



CASE REPORT

REVISED **Case Report: A case of disseminated cutaneous listeriosis following appendicitis from Lao PDR [version 2; peer review: 4 approved, 1 approved with reservations]**

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Abstract

Background

Listeria monocytogenes is a food-borne pathogen that is a rare cause of bacteraemia and meningitis in immunosuppressed patients, and carries a high mortality rate. Cutaneous manifestations of listeriosis are rare, and are usually associated with direct inoculation of the skin.

Case

A 41-year-old woman who initially presented to a hospital in Laos with appendicitis was diagnosed with disseminated listeriosis with cutaneous involvement. Intra-abdominal pathology probably contributed to bacterial bloodstream invasion. Initial treatment with meropenem was switched to ampicillin based on best practice, however our patient died 5 days after diagnosis.

Conclusions

This case highlights listeriosis as an important cause of mortality in low- and middle-income countries, exacerbated by poor availability of laboratory diagnostics and ineffective empiric antibiotic regimens. Improvements in food hygiene, surveillance, and increased laboratory capacity are important strategies to reduce rates of infection and

Open Peer Review

Approval Status ✓✓✓?✓

	1	2	3	4	5
version 2 (revision) 15 May 2024					✓ view
version 1 07 Nov 2023	✓ view	✓ view	✓ view	? view	? view

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clinical outcomes.

Keywords

Listeria, food-borne, bacteraemia, meningitis, pustular rash, sarcoidosis, southeast Asia, Laos

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Any reports and responses or comments on the article can be found at the end of the article.



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REVISED Amendments from Version 1

The text has been modified to highlight the fact that the patient was immunosuppressed due to oral steroids, and that glucocorticoids have been associated with mortality in listeria. The antibiotic susceptibility pattern of the *Listeria* isolates are now included. Finally, the possibility that the *Listeria* infection was chronic is explored.

Any further responses from the reviewers can be found at the end of the article

Introduction

Listeriosis is a food-borne infection caused by the bacterium *Listeria monocytogenes*, manifesting as a wide spectrum of clinical disease, typically ranging from mild gastrointestinal upset to bacteraemia and meningo-encephalitis in susceptible hosts¹. The global burden of listeriosis is insufficiently described, particularly in low- and middle-income countries (LMICs)². Early recognition of *L. monocytogenes* infection is important as it is not optimally treated by most empirical antibiotic regimens for bacterial sepsis, and invasive infections have a high mortality rate of 20–40%^{3–5}. Increasing clinicians' knowledge of the patterns of disease caused by *L. monocytogenes* is therefore critical.

Although recognised in approximately 10% of invasive neonatal infections⁶, cutaneous manifestations of listeriosis in adults are rare. A review of prior case reports found most adult cases were caused by direct inoculation of the skin, either in farmers or veterinarians who had exposure to animal products of conception. Accordingly, skin lesions were localised to the site of inoculation. Cutaneous disease from haematogenous spread was infrequent and associated with severe immunocompromise, including haematological malignancy and HIV⁷.

We report a case of disseminated cutaneous listeriosis following appendicitis in a female patient diagnosed with sarcoidosis and taking prednisolone. This case reinforces the potential for haematogenous spread as a cause of disseminated cutaneous listeriosis.

Case report

We report the case of a 41-year-old Lao woman who lived in Vientiane Capital, Laos. She was diagnosed with sarcoidosis two years prior to presentation, although details of the diagnostic work-up were unavailable. She had no other notable past medical history apart from early menopause aged 39 years old.

One month before her admission with appendicitis, she was admitted to our hospital with cough and dyspnoea. A thoracic computerised tomography (CT) scan demonstrated a mild-to-moderate left-sided pleural effusion alongside widespread peribronchovascular honeycombing and hilar-mediastinal lymphadenopathy; this was diagnosed as stage IV sarcoidosis. Investigations for tuberculosis were not performed. She remained

in hospital for 2 weeks, and on discharge was prescribed prednisolone 40 mg daily to control a sarcoid flare.

She re-presented 2 weeks later with a five-day history of worsening abdominal pain in the right upper and lower quadrants, and diarrhoea. On admission she was afebrile, with unremarkable vital signs (blood pressure 110/80 mmHg, heart rate 74 bpm, peripheral oxygen saturations 98% on room air, and respiratory rate 20/min). An abdominal ultrasound scan demonstrated hepatomegaly; the appendix was not described. She was diagnosed clinically with appendicitis and taken for surgery the same day. Intra-operative findings included peritonitis, copious amounts of pus and a caecal mass (10 × 10 cm). She underwent a hemicolectomy with primary ileo-colic anastomosis. The caecal mass was excised and sent for histopathological examination, and showed suppurative appendicitis.

