A case of Bartonellosis presenting as a puzzling multisystem disorder complicated by nosocomial COVID-19 infection

Huw Garland ,[1] Sarah Stoll,[2] Shalinee Patel,[2] Rahul Mogal[3]

[1]Watford General Hospital, Watford, UK
[2]West Hertfordshire Hospitals NHS Trust, Watford, UK
[3]Department of Respiratory Medicine, Watford General Hospital, Watford, UK

Correspondence to
Dr Huw Garland;
huw.garland@nhs.net

Accepted 8 August 2021

SUMMARY

The most commonly considered infection with a *Bartonella* species is cat-scratch disease caused by *Bartonella henselae*. Here, we discuss a unique case of a 60-year-old man who presented with *Bartonella* infection complicated by nosocomial COVID-19. He was admitted with a history of chest pain, persistent fever, rash and influenza-like symptoms. Positive *Bartonella* serology confirmed diagnosis and the patient developed complications of pericardial effusion in addition to COVID-19 infection, requiring non-invasive ventilation and admission to the intensive care unit. We discuss his symptoms, investigations, treatment and outcomes, while also highlighting the challenges of assessing patients presenting with fever of unknown origin during the COVID-19 pandemic.

BACKGROUND

This case illustrates the puzzling multisystem disease caused by systemic *Bartonella* infection, the cause of which was not immediately apparent until a panel of serological tests exposed the causative organism. It highlights that systemic Bartonellosis can occur in immunocompetent individuals with no exposure to cats. Finally, to our knowledge, this is the only published case of *Bartonella*–COVID-19 coinfection.

CASE PRESENTATION

A previously well 60-year-old man was admitted with a 10-day history of chest pain, influenza-like symptoms, sore throat, fatigue, myalgia, night sweats and arthralgia. He had worsening pleuritic chest pain in the 2 days prior to presentation. He had no recent travel outside the UK and was not known to be immunocompromised. He had a pet dog but reported no contact with cats; however, he did report a severe dog bite 2 years prior to presentation, which had required surgical intervention. He is a regular gardener but cannot recall any injuries and is normally fit and well with no significant medical history.

There was no palpable lymphadenopathy on examination or other notable findings. He was started on intravenous piperacillin-tazobactam for possible lower respiratory tract infection. He developed a urticarial-type rash on day 1 of his admission, as seen in figure 1.

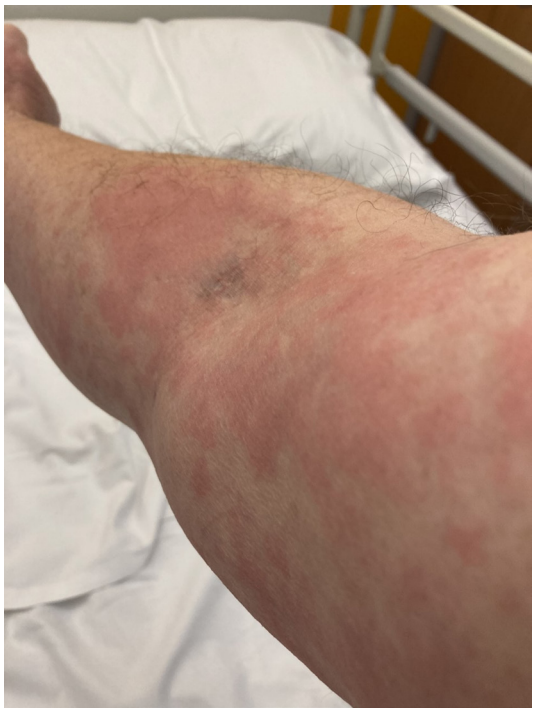

Figure 1 A confluent erythematous rash which developed across the patient's body on the first day of admission, seen here on his arm. At the time, it was thought to represent a urticarial rash but with the benefit of hindsight, the authors wonder if this may have been a Jarisch–Herxheimer reaction which has been seen in association with *Bartonella*.[2]

INVESTIGATIONS

On admission, he was feverish and had raised inflammatory markers including white cell count of 20.3×10^9/L (normal value $3.2–10.5\times10^9$/L) and C reactive protein of 328 mg/L (normal value 0–5 mg/L).

