestingly, these cases have affected individuals of varying ages, ranging from children to the elderly. Three cases stood out because they presented distinct cutaneous LCV without the involvement of other organs and were documented by López et al. [5], Orlandini et al. [6], and Taooka et al. [7] To our best knowledge, no previous cases were documented exhibiting pustules similar to those in our case. This is noteworthy, as it may represent the first such instance, potentially indicating pustular vasculitis. Other reported cases exhibited extra respiratory symptoms, including musculoskeletal; polyarthritis [8,9] and arthralgia by Trčko et al. [3], neurological; encephalitis by Perez et al. [10], ocular; retinal vasculitis by Greco et al. [11], and renal; glomerulonephritis by Lee et al. [9]. Only one case developed severe acute respiratory distress syndrome and pancreatitis reported in Van Bever et al. [12]. All patients, including ours, were diagnosed based on clinical, laboratory, and histopathologic evidence, and almost all cases exhibited favorable clinical outcomes after treatment with macrolides and a short course of corticosteroids. Interestingly, a case by Rao et al. [13] had a good resolution without the need for any antibiotics.

The pathogenesis of vasculitis in *M. pneumoniae* remains incompletely elucidated. The possible pathomechanism involves the bacterial ability to evade the host immune response, resulting in the release of pro-inflammatory cytokines, complement activation, and subsequent endothelial damage. This inflammatory process is mediated by a type III immunological reaction (Arthus type) [13], where the antigen combines with its specific antibody and complement, forming circulating immune complexes. Another proposed pathogenic mechanism could be secondary to microthrombosis of vessels associated with cold agglutinins [11].

The diagnosis of *M. pneumoniae* infection can be established through antibody detection. The available methods are the complement fixation assay, indirect immunofluorescence assay, PA, and enzyme immunoassay (ELISA). A positive test is defined by a four-fold increase in IgM or IgG titers. Furthermore, a diagnostic criterion for a single IgM titer equal to or greater than 1: 64 exhibits variable sensitivities (35%-77%) and specificities (49%-100%). Given the fastidious nature and slow growth of *M. pneumoniae*, culture is impractical for acute diagnosis, as it requires 1-3 weeks. Using the specific polymerase chain reaction (PCR) for the detection of *M. pneumoniae* DNA has shown sensitivities ranging from 78% to 92% and specificities from 92% to 100% [14].

The clinical and histological confirmation of LCV in our patient was established through histopathology and positive findings from DIF. Crucial for the confirmation of the diagnosis of *M. pneumoniae* infection was the positive result in *M. pneumoniae* antibody titers, which were registered at 1:80 through the gelatin PA test kit. However,

Table 1. *Published cases of cutaneous vasculitis associated with M. pneumoniae infection in the literature.*

CASE	AGE† /SEX	CLINICAL SYMPTOMS OF *M. PNEUMONIAE* INFECTION			LAB INVESTIGATIONS			TREATMENTS		OUTCOME
		EXTRAPULMONARY SYMPTOMS		PULMONARY SYMPTOMS	DIAGNOSIS OF *M. PNEUMONIAE* INFECTION	SKIN BIOPSY	OTHERS	*M. PNEUMONIAE* INFECTION	LCV	
		CUTANEOUS VASCULITIS	OTHERS							
1	13/M	+ EM-like with bullous lesion	Pancreatitis	Acute respiratory distress syndrome	-CF ; seroconversion 1/100→1/800	LCV DIF: +IgA, IgM, C3 at vascular wall	-	Erythromycin Cefotaxime Ceftazidime Cloxacillin Doxycycline Cotrimoxazole Acyclovir	-	Resolution with residual abnormalities of lung function
2	28/F	+	Polyarthritis	-	-IgM (IF) 1:32 -PA; seroconversion 1:640→1:1,280	LCV DIF: negative	-	Erythromycin	Indomethacin	Resolution
3	75/M	+	Encephalitis	RLL pneumonia	-IgM (ELISA) + -PA; seroconversion 1:340→1:40	LCV	MRI brain: multiple small subcortical and brainstem foci	Amoxycillin/clavulanate Erythromycin	Prednisone	Resolution
4	16/M	+	-	-	ELISA; seroconversion	LCV	-	Roxithromycin	-	Resolution
5	7/M	+	Bilateral retinal vasculitis	-	-Anti-MP(MA) 1:320 -IgA, IgM, IgG Ab +	LCV	-	Clarithromycin	Prednisone	Resolution
6	27/M	+ Hemorrhagic blisters/ ulcers	Arthralgia	RUL pneumonia	-IgM Ab+ -NP swab for MP PCR+	LCV	-	Azithromycin Moxifloxacin	Prednisolone	Resolution
7	52/M	+ Ulceration	Glomerulonephritis Oligoarthritis	-	PA; seroconversion 1:1,280→1:2,560	- Necrotic LCV - Panniculitis	Renal biopsy	Azithromycin	Prednisolone	Resolution
8	24/M	+ Hemorrhagic blisters	-	Upper respiratory symptoms	-IgM, IgG Ab+	- Epidermal spongiosis, subepidermal vesicles, pustular formation - LCV	-	-	Prednisone famotidine hydroxyzine methylprednisolone colchicine	Resolution
9	56/F	+ Annular LCV	-	-	IgM Ab+	LCV	-	Azithromycin	Prednisolone	Resolution