Post-operatively, she was treated with ceftriaxone (2 g intravenously, every 24 hours), gentamicin (5 mg/kg intravenously, once daily) and metronidazole (500 mg intravenously, every 8 hours), and she initially improved. However, a florid, disseminated pustular rash developed the following day, initially across her left chest, before spreading to her upper thighs and lower abdomen (Figure 1A). The rash consisted of numerous small, well-demarcated erythematous lesions of varying sizes, many with pustules (Figure 1A, inset). On direct questioning, the patient's family revealed, surprisingly, that a milder version of this rash had first appeared on the patient's arms and legs two months earlier, although it is unclear if it truly had the same appearance and aetiology. Of note, a biopsy of one of these lesions was taken prior to this admission, in connection with her admission for presumed sarcoidosis. The skin biopsy demonstrated a nodular infiltrate in the dermis, composed of a histiocytic aggregation and neutrophilic micro-abscesses admixed with plasma cells, and multinucleated giant cells. No sarcoid granulomas or bacteria were seen. The histopathology report commented that the observed mixed cell granulomas can be associated with chronic granulomatous infections; notably, these findings are consistent with listeriosis.

On the fourth post-operative day, the patient deteriorated with septic shock and respiratory failure, with a blood pressure of 80/50 mmHg, respiratory rate of 38/minute and peripheral oxygen saturations of 85% on room air. She was transferred to the Intensive Care Unit for inotropic and vasopressor support with noradrenaline, and was intubated 3 days later due to further respiratory deterioration. Of note, prior to intubation, the patient did not exhibit any signs of meningitis. The antibiotics were escalated empirically to meropenem (1 g intravenously, every 8 hours) and a blood culture was sent, along with a bacterial swab of the pustular rash.

The blood culture flagged positive after 18 hours, with Gram-positive rods seen on Gram stain, subsequently identified as *Listeria monocytogenes* by MALDI-ToF. At the same time, *L. monocytogenes* also grew from the pus swab, confirming a

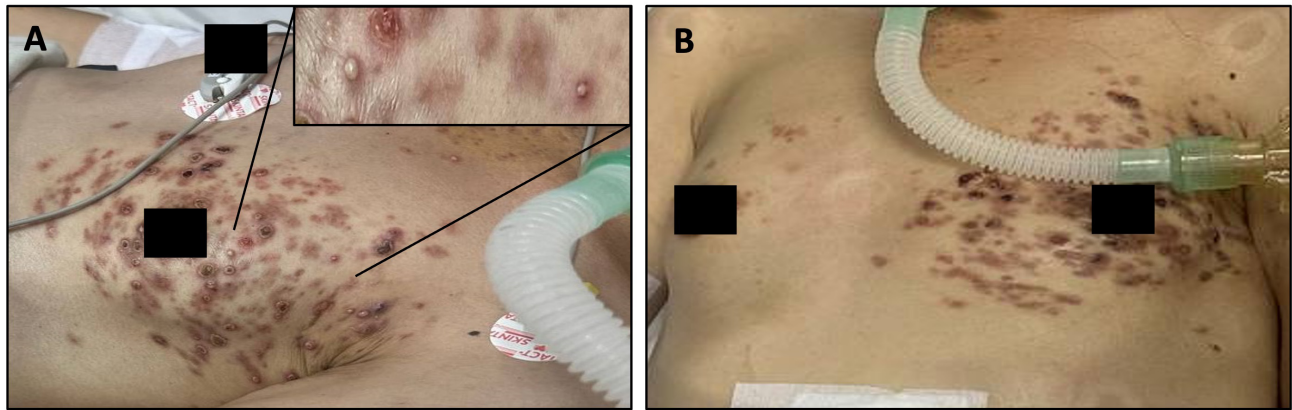


Figure 1. **A:** Disseminated papulo-pustular rash concentrated on the left chest. Inset: A cluster of lesions with pustules at a variety of stages. **B:** Initial resolution of the rash, with improvement in the pustules.

diagnosis of disseminated listeriosis. Initially, meropenem was continued to provide ongoing broad-spectrum coverage given the recent intra-abdominal pathology. Two days after *L. monocytogenes* was isolated, the antibiotic was switched to high-dose intravenous ampicillin (2 g, 6 times daily), which was continued for the remainder of the admission. The isolates from both blood and pus were sensitive to penicillin, meropenem, co-trimoxazole and erythromycin, as determined by disk diffusion testing (<https://www.eucast.org>).

