8. Ulick S, Kodama T, Gunczler P, Zanconato G, Ramirez LC, Wolfgang R, et al. A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. J Clin Endocrinol Metab. 1979;49:757–64, http://dx.doi.org/10.1210/jcem-49-5-757.
9. Yadav M, Aditi S, Hari P, Bagga A. Impaired distal tubular acidification, renal cysts and nephrocalcinosis in monogenic hypertension. Indian J Pediatr. 2021;88:579–81, http://dx.doi.org/10.1007/s12098-020-03516-4.
10. Young WF. Apparent mineralocorticoid excess syndromes (including chronic licorice ingestion). En: UpToDate, Sterns RH (Ed), UpToDate, Forman JP [Accessed 10 January 2024]. Available from: https://www.uptodate.com/contents/apparent-mineralocorticoid-excess-syndromes-including-chronic-licorice-ingestion?search=mineralocorticoid%20excess%20syndrome&source=search_result&selectedTitle=1%7E120&usage_type=default&display_rank=1.

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Q fever as a cause of fever of unknown origin in a patient on hemodialysis

Fiebre Q como causa de fiebre de origen desconocido en un paciente en hemodiálisis

Dear Editor,

Q fever is a worldwide zoonosis caused by *Coxiella burnetii* acquired mainly by inhalation.[1] Clinical manifestations of acute Q fever include self-limited flu-like illness, pneumonia, and mild hepatitis. Chronic infection usually presents as a culture-negative endocarditis, but other uncommon forms of persistent focalized infection and secondary non-Hodgkin lymphoma are also possible.[2,3]

We present the case of a 70-year-old man with a history of hypertension, type 2 diabetes mellitus, and chronic ischemic dilated cardiomyopathy. The patient was also being monitored by Hematology due to a monoclonal gammopathy of undetermined significance and had stage V chronic kidney disease, secondary to mesangiocapillary glomerulonephritis with heavy chain deposition. A Quantiferon-TB Gold plus had been performed with positive results and therefore he had been taking rifampicin 600 mg QD for 4 months as treatment for latent tuberculous infection. Regarding the immunosuppressive treatment, in December 2022 the patient received induction treatment with methylprednisolone pulses and a single Rituximab dose, due to progressive kidney failure. He finally started chronic hemodialysis program 2 days/week through a tunneled central venous catheter at the end of December 2022. A blood test in January 2023 revealed low IgG (488 mg/dL) with normal IgM and IgA levels.

In April 2023, he consulted after a hemodialysis session complaining of general malaise, impaired mobility, pain in the right hypochondrium and moderate fevers for 2 weeks. The analytical findings suggested an infectious process: C-reactive protein (CRP) 364 mg/L, procalcitonin 1.71 ng/mL, leukocytosis 19,200/mm^3, Hb 11.9 g/dL, LDH 300 U/L, GGT 211 U/L, ferritin 1452 ng/mL. He was referred to the emergency department (ED) where an abdominal ultrasound and CT scan were performed, describing multiple small nodular liver images, with a hypodense center and ring enhancement, suggestive of microabscesses. Chest-X ray was normal. The patient was then admitted to our Infectious Diseases Unit and antibiotics stopped. Initial microbiological and analytical results are included in Table 1. After all these diagnostic proceedings yielded no result, a liver biopsy was performed. The patient was sent home pending results and he felt much better without any antimicrobial being started. CRP and procalcitonin declined spontaneously and the patient remained on close monitoring as an outpatient.

6 weeks thereafter (June 2023) the patient visited the ED again complaining of right hypochondrium pain, general

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Table 1 – Relevant results of the two hospital admissions.