CT pulmonary angiogram imaging of the chest showed enlarged mediastinal and pretracheal lymph nodes in addition to a pericardial effusion, as demonstrated in figure 2. He underwent endobronchial ultrasound (EBUS) with transbronchial needle aspiration of the mediastinal lymph nodes and endobronchial washings were taken from right lower lobe. EBUS showed lymphadenopathy with benign features and cytology was reported as an excess of lymphoid blasts.

For the pericardial effusion noted on CT imaging, the patient underwent multiple transthoracic echocardiograms and one transoesophageal echocardiogram, which demonstrated no evidence of infective endocarditis but demonstrated growth followed by resolution of the pericardial effusion. MRI of his

To cite: Garland H, Stoll S, Patel S, *et al*. *BMJ Case Rep* 2021;**14**:e244002. doi:10.1136/bcr-2021-244002

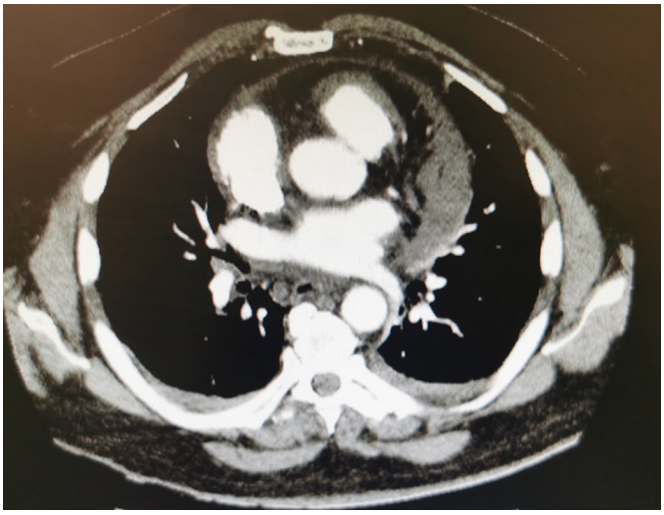

Figure 2 A slice from a CT pulmonary angiogram demonstrating the pericardial effusion.

spine excluded spondylodiscitis and a subsequent CT of his head showed no acute intracranial abnormalities. CT imaging of the abdomen revealed no intra-abdominal source of infection.

Urine dipstick showed proteinuria, and on day 6 of admission, urine microscopy showed cellular and granular casts with simultaneous blood workup showing acute kidney injury (AKI).

Despite six previous negative swab results during this admission, he swabbed positive for COVID-19 on day 12 of admission, therefore, thought to be nosocomial. Throughout admission, nine blood cultures were carried out, all of which showed no growth. Procalcitonin levels were carried out and initially showed a level of 3.57 ng/mL (normal value <0.10 ng/mL), indicative of bacterial infection, which warranted further microbiology testing. Multiple screens were sent for ongoing fever including *Mycoplasma*, *Legionella*, hepatitis B, hepatitis C, HIV, Epstein-Barr virus, cytomegalovirus, parvovirus 19, syphilis, gonorrhoea, acid-fast bacilli culture, *Aspergillus*, beta D-glucan, toxoplasma, *Coxiella burnetii*, *Brucella*, *Bartonella* and respiratory viral screen.

He was discharged with outpatient follow-up on day 14 to await pending investigation results and a positron emission tomography scan.

