Rickettsia sibirica mongolotimonae infection in Cantabria, Spain

Infeccion por Rickettsia sibirica mongolotimonae *en Cantabria, España*

Dear Editor,

Rickettsia sibirica mongolotimonae was isolated for the first time in 1992 in Beijing as a subspecies of *R. sibirica* from ticks from the Inner Mongolia region, hence its name.[1] Its pathogenicity has been verified in humans, and although the number of cases described is small, in recent years it has been increasingly reported.[2]

We present the case of a 29-year-old male with no medical history of interest who sought treatment at our centre in June 2021 for fever, general malaise, myalgia and headache lasting four days. He had returned two days earlier from a holiday in a rural area in the Luena Valley (Cantabria), in northern Spain, and said that he had suffered an insect bite on the outer side of his right forearm two days before the start of symptoms. On physical examination, his temperature was 38°C, his blood pressure was 110/70 mmHg and his heart rate was 90 bpm. He had a necrotic eschar on his right forearm of approximately 1 cm in diameter, accompanied by proximal lymphangitic streaking (Fig. 1) and a painful axillary adenopathy of approximately 1 cm not attached to deep planes. The rest of the examination was normal. The complete blood count showed a leukocyte count of 6,100, with an absolute lymphocyte count of 930, and normal haemoglobin and platelet counts. Biochemical test results, including transaminases, were normal, except for C-reactive protein, which was 16 mg/l (normal: <10.0 mg/l). There were no relevant findings on the chest X-ray. Detection of antibodies to *Rickettsia*, *Borrelia*, *Francisella tularensis* and *Anaplasma phagocytophilum* was negative, while a real-time PCR (polymerase chain reaction) test (performed at the Centro Nacional de Microbiología Carlos III, [Carlos III National Centre for Microbiology] in Majadahonda, Madrid) on a biopsy of the necrotic eschar was positive for *Rickettsia sibirica mongolotimonae*. The patient was treated with doxycycline 100 mg every 12 h for 10 days, showing progressive clinical improvement until complete recovery and disappearance of the skin lesions and adenopathy. Six months later he remains asymptomatic.

Figure 1. Lymphangitic streaking proximal to the necrotic eschar.

In addition to general symptoms such as fever, general malaise and myalgia, the skin manifestations of *Rickettsia mongolotimonae* are very characteristic, which allows for a rapid diagnosis of suspicion. As in our case, a small necrotic eschar on a limb is typically found in up to 90% of patients,[3] and cases have even been described with multiple accompanying eschars. This lesion can be continued by reddish proximal lymphangitic streaking, which is identified in approximately 45% of cases and is accompanied by local adenopathies,[4] for which the name lymphangitis-associated rickettsiosis (LAR) has been proposed.[5] Other types of local lesions have also been described, such as erythematous papular rash on the trunk and limbs, lymphadenopathy and scarring alopecia.[6] The infection is generally mild and responds well to treatment with tetracyclines, but cases with severe manifestations have been described, such as retinal vasculitis, hyponatraemia, shock, myopericarditis, encephalitis and acute renal failure.[6]

Diagnosis has improved remarkably since specific PCR studies have been available on biopsy samples or smears from skin eschar.[6] Serological methods are less sensitive and have the drawback of cross-reactions with other *Rickettsia* that are present in our environment.[7]

In Europe, *Rickettsia sibirica mongolotimonae* has been isolated from ticks of the genera *Rhipicephalus* and *Hyalomma*, and the first infection in humans was diagnosed in 1996 in southern France.[2] Since then, multiple cases have been reported, mostly in the Mediterranean region (France, Spain, Portugal, Greece and Turkey). Cases have also been reported in some African countries (Algeria, Egypt, Cameroon and South Africa).[8] In Spain, several cases have been described, predominantly in the Mediterranean coastal region, and in the centre and north of the peninsula.[9] As far as we have been able to ascertain, our case is the first reported case of contagion in the community of Cantabria.

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DOI of refers to article: https://doi.org/10.1016/j.eimc.2022.06.012

Sarah Davila-Arias[a,*], Elena Rabadan-Rubio[b], Alvaro Rabadan-Rubio[c], Jose Alberto Arranz-Caso[a]

[a] Servicio de Medicina Interna, Hospital Universitario Principe de Asturias, Alcala de Henares, Madrid, Spain
[b] Servicio de Reumatologia, Hospital Universitario Principe de Asturias, Alcala de Henares, Madrid, Spain
[c] Veterinario clínico, Ciudad Real, Spain

* Corresponding author.
E-mail address: sarah9201@hotmail.com (S. Davila-Arias).

https://doi.org/10.1016/j.eimce.2023.04.001

Proposal for antimicrobial therapy stewardship of lower respiratory tract infection in mechanically-ventilated patients based upon the Biofire® Filmarray® Pneumonia Plus panel results

Propuesta para la administración de la terapia antimicrobiana en la infección del tracto respiratorio inferior en pacientes con ventilación mecánica basada en los resultados del panel Biofire® Filmarray® Pneumonia Plus