	First admission (April 2023)	Second admission (June 2023)
SARS-CoV-2 PCR nasal swab	Negative	Negative
Blood cultures (venipuncture and through hemodialysis catheter)	Negative	Negative
Urine culture	Negative	Negative
HIV	Negative	
CMV	IgG positive	
EBV	IgG positive	
Herpes ½	IgG positive	
VZV	IgG positive	
Hepatitis A	IgG positive	
Hepatitis B	Anti-HBs positive	
Hepatitis C	Negative	
Measles	IgG positive	
Coxiella burnetii	IgG positive	IgG positive
- Phase I IFA	- Negative	- Negative
- Phase II IFA	- Negative	- Positive 1/128
Bartonella henselae	Negative	Negative
Rickettsia conorii	Negative	Negative
Brucella melitensis	Negative	Negative
Francisella tularensis		Negative
Echinococcus granulosus	Negative	
Toxoplasma gondii	IgG positive	
Leishmania spp.	Negative	
Blood beta-D-glucan	Negative	
Transthoracic echocardiogram	No signs of endocarditis	
Antinuclear antibodies	Negative	
Extractable antinuclear antigen	Negative	
Anti-LKM Ab	Negative	
Anti-mitochondrial Ab	Negative	
Anti-smooth muscle Ab	Negative	
Bone-marrow aspiration		
- *Mycobacterium tuberculosis* PCR		- Negative
- Non-tuberculous mycobacteria PCR		- Negative
- *Leishmania* spp. PCR		- Negative
PCRs in deparaffinized liver biopsy		
- *Francisella tularensis*		- Negative
- *Rickettsia* spp.		- Negative
- *Coxiella burnetii*		- Negative
- *Bartonella henselae*		- Negative
- *Leishmania* spp.		- Negative

discomfort, hematuria, and low-grade fever. Blood CRP was >480 mg/L and procalcitonin 6.73 ng/mL. He was readmitted to our Infectious Diseases Unit again. Second abdominal CT was carried out with similar results than the first one. Table 1 shows all microbiological results.

The patient was diagnosed of Q fever based on serological results and the result of the liver biopsy (Fig. 1). According to this, doxycycline was started (100 mg BID for 28 days). He became afebrile, and another blood analysis had normal parameters including CRP and procalcitonin. Follow-up serology 7 months after first admission was performed with negative phase I and positive phase II with a title of 1/200. All liver lesions resolved in a control CT-scan.

C. burnetii infection is a well-known cause of prolonged fever all over the world. Acute infection usually manifests as an atypical pneumonia or mild hepatitis, although most patients experience an acute self-limiting infection.[4,5] Granulomatous hepatitis with fibrin-ring granuloma is the classic pathological form in liver biopsy but this is non-specific and non-sensitive because Q fever can produce other forms of granulomatous hepatitis.[6,7] We found a report of a kidney transplant patient who suffered acute Q fever presenting liver and spleen abscesses with a splenic biopsy that showed extensive abscess formation and focal poorly formed non-necrotizing granulomatous inflammation.[8]

There is a wide differential diagnosis for a patient with granulomatous liver disease and prolonged fever.Diagnostic options may be grouped into several categories: sarcoidosis, autoimmune (primary biliary cirrhosis above all), infectious diseases (tuberculosis being the main, *Mycobacterium avium-intracellulare* complex in immunocompromised patients, fungal infections like histoplasmosis, unfrequently viral infec-