He was readmitted on day 15 with low oxygen saturations, cough and worsening shortness of breath. Serological tests confirmed the diagnosis of active Bartonellosis and the presence of strongly positive *Bartonella* antibodies had, by this time, been detected. However, further information regarding subspecies was not available. All other microbiology tests were unremarkable except for a single sputum culture demonstrating *Mycobacterium chimaera* but this was not reproduced in any other sample. Procalcitonin level on day 18 of admission was 106.15 ng/mL and he was treated with meropenem and doxycycline. Additionally, he was given intravenous dexamethasone and then swapped to a weaning regime of prednisolone for COVID-19 pneumonia. He was also noted to have intermittent fevers, some associated with rigours, during this admission. On day 19 of admission, he developed stage 2 AKI requiring intravenous fluids. Unfortunately, he deteriorated from COVID-19 and was started on non-invasive ventilation 12 days after swabbing positive and was transferred to the intensive care unit. He developed melena which was managed with intravenous proton pump inhibitors and ablation of the causative duodenal ulcer at oesophagogastroduodenoscopy.

Repeat CT imaging of his chest towards the end of his admission showed extensive multifocal consolidation and ground-glass changes consistent with COVID-19 pneumonitis. There was a small amount of reactive mediastinal lymphadenopathy. He recovered well on the ward with oxygen saturations above 94% in room air and was discharged once clinically improved.

DIFFERENTIAL DIAGNOSIS

This patient was diagnosed with systemic Bartonellosis on the basis of serological investigations. *Bartonella* was never cultured so a species is not known. Repeat serological investigations showed a rapid drop in antibody levels consistent with resolving acute infection. Coinfection with COVID-19 was diagnosed by viral PCR and supported by radiographic findings.

TREATMENT

This patient received antimicrobial therapy initially empirically with piperacillin and tazobactam for 9 days in his first admission which was converted to doxycycline and meropenem on readmission for 14 days once the diagnosis of Bartonellosis was confirmed. COVID-19 pneumonia was managed with steroids and supportive care including continuous positive pressure ventilation for type 1 respiratory failure.

OUTCOME AND FOLLOW-UP

This patient was discharged alive 46 days after his initial presentation to complete a weaning course of prednisolone given following dexamethasone for COVID-19 pneumonia. He was discharged to a rehabilitation ward to continue his convalescence. He did not require supplementary oxygen at the point of hospital discharge.

DISCUSSION

Bartonella are an uncommon Gram-negative coccobacilli, which have a tropism for endothelial cells and erythrocytes. It is a zoonotic infection which commonly infects domesticated cats and dogs and can be spread directly by an animal bite as well as by using fleas, body lice and tics as vectors, depending on the species.[1] Bartonellosis is most commonly seen as an infection of children following a bite or scratch from an infected cat, which has given rise to the term cat-scratch disease which refers specifically to *Bartonella henselae*. Infection with *Bartonella* species must be considered in the differential of patients with fever of unknown origin or those with perplexing multisystem syndromes. The presentation of *Bartonella* disease can present differently depending on age group. In older groups of patients, it can present atypically with features of endocarditis and an absence of lymphadenitis.[2]

The confluent erythematous rash (figure 1) seen on the day of admission was diagnosed as urticaria but with the benefit of retrospect may represent a Jarisch–Herxheimer reaction which has been reported with a variety of Gram-negative organisms including *Bartonella* species.[3] It is possible that this rash masked the ability to identify a primary inoculation lesion as one was not found in this patient. However, it is important to remember that a thorough examination of the skin including interdigital spaces, skin creases, scalp and mucus membranes is required in patients presenting with fever of unknown origin. *Bartonella* has a number of cutaneous manifestations including oral ulcers, non-suppurative conjunctivitis and ocular granuloma. Many other causes of fever of unknown origin are associated with cutaneous findings such as eschars in spotted fever group rickettsioses.

The presence of granular and cellular casts in the urine on day 6 of admission associated with a stage 1 AKI and proteinuria raises the possibility of a glomerulonephritis. An autoantibody screen was negative. Unfortunately, renal histology is not available to confirm the presence of glomerulonephritis but this has been commonly reported in *Bartonella* including the absence of endocarditis.[4 5]

Bartonella is a rare cause of pericardial effusion but has been reported twice in the literature previously.[6] Here, it was able to be managed conservatively and drainage was not undertaken.