(Continued)

CASE	AGE† /SEX	CLINICAL SYMPTOMS OF *M. PNEUMONIAE* INFECTION			LAB INVESTIGATIONS			TREATMENTS		OUTCOME
		EXTRAPULMONARY SYMPTOMS		PULMONARY SYMPTOMS	DIAGNOSIS OF *M. PNEUMONIAE* INFECTION	SKIN BIOPSY	OTHERS	*M. PNEUMONIAE* INFECTION	LCV	
		CUTANEOUS VASCULITIS	OTHERS							
10	67/F	+	-	Upper respiratory symptoms	IgM Ab+ with four-fold rising	LCV DIF: +C3 at vascular wall	-	Clarithromycin	Topical diflucortolone valerate	Resolution
Our case	44/M	+ Pustules	-	-	PA 1:80	LCV DIF: +C3 at DEJ, vascular wall	-	Ceftriaxone Clindamycin Doxycycline Azithromycin	Colchicine Chloroquine	Resolution

Abbreviation: LCV, leukocytoclastic cutaneous vasculitis; EM, erythema multiforme; PA, particle agglutination; CF, complement fixation; NP, nasopharyngeal; ELISA, enzyme-linked immunosorbent assay; MRI, Magnetic Resonance Imaging; DIF, Direct Immunofluorescence; RLL, right lower lung; RUL, right upper lung; IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; Ab, antibody; MP, Mycoplasma pneumoniae; PCR, polymerase chain reaction.

†Age is in years.

it is imperative to acknowledge the potential for a false positive result, which might indicate the presence of a previous infection. In particular, *M. pneumoniae* IgM can persist for up to a year after the initial infection [15].

Importantly, alternative etiologies of vasculitis, including autoimmune diseases, drug-induced, or infectious agents, were systematically excluded through negative results in the investigations. Blood analysis showed acute anemia, indirect hyperbilirubinemia, and acute transaminitis were explained by infection-induced acute hemolysis in the context of Hb H disease. It is also possible that fever and LCV in our patient may have been precipitated by the administration of ibuprofen, a commonly identified cause of LCV. But the rashes appeared one day before taking the medication and barely progressed afterward.

Management of *M. pneumoniae*-associated vasculitis involves a tailored approach. Macrolides are the antibiotics of choice for the treatment of *M. pneumoniae* infections. It is recommended to immediately begin antibiotic therapy to reduce bacterial concentrations and speed up recovery from atypical bacteria. Furthermore, the treatment of vasculitis involves the inclusion of anti-inflammatory agents to diminish immune-mediated damage [10].

In this specific case, even with the early prescription of empirical antibiotics, namely ceftriaxone, doxycycline, and clindamycin, symptoms did not respond well. Subsequently, after the detection of *M. pneumoniae* on the fifth day of the illness, the patient indicated a rapid improvement after azithromycin 500 mg daily was administered, supporting the diagnosis. Additionally, the concurrent administration of colchicine 0.6 mg daily and chloroquine 250 mg daily for 5 days contributed significantly to the resolution of skin lesions. Colchicine primarily acts by inhibiting neutrophilic chemotaxis and cellular motility [16], while chloroquine exerts anti-inflammatory effects by suppressing antigen presentation, cell-mediated immunity, and the production of proinflammatory cytokines [17].

Conclusion

Mycoplasma pneumoniae is a globally recognized etiological agent of atypical pneumonia, which exhibits the potential for extrapulmonary manifestations such as cutaneous vasculitis. This case report illustrates a rare presentation of cutaneous vasculitis due to *M. pneumoniae* infection that lacks pulmonary involvement. The diagnosis was confirmed by clinical, laboratory, and histopathologic evidence. The prompt initiation of appropriate antibiotic therapy coupled with vasculitis management resulted in the complete resolution of skin lesions without scarring. Therefore, clinical consideration of *M. pneumoniae* infection demands a high index of suspicion when encountering febrile patients accompanied by cutaneous vasculitis, even in the absence of respiratory symptoms or other clinical indications [2]. A thorough diagnostic

workup is imperative to guide targeted treatment decisions, thus facilitating rapid clinical improvement.

What is new?

The authors report on distinct cutaneous vasculitis due to *M. pneumoniae* infection without pulmonary involvement. Because it is critical to demonstrate that this rare cutaneous manifestation has a high index of suspicion for early diagnosis and treatment.