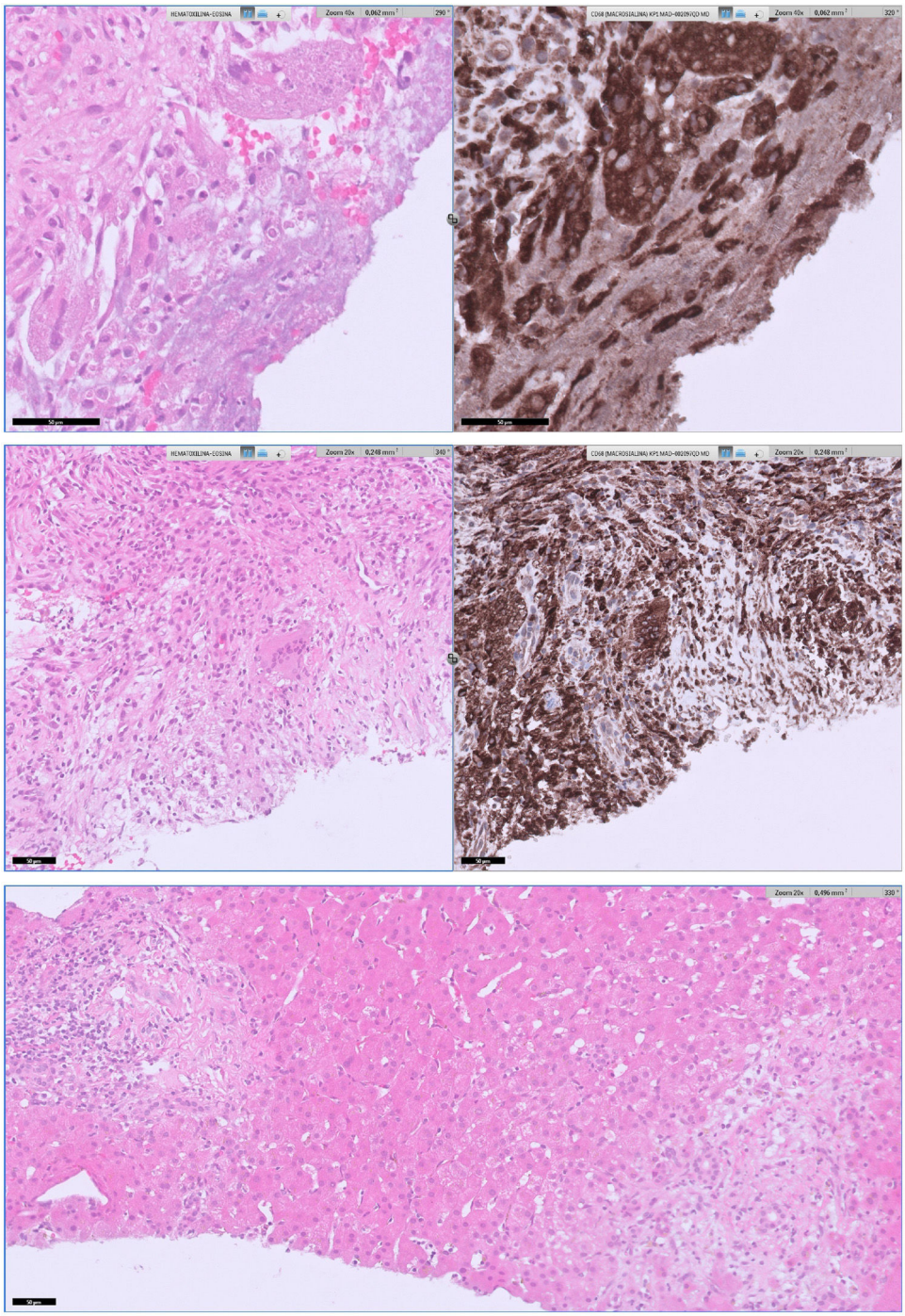

Fig. 1 – Upper section: areas of necrosis with portal and lobular involvement produced an alteration in the hepatic architecture. A histiocytic ring surrounding the necrosis is highlighted with CD68 immunostaining, configuring histiocytic granulomas of variable size. No fibrin-ring granulomas were not observed on the serialized slides nor ancillary techniques performed. Middle section: giant cells were scarce, localized in the lobule, and their presence was more detectable with CD68 staining. Lower section: in addition, some portal-periportal inflammation with T lymphocytes prevalence, scarce B lymphocytes and very few plasma cells, with focal extension to interphase and lobules was present.

tions, and zoonosis like *Rickettsia conorii* and *C. burnetii*), drugs, cancer and idiopathic.[9]

Some diagnostic issues may be highlighted with respect to Q fever: gold standard is still IFA serology, and it usually takes 2–4 weeks to turn positive. *C. burnetii* has a peculiarity called antigenic phase variation: phase I has the more complex lipopolysaccharide (LPS) and it is the virulent-infectious

phase. *C. burnetii* quickly turns into phase II, with a loss in the LPS complexity, virulence and infectivity.[10]

Phase II serology positivity is found in acute infection. Serological diagnosis of acute Q fever can be made either with phase II IgG ≥ 1/128 or IgM ≥ 1/32 or a 4-fold increase between two serum samples taken 3–6 weeks apart.[1,11] IFA serologies used by our reference laboratory do not differentiate IgG from IgM.

On the contrary, high phase I serology (usually IgG ≥ 1/800) is suspicious of chronic Q fever and should lead to further testing (echocardiogram, PET-CT). The general recommendation is to perform serological follow-up until 1–2 years after acute infection in patients at risk of progression (immunocompromised, chronic valvular disease, vascular graft, etc.).[1]

Some patients can be diagnosed by PCR in blood or tissue samples, but PCR is not widely available. PCR in blood specimens has high specificity but sensitivity is only good enough during the first days of the disease and when antimicrobials have not yet been started. PCR for *C. burnetii* targets the IS1111a insertion element.[12] We performed a PCR in deparaffinated liver biopsy which resulted negative but deparaffination could reduce sensitivity of this technique. We didn't start doxycycline until a positive phase II serology because we still had tuberculosis in our differential diagnosis and the patient became suddenly afebrile and asymptomatic before his second hospital admission.