Echocardiogram on day 1 of admission showed a pericardial effusion which was shown to have increased in size when the echocardiogram was repeated on day 6 with a maximum depth of 1.8 cm adjacent to the left ventricle. This repeat echo suggested possible interventricular dependence. A further repeat echocardiogram on day 19 showed resolution of the pericardial effusion but did demonstrate abnormal septal bounce potentially indicating a degree of constrictive pericarditis. To our knowledge, there is only one case report of constrictive pericarditis following infection with *Bartonella* species in the literature.[7]

Work to define the optimal treatment of *Bartonella* remains ongoing. There is poor correlation between the in vitro and in vivo antibiotic sensitivity. This is thought to reflect the protective nature of the intra-erythrocytic phase. Aminoglycosides, macrolides and tetracyclines are commonly recommended.[8] Despite their effectiveness, the utility of tetracyclines is limited by concerns around dental discolouration in children but they can be used effectively in older children and adults. Doxycycline and meropenem show good activity against *Bartonella* species, which led to our decision to use them in combination here but as already mentioned the poor correlation between in vitro and in vivo sensitivities means that it is unclear whether this was the optimal treatment.[9]

Furthermore, there are other case reports that have highlighted that due to the COVID-19 pandemic, there have been delays in diagnosis of tick-borne infections due to changes in the way that clinical care is delivered.[10]

Our case shows an interesting presentation of a patient infected with *Bartonella* which was complicated by nosocomial COVID-19 infection, adding a layer of complexity in diagnosis.

Learning points

- This case of systemic *Bartonell*a infection with multisystem involvement in an immunocompetent individual demonstrates the non-specific presenting symptoms and puzzling multisystem involvement and therefore the need to consider *Bartonella* even in patients without a history of exposure to felines.
- Patients may be infected by exposure to sandflies, canines or the human body louse.
- To our knowledge, this patient is the first reported case of Bartonellosis with COVID-19 coinfection.

Contributors The manuscript was drafted by HG, SS and SP. RM oversaw the project and provided advice and comments on the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Huw Garland http://orcid.org/0000-0002-8704-4297

REFERENCES

1 Dehio C. Bartonella interactions with endothelial cells and erythrocytes. *Trends Microbiol* 2001;9:279–85.
2 Ben-Ami R, Ephros M, Avidor B, Ronen BA, Moshe E, Boaz A, *et al*. Cat-Scratch disease in elderly patients. *Clin Infect Dis* 2005;41:969–74.
3 DallaPiazza M, Akiyama MJ. The first report of Bartonella quintana immune reconstitution inflammatory syndrome complicated by Jarisch-Herxheimer reaction. *J Int Assoc Provid AIDS Care* 2017;16:321–3.
4 Bannon L, Choshen G, Giladi M, *et al*. *B artonella* endocarditis masquerading as systemic vasculitis with rapidly progressive glomerulonephritis (aka 'Löhlein nephritis'). *BMJ Case Rep* 2019;12:e231413.
5 Singhania G, Singhania N. Do we care if you have a cat? Bartonella infection related glomerulonephritis with no endocarditis. *Infez Med* 2019;27:441–4.
6 Levy PY, Fournier PE, Carta M, *et al*. Pericardial effusion in a homeless man due to Bartonella quintana. *J Clin Microbiol* 2003;41:5291–3.
7 Bharti DR, Mehta AV. Constrictive pericarditis following cat-scratch disease in a 12-year-old female: a rare association. *Tenn Med J* 2003;96:509–10.
8 Rolain JM, Brouqui P, Koehler JE, *et al*. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother* 2004;48:1921–33.
9 Pendle S, Ginn A, Iredell J. Antimicrobial susceptibility of Bartonella henselae using Etest methodology. *J Antimicrob Chemother* 2006;57:761–3.
10 Wormser GP, Jacobson E, Shanker EM. Negative impact of the COVID-19 pandemic on the timely diagnosis of tick-borne infections. *Diagn Microbiol Infect Dis* 2021;99:115226.