Ventilator-associated lower respiratory tract bacterial infection (VA-LRTBI) is associated with high morbidity and mortality, notably when multidrug-resistant bacteria (MDRB) are involved and empirical antimicrobial therapy (EAT) is inadequate.[1,2] Conventional semiquantitative culture-based antimicrobial susceptibility testing (AST) procedures performed on lower respiratory tract specimens return results approximately 48–72 h after specimen receipt. The BioFire® FilmArray® Pneumonia/Pneumonia plus Panel (FA-PP) (BioFire Diagnostics, LLC, Salt Lake City, UT) is a multiplex PCR panel that, in addition to respiratory viruses and "atypical" bacteria, tests for several bacteria commonly involved in VA-LRTBI (yielding semiquantitative estimates of bacterial loads) and seven genetic antibiotic resistance markers (*mecA/C* and MREJ, $bla_{\text{CTX-M}}$, bla_{KPC}, bla_{VIM}, $bla_{\text{OXA-48-like}}$, bla_{IMP}, and bla_{NDM}); its use may provide clinically actionable results within about an hour of specimen reception. We and others previously demonstrated that FA-PP notably increases the diagnostic yield in LRTBI and narrows the time window for results compared with culture-based methods; this may prompt early EAT adjustment, which could be cost-beneficial by decreasing antimicrobial use and shortening the intensive care unit (ICU) stay.[3,5,8,9] Nevertheless, consensus criteria for antimicrobial stewardship according to FA-PP results need to be established. Here, we present an actionable antimicrobial stewardship algorithm (Fig. 1) for early EAT adjustment in patients with suspicion of VA-LRTBI at the ICU of the Hospital Clínico Universitario of Valencia, based upon the FA-PP results, planned to be formally evaluated beginning June 2023 upon approval by the INCLIVA (Instituto de Investigación Sanitaria, Hospital Clínico Universitario) Ethics Committee. The algorithm was built based on several assumptions mainly derived from the literature available regarding FA-PP's analytical and clinical performances[3–9]: (i) the high negative predictive value of the assay for all targets in the panel; (ii) the potential etiological relevance of all detectable bacteria at any load (limit of detection: $\geq 10^{3.5}$ $\log_{10}$/ml; limit of quantification, 10^4 $\log_{10}$ copies/ml) in patients undergoing EAT; (iii) the frequent involvement of lower respiratory tract-colonizing MDRB in VA-LRTBI; (iv) bacteria other than those targeted by the FA-PP panel could be involved in VA-LRTBI (i.e. some Enterobacterales species and *Stenotrophomonas maltophilia*). As per protocol, based on consensus guidelines[10] and local epidemiology, a combination of two antimicrobials displaying antipseudomonal activity, including a beta-lactam/beta-lactamase inhibitor (such as ceftolozane/tazobactam, ceftazidime/avibactam, meropenem or piperacillin/tazobactam) plus amikacin, quinolone or inhaled colistin, and an additional drug covering methicillin-resistant *Staphylococcus aureus* (MRSA) (mainly linezolid) is used as EAT for VA-LRTBI at our center. Proposed EAT adjustments based on FA-PP results are the following: (i) withdraw antimicrobial coverage of Gram-positive bacteria if MRSA is not detected; (ii) withdraw one of the two antipseudomonal agents if Gram-negative bacteria are not detected. In this scenario, quinolone therapy might be maintained if *S. maltophilia* is potentially relevant according to local epidemiology; (iii) maintain coverage of Gram-positive bacteria if MRSA is detected and consider discontinuing one antipseudomonal agent; (iv) discontinue one antipseudomonal agent if Enterobacterales with no genotypic resistant trait are detected; (v) withdraw EAT and administer ertapenem when extended spectrum β-lactamase-(ESBL)-producing Enterobacterales are detected; (vi) de-escalate to ceftazidime-avibactam if blaOXA-48-like-producing Enterobacterales is detected; (vii) de-escalate to ceftolozane-tazobactam if non-metallo-β-lactamase-producing *Pseudomonas aeruginosa* is detected; (viii) upon detection of metallo-β-lactamase-producing *P. aeruginosa*, administer ceftazidime-avibactam and aztreonam and inhaled colistin or cefiderocol in monotherapy; (ix) detection of *Acinetobacter baumanii* should prompt the administration of tigecycline and inhaled colistin or cefiderocol in monotherapy; (x) add oseltamivir if influenza virus is detected.

Several considerations related to the above: (i) in all the above scenarios, consider maintaining primary EAT regardless of FA-PP results when patients are severely immunosuppressed, present with septic shock, an additional infection source is suspected or MDR bacterial species not included in the panel are likely to be involved according to patient's risk factors or local epidemiology; (ii) detection of two or more Gram-negative bacterial targets harboring genotypic resistant traits (if particular fermenting and non-fermenting bacteria are detected in combination) will require individualized antimicrobial therapy tailoring; (iii) the algorithm has been designed taking into consideration the bacterial epidemiology at our ICU, which may not be extrapolatable to other settings.

The suitability of ongoing antimicrobial therapy (either adjusted or not upon FA-PP results) in terms of coverage as well as treatment duration should be re-assessed within 48 h, following receipt of microbiological results from standard semiquantitative cultures and conventional AST, taking into consideration the patient's clinical status. A concluding remark: this is a list of some of the many potential actions in terms of EAT adjustments that may be derived from FA-PP results. We naturally open our proposal for discussion, which we are confident will translate into tangible benefits for our ICU patients.