An interesting question is whether anti-CD20 therapy could justify a longer duration of the febrile process and delay *C. burnetii* serology turning positive. There is a clear negative association between anti-CD20 therapies and SARS-CoV-2 seroconversion after SARS-CoV-2 mRNA vaccine.[13] There is also an association between rituximab and low immunoglobulins just like the case of our patient. It would be reasonable to hypothesize of a low level of phase II antibodies in patients under anti-CD20 therapy who suffer acute Q fever.

To conclude we would like to suggest an initial protocol for the diagnosis and management of patients with prolonged fever (>7 days). In stable patients a first set of explorations should be performed: chest-X ray, serial blood cultures (also through catheters if available), urine culture, and an initial round of viral PCRs (influenza, RSV, SARS-CoV-2) and serologies (basic are EBV, CMV and HIV). If all these results are negative and the patient has a slight elevation of liver enzymes, LDH and CRP/procalcitonin, we recommend a therapeutic trial with doxycycline. Doxycycline is an antibiotic with a good efficacy/security profile. It is administered at a dose of 100 mg twice daily and do not require adjustment in any grade of renal or hepatic failure.[14] Confirmative serology for *C. burnetii* (and other zoonosis like *Rickettsia* spp., *Leptospira interrogans* and *Bartonella henselae*) will always take time, and maybe longer in immunosuppressed patients who may also suffer from atypical or more prolonged forms of the disease. A high index of suspicion is required to better reach this diagnosis.

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Authors' contribution

Emilio Guirao-Arrabal: Conceptualization, writing-original draft. Ana Delgado-Ureña: supervision, collected patient data and informed consent, writing-review and editing. Elena Borrego-García: conceptualization, writing-review and editing. Rosa Ríos-Pelegrina: writing-original draft, collected pathological figures. All authors revised, read, and approved the final manuscript.

Informed consent statement

Written informed consent was obtained from the patient.

Conflict of interest

All authors declare no competing interest that could influenced the work presented in this paper.

REFERENCES

1. Eldin C, Mélenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, et al. From Q fever to *Coxiella burnetii* infection: a paradigm change. Clin Microbiol Rev. 2017;30:115–90, http://dx.doi.org/10.1128/CMR.00045-16.
2. Melenotte C, Million M, Raoult D. New insights in *Coxiella burnetii* infection: diagnosis and therapeutic update. Expert Rev Anti Infect Ther. 2020;18:75–86, http://dx.doi.org/10.1080/14787210.2020.1699055.
3. Melenotte C, Mezouar S, Mège JL, Gorvel JP, Kroemer G, Raoult D. Bacterial infection and non-Hodgkin's lymphoma. Crit Rev Microbiol. 2020;46:270–87, http://dx.doi.org/10.1080/1040841X.2020.1760786.
4. Haidar G, Singh N. Fever of unknown origin. N Engl J Med. 2022;386:463–77, http://dx.doi.org/10.1056/NEJMra2111003.
5. Guirao-Arrabal E, Muñoz-Medina L, Anguita-Santos F, Vinuesa-García D, Hernández-Quero J. Empirical treatment with doxycycline of fever of intermediate duration. Eur J Clin Microbiol Infect Dis. 2021;40:2047–50, http://dx.doi.org/10.1007/s10096-021-04322-2.
6. Geha R, Peters M, Gill RM, Dhaliwal G. Histology rings true. N Engl J Med. 2017;376:869–74, http://dx.doi.org/10.1056/nejmcps1609391.
7. Lee M, Jang JJ, Kim YS, Lee SO, Choi SH, Kim SH, et al. Clinicopathologic features of Q fever patients with acute hepatitis. Korean J Pathol. 2012;46:10–4, http://dx.doi.org/10.4132/KoreanJPathol.2012.46.1.10.
8. Sarrell BA, Laurenzano J, Freitas J, Concepcion BP. Q fever presenting with hepatic and splenic lesions in a kidney transplant recipient. Transpl Infect Dis. 2021;23, http://dx.doi.org/10.1111/tid.13699.
9. Flamm SL. Granulomatous liver disease. Clin Liver Dis. 2012;16:387–96, http://dx.doi.org/10.1016/j.cld.2012.03.013.
10. España PP, Uranga A, Cillóniz C, Torres A. Q fever (*Coxiella burnetii*). Semin Respir Crit Care Med. 2020;41:509–21, http://dx.doi.org/10.1055/s-0040-1710594.
11. Fariñas MTF, Collado CM. Infección por *Coxiella burnetii* (fiebre Q). Enferm Infecc Microbiol Clin. 2010;28 Suppl. 1:29–32, http://dx.doi.org/10.1016/S0213-005X(10)70005-7.
12. Bolaños-Rivero M, Carranza-Rodríguez C, Hernández-Cabrera M, Pisos-Álamo E, Jaén-Sánchez N, Pérez-Arellano JL. Usefulness of the early molecular diagnosis of Q fever and