The appearance of the rash improved, with some resolution of the pustules, but unfortunately, the patient's clinical condition was unchanged, with on-going cardiorespiratory failure. Given the lack of clinical improvement, the severity of the infection, and the poor prognosis of invasive listeriosis, after one week of intensive care treatment, the decision was taken by the patient's family to stop active treatment. It was arranged for her to be taken home for end-of-life care.

Discussion

This patient was diagnosed with listeriosis with dissemination to the skin, and this was associated with appendicitis. We could find only one other case where listeriosis was associated with appendicitis⁸ although cases complicating a range of other intra-abdominal pathologies have been reported⁹. Appendicitis in this case was likely caused by *Listeria* infection, which to our knowledge has not been described before.

No microbiological samples were sent on admission or intra-operatively, and therefore it is not known when our patient developed invasive disease. Neither is it possible to say with certainty when the patient ingested *Listeria* due to the incubation period that can exceed 30 days⁵. Our patient was diagnosed with listeriosis on day 5 of her admission, and although hospital-acquired outbreaks are well documented, we have not noted any other cases in our hospital.

Although the vesiculo-pustular rash was disseminated, it was concentrated in several discrete dermatomes, such as the left T4 dermatome as shown in Figure 1. This initially raised the possibility of super-infected shingles. However, lesions were bilateral, which was more clearly appreciated on the thighs and lower abdomen. Viral swabs of the vesicles were not taken, however cultures confirmed *Listeria* and retrospective testing demonstrated the patient was not viraemic with varicella-zoster virus at the time the positive blood culture was taken, making shingles unlikely.

A lumbar puncture was not performed during admission and so central nervous system infection by *L. monocytogenes* was not excluded, although the patient never displayed symptoms suggestive of meningitis. However, the dose of ampicillin selected was adequate to cover the possibility of meningoencephalitis (*i.e.*, 2 g intravenously, every 4 hours).

Finally, regarding the clinical presentation, it is important to consider the possibility that the bilateral pneumonia, pleural effusion and lymphadenopathy described above that were attributed to a sarcoid flare may in fact have been due to progression of chronic listeriosis.

Several previously identified risk factors for severe disseminated disease were present in this case. First, the integrity of the patient's colonic mucosa was impaired due to appendicitis. Second, treatment with broad-spectrum antibiotics removed the protective effects of the normal gut microbiota¹⁰. Third, the patient had been receiving high-dose oral corticosteroids, and although these were stopped prior to admission, glucocorticoids are a risk factor for invasive listeriosis and strongly associated with fatal outcomes¹¹; they likely accelerated the fulminant course of this infection. Finally, the patient may have been immunosuppressed to some extent by her sarcoidosis. Sarcoidosis is associated with peripheral lymphopenia, including depressed CD4 counts, although not to

the extent seen in advanced HIV infection¹². This may affect T-cell-mediated immunity, which is important in the response to *Listeria* infection. Together, these factors may have resulted in a large and overwhelming bacterial burden.

Ampicillin or amoxicillin (2 g intravenously, every 4–6 hours, usually for at least 2 weeks for bloodstream infection, and at least 3 weeks for meningitis) is the first-choice antibiotic for listeriosis, usually in combination with gentamicin due to synergistic action observed *in vitro*. In this case, the preceding intra-abdominal pathology necessitated broad-spectrum antibiotic therapy, and precluded an immediate antibiotic switch from meropenem to ampicillin, which occurred 48 hours after *Listeria* was first isolated. Meropenem has *in vitro* activity against *Listeria*, and features on some treatment guidelines at high dose (2 g intravenously, every 8 hours; [John Hopkins ABX guide](#)). There is no data from controlled trials comparing meropenem to ampicillin. However, a Danish retrospective observational study showed that treatment with meropenem was associated with a higher 30-day mortality rate (25% compared to 11% for those treated with penicillins; odds ratio 0.4) – but the impact of confounding factors in this retrospective review cannot be accounted for¹³. While there are indeed case reports of treatment failure with meropenem¹⁴, there are also reports of patient recovery only after a switch to meropenem¹⁵. The consensus remains that listeriosis is most securely treated with ampicillin or amoxicillin. Dual therapy with amoxicillin and broad-spectrum agent may a role – either for listeriosis alone, or to simultaneously treat listeriosis and other infections¹⁶.