List of Abbreviations

C3	Complement 3
C4	Complement 4
DEJ	Dermo-epidermal junction
DIF	Direct immunofluorescence
Hb	Hemoglobin
Hct	Hematocrit
LCV	Leukocytoclastic vasculitis
M. pneumoniae	*Mycoplasma pneumoniae*

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

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Consent to participate

None.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report with the accompanying image.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

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References

1. Sánchez-Vargas FM, Gómez-Duarte OG. *Mycoplasma pneumoniae*-an emerging extra-pulmonary pathogen. Clin Microbiol Infect. 2008;14(2):105–17. https://doi.org/10.1111/j.1469-0691.2007.01834.x
2. Narita M. Classification of extrapulmonary manifestations due to *Mycoplasma pneumoniae* infection on the basis of possible pathogenesis. Front Microbiol. 2016 Jan 28;7:23. https://doi.org/10.3389/fmicb.2016.00023
3. Trčko K, Marko PB, Miljković J. Leukocytoclastic vasculitis induced by *Mycoplasma pneumoniae* infection. Acta Dermatovenerol Croat. 2012;20(2):119–22.
4. Terraneo L, Lava SA, Camozzi P, Zgraggen L, Simonetti GD, Bianchetti MG, et al. Unusual Eruptions Associated with *Mycoplasma pneumoniae* respiratory infections: review of the literature. Dermatology. 2015;231(2):152–7. https://doi.org/10.1159/000430809
5. Pérez López I, Aguayo Carreras P, Navarro-Triviño FJ, Aneiros Fernandez J, Ruiz Villaverde R. Annular leukocytoclastic vasculitis and infection by *Mycoplasma pneumoniae*. Med Clin (Barc). 2017 Aug 22;149(4):e21. https://doi.org/10.1016/j.medcli.2016.10.008
6. Orlandini V, Dega H, Dubertret L. Vascularite cutanée révélant une infection b *Mycoplasma pneumoniae* [Cutaneous vasculitis revealing a *Mycoplasma pneumoniae* infection]. Presse Med. 2004 Nov 6;33(19 Pt 2):1365–6. https://doi.org/10.1016/s0755-4982(04)98934-8
7. Taooka YIY, Higashi Y, Takezawa G. *Mycoplasma* infection-induced leukocytoclastic vasculitis. Int J Case Rep Images. 2018;9:100903Z01YT2018. https://doi.org/10.5348/100903Z01YT2018CL
8. Perez C, Mendoza H, Hernandez R, Valcayo A, Guarch R. Leukocytoclastic vasculitis and polyarthritis associated with *Mycoplasma pneumoniae* infection. Clin Infect Dis. 1997;25(1):154–5. https://doi.org/10.1086/516888
9. Lee H, Moon KC, Kim S. Cutaneous vasculitis and renal involvement in *Mycoplasma pneumoniae* infection. Korean J Intern Med. 2015;30(3):402–5. https://doi.org/10.3904/kjim.2015.30.3.402
10. Perez C, Montes M. Cutaneous leukocytoclastic vasculitis and encephalitis associated with *Mycoplasma pneumoniae* infection. Arch Intern Med. 2002;162(3):352–4. https://doi.org/10.1001/archinte.162.3.352
11. Greco F, Sorge A, Salvo V, Sorge G. Cutaneous vasculitis associated with *Mycoplasma pneumoniae* infection: case report and literature review. Clin Pediatr (Phila). 2007;46(5):451–3. https://doi.org/10.1177/0009922806298638
12. Van Bever HP, Van Doorn JW, Demey HE. Adult respiratory distress syndrome associated with *Mycoplasma pneumoniae* infection. Eur J Pediatr. 1992;151(3):227–8. https://doi.org/10.1007/bf01954392
13. Rao M, Agrawal A, Parikh M, Banayat R, Thomas MJ, Guo T, et al. Mycoplasmal upper respiratory infection presenting as leukocytoclastic vasculitis. Infect Dis Rep. 2015;7(1):5605. https://doi.org/10.4081/idr.2015.5605
14. Vervloet LA, Marguet C, Camargos PA. Infection by *Mycoplasma pneumoniae* and its importance as an etiological agent in childhood community-acquired pneumonias. Braz J Infect Dis. 2007;11(5):507–14. https://doi.org/10.1590/s1413-86702007000500012
15. Okimoto N, Uchida K, Tanaka H, Kato T, Hayashi T, Kurihara T, et al. Association between ImmunoCard *Mycoplasma* test and particle agglutination (PA) method in *Mycoplasma pneumonia* diagnosis. Kawasaki Med J. 2014;40:61–3. https://doi.org/10.11482/KMJ-E40(2)61
16. Konda C, Rao AG. Colchicine in dermatology. Indian J Dermatol Venereol Leprol. 2010;76(2):201–5. https://doi.org/10.4103/0378-6323.60552
17. Ochsendorf FR. Use of antimalarials in dermatology. J Dtsch Dermatol Ges. 2010;8(10):829–44. https://doi.org/10.1111/j.1610-0387.2010.07490.x

Summary of case

1	Patient (gender, age)	44 years old, Male
2	Final diagnosis	Cutaneous LCV caused by *M. pneumoniae* infection
3	Symptoms	High-grade fever with generalized erythematous papules, some pustules and patches for 3 days, with no chest symptoms
4	Medication (Generic)	Ceftriaxone (IV), Doxycycline, Clindamycin (IV), Azithromycin, Colchicine, Chloroquine
5	Clinical procedure	Skin biopsy
6	Specialty	Dermatology