rickettsial diseases in patients with fever of intermediate duration. Enferm Infecc Microbiol Clin. 2017;35:655–8, http://dx.doi.org/10.1016/j.eimc.2016.02.026.
13. Gressens SB, Fourati S, Le Bouter A, Le Bras F, Dupuis J, Hammoud M, et al. Anti-SARS-CoV-2 antibody response after 2 and 3 doses of BNT162b2 mRNA vaccine in patients with lymphoid malignancies. Clin Microbiol Infect. 2022;28, http://dx.doi.org/10.1016/j.cmi.2022.02.029, 885.e7–e11.
14. Holmes NE, Charles PGP. Safety and efficacy review of doxycycline. Clin Med Ther. 2009;1, http://dx.doi.org/10.4137/cmt.s2035. CMT.S2035.

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Ultrasonography of vascular access in the hands of nephrology and nephrological nursing professionals in advanced chronic kidney disease units: A tool to improve the quality of care

Ecografía del acceso vascular en manos de los profesionales de la nefrología y de la enfermería nefrológica en las unidades de enfermedad renal crónica avanzada: una herramienta para mejorar la calidad asistencial

Dear Editor,

The success of haemodialysis (HD) as a renal replacement therapy technique depends largely on an adequate vascular access (VA), which maydetermine the success of a given HD programme.[1,2] The use of ultrasound in the advanced chronic kidney disease (ACKD) unit,[3,4] as well as interdisciplinary work,[5,6] plays an important role in this activity.

Clinical guidelines show a degree of discordance regarding the performance of preoperative vascular mapping and the ultrasound monitoring of arteriovenous fistulas (AVF) in the ACKD stage.[7–9] The results from our ACKD unit following the introduction of VA ultrasound are presented. Our hypothesis is that performing preoperative vascular mapping and ultrasound follow-up improves quality of care. This is in line with the recommendations of the Spanish Multidisciplinary Vascular Access Group (GEMAV) Clinical Guidelines.[7]

Our unit covers around 430,000 inhabitants with 343 prevalent HD patients. In order to optimise resources and actions to increase the number of incident and prevalent patients with native arteriovenous fistula (nAVF), as well as to reduce their complications and increase their longevity, in June 2020, our hospital's nephrology department opened a specific VA ultrasound outpatient consult, associated with the ACKD unit, and managed by the same team. Following the incorporation of the VA ultrasound consult, the next step, to improve the management and consequently the outcomes of VA, was the creation of a vascular access programme for haemodialysis, based on the training and implementation of an interdisciplinary team including of nephrologists, nephrology nursing, cardiovascular surgery (CVS) and interventional vascular radiology (IVR), with the assignment of specific functions.

To analyse the impact of launching the programme in June 2020, the number of patients who started HD with AVF was assessed in four periods: two years prior to the creation of the consults facility (2019–2020) and two years after (2021–2022) (Fig. 1). A total of 154 HD incident patients from the ACKD unit were analysed from these periods. The percentages of patients who started HD through AVFwere 63.27% ($n=31$), 50% ($n=16$), 74.36% ($n=29$) and 85.29% ($n=29$) in the 1st, 2nd, 3rd, and 4th periods, respectively. The Pearson Chi-square shows that there is a higher expected frequency of fistulas in period 4, while there is a lower frequency than expected in period 2 ($p<0.05$). The current percentage of AVF and CVCs (central venous catheters) in prevalent patients in the HD

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