The risk of listeriosis in low- and middle-income countries may be increased due to less access to reliable refrigeration and microbiological food safety monitoring. A recent systematic review of *Listeria* contamination in food, environmental and animal sources in southeast Asia found that up to 43% of food samples in Malaysia, 15% in Thailand, and 16% in Indonesia were affected, with an overall prevalence in southeast Asia of 16%¹⁷. A global review of listeriosis concluded that urgent efforts were needed to fill the knowledge gaps concerning the burden of listeriosis in low- and middle-income countries². No incidence data for the southeast

Asia region was found at all. To our knowledge, there are no studies of the prevalence of *Listeria* contamination of food or the environment, or of clinical listeriosis in Laos. However, in our laboratory alone, we have isolated *L. monocytogenes* from seven patients since 2017: in addition to the patient reported here, two patients had *L. monocytogenes* isolated from both blood cultures and CSF, and four had *L. monocytogenes* isolated from blood cultures only. The patients' ages ranged from 0 to 90 years old – pointing to a diverse case mix in our setting.

Conclusions

To conclude, listeriosis is likely an under-recognised condition in LMICs, and the commonly used cephalosporin-based empiric antibiotic regimens are not active against it. This underscores the ongoing need to build microbiology diagnostic capacity. Dissemination with cutaneous presentations may follow apparently subtle immunosuppression, and may be associated with significant intra-abdominal pathology.

Public and patient involvement

There was no formal patient or public involvement in the design or conduct of this work.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the relative of the patient.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Acknowledgements

We would like to thank the patient's family for consenting to the publication of this report. We also acknowledge the expertise provided by surgical, infectious diseases and intensive care teams as well as the microbiology laboratory staff at Mahosot Hospital. Finally, we thank Dr Tamalee Roberts for providing additional laboratory data.

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Version 2

Reviewer Report 23 May 2024

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 **Bruno Hassunuma Carneiro** 
Federal University of Paraná, Curitiba, Brazil

No further suggestions to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Internal Medicine and Infectious Diseases



I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 29 April 2024

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 **Bruno Hassunuma Carneiro** 
Federal University of Paraná, Curitiba, Brazil

The article is very well-written as it illustrates a severe case of invasive listeriosis presenting with cutaneous manifestations after hematogenous spread in the context of a complicated intra-abdominal infection.

I would not say the patient's background had no recognized risk factors for invasive listeriosis. In fact, she had received high-dose glucocorticoids for recently diagnosed sarcoidosis. In a large, nationwide prospective study (MONALISA Study), glucocorticoid use was not only a risk factor for invasive listeriosis but also strongly associated with mortality in patients with bacteremia and neuroinfection¹.

The case presentation includes details of the investigation, showcases the cutaneous lesions mimicking Herpes Zoster and the presence of *Listeria monocytogenes* recovered from blood and pus cultures. It is important to note that, from a pharmacological standpoint, noradrenaline has some inotropic activity, as cited by the authors; however, its main use in septic shock is as a vasopressor².

The authors provide the rationale for the treatment and the employed diagnostic methods very clearly. The patient was treated with broad-spectrum antibiotic regimens to cover intra-abdominal bacteria. As mentioned, gentamicin has historically been used as an adjuvant to treat invasive listeriosis, usually in combination with an aminopenicillin, and meropenem has also been reported to be an effective strategy in some cases. In this particular scenario, to maintain broad-spectrum activity against intra-abdominal pathogens and at the same time include a first-line choice for *Listeria monocytogenes*, the combination regimen of meropenem plus ampicillin could be considered, as this regimen has been previously used for complicated listeriosis. Although the experience with this combination is limited to case reports and has had mixed results, it is worth mentioning³.

The authors precisely conclude that listeriosis is probably underrecognized and that most broad-spectrum antibiotic regimens that include cephalosporins are not active against *Listeria monocytogenes*, a deadly combination of factors that add up to the complexity of the management of intra-abdominal infections and immunocompromised patients.

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Internal Medicine and Infectious Diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 04 March 2024

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Gauri Godbole 

United Kingdom Health Security Agency, Gastrointestinal Pathogens and Food Safety (One Health) Division, London, UK

This a very nicely written case report showcasing the various complications of listeriosis in an immunosuppressed adult.

Case report:

The case is chronologically well presented, with adequate detail, some additional parameters such as white cell count, CRP during her first admission (paragraph 2) should be described, did she have fever? (not mentioned, worth mentioning if she didn't have fever) was she treated with antibiotics for the chest infection during that admission? which ones?

Regarding the second admission, was the antibiotic susceptibility of the *Listeria monocytogenes* checked (as there is some drug resistance in LMIC) and was synergistic gentamicin given? If it wasn't, is there a reason for omission?

Discussion:

It is well presented, T cell dysfunction associated with increased risk of listeriosis is described. The outcome studies for meropenem are appropriately referenced.

Conclusion:

After reading this report I have concluded that this patient had chronic listeriosis which clinically manifested 2 months prior to admission as a skin rash (the later biopsy confirmed classical features seen in Listeriosis such as micro abscesses and mixed cell granulomas not typical of sarcoid. Were any bacteria seen on histology? The bilateral pneumonia, lymphadenopathy and pleural effusions are all consistent but a rare presentation of disseminated listeriosis which was

progressing as was untreated. Hey, were mistaken for a sarcoid flare and t's important to draw that out in the discussion.

The patient was further immunosuppressed with prednisolone which will have rapidly accelerated the fulminant course and dissemination. Involvement of various parts of intestinal tract, the appendix and caecum and peritoneum are not a surprising, cutaneous manifestations are a feature of widespread dissemination and are not due to appendicitis, all compounded by absence of appropriate antibiotics.

The title of the case report should be changed to disseminated chronic listeriosis with widespread cutaneous manifestations in an immunocompromised adult from Lao PDR

Overall comments:

This is an important case report raise awareness of this pathogen in LMIC. The authors highlight lack of laboratory facilities which are extremely important for diagnosis and prevention of poor outcomes. It highlights 2 rare presentations of Listeria in immunocompromised adults- skin manifestations without occupational inoculation and chronic course of illness with widespread pulmonary and gastrointestinal involvement including appendicitis and peritonitis.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Gastrointestinal bacteria, One health AMR and parasitology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 February 2024

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Ioana Diana Olaru 

Department of Clinical Research, University of Münster, Münster, Germany

The authors report on a case of disseminated listeriosis in an immunosuppressed patient. The manuscript is well written and relevant for clinical practice. The report is particularly important for LMIC where bacterial identification can be challenging. I have only a few minor comments

1. Do you have any laboratory results for haematology and chemistry
2. Can you comment whether anyone else from the household/ contacts may have suffered from a mild form of infection

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases & microbiology, antimicrobial resistance, diagnostics in LMIC

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 29 Feb 2024

Terry Evans

The authors appreciate the reviewer's careful and critical reading of our case. In this case, there was no history of unwell contacts. Patients' medical records are not computerized in our hospital, and therefore obtaining these results retrospectively can sometimes be challenging.

Competing Interests: No competing interests were disclosed.

Reviewer Report 20 February 2024

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Tengku Jamaluddin

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The authors have described the case adequately and provided relevant clinical descriptions, including images depicting the cutaneous involvement of the disease.

Discussion pertaining clinical diagnosis explored other possibilities, ie. herpes zoster super-infection etc. Authors aptly justified, and discuss the diagnostic approach of the case.

This case will definitely contribute in highlighting awareness on this rare and under-diagnosed disease.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infection prevention and control, Antimicrobial resistance, Molecular medical microbiology, One Health, Antimicrobial Stewardship and Diagnostic Stewardship.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 January 2024

<https://doi.org/10.21956/wellcomeopenres.22379.r71636>

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✓ **Yvan Caspar** 

Bacteriology Laboratory, Institute of Biology and Pathology, CHU de Grenoble Alpes, Grenoble, France

This case report presents a rare clinical manifestation of listeriosis in an immunocompromised patient. It is well written and described. Data in low and middle income countries are insufficient which also adds to the significance of this report.

I only have a few minors queries :

Introduction section :

line 3 : replace "Poorly understood" by « insufficiently described » or or state that there are knowledge gaps in low and middle income countries as there is a known burden but which is not well documented.

Case report section :

- MALDI-TOF : expand in full letter (except if accepted by the journal guidelines)
- How long was post-operative antibiotic treatment ?
- Can you provide more description of the skin lesions ? Were they painful ? pruritic ?
- a bacterial swab was taken from the pustular rash but the culture is positive from the pus swab.
- I imagine these are the same swabs but may cause confusion for the reader. Was the content of the vesicles clear liquid or pus ?
- "it is unlikely that any changes to the antibiotic therapy would have altered the outcome in this complex case." I agree with the statement but it may be useful not to presume anything and to delete this part of the sentence as both treatment are effective to treat listeriosis.

Discussion section :

There is debate about the use of dexamethasone in listeriosis meningitis outcome [1] Was prednisolone stopped during acute infection ? Is there any litterature about the potential effect of prednisolone of the outcome of listeriosis ?

References

1. Brouwer MC, van de Beek D: Adjunctive dexamethasone treatment in adults with listeria monocytogenes meningitis: a prospective nationwide cohort study. *EClinicalMedicine*. 2023; **58**: 101922 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical microbiology, Rapid diagnosis methods, tularemia

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 29 Feb 2024

Terry Evans

The authors thank the reviewer for his expert and thoughtful comments that clarify several important aspects of the presentation and treatment of this case.

Competing Interests: No competing interests were disclosed.