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SCIENTIFIC LETTERS

Mediterranean spotted fever in a patient with Crohn's disease under adalimumab: First case report and review of the literature

Fiebre botonosa en un paciente con enfermedad de Crohn con tratamiento de adalimumab: Observación clínica y revisión de la literatura

A 49 years old man with Crohn's disease and ankylosing spondylitis had been treated with adalimumab 40 mg every other week, with clinical remission. After 18 months of starting adalimumab and only three days after last subcutaneous injection, a diffuse pruriginous maculopapular rash was elicited in the abdomen, chest and upper and lower limbs (including palms and soles). He simultaneously had headache, malaise, myalgia and high-grade fever (39.5 °C). He came on to our Emergency Department five days after the first symptoms. Upon admission, he was febrile (39.2 °C), with no other findings on physical evaluation besides the rash and the presence of a small raspberry lesion on the left shoulder. Blood analysis showed elevated C-reactive protein (60.4 mg/L), without leucopenia or thrombocytopenia. Abdominal ultrasound was unremarkable.

Our patient lived in an urban apartment, but he had recently spent two weeks in a rural area, with contact with several farm animals (chickens, dogs and horses), until three days before admission. The lesion on the left shoulder was consistent with a tick bite (Fig. 1). He was treated with doxycycline (100 mg bid) for spotted fever, with an excellent clinical and analytical response. He was discharged on the fifth day without fever and with no rash, and the lesion on the left shoulder was almost completely resolved; blood inflammatory markers returned to normal.

Mediterranean spotted fever (MSF) is a tick-borne disease caused by *Rickettsia conorii*. Although mortality rates for MSF are low and generally range from 0% to 3%,[1] a delay in the diagnosis or inadequate treatment can increase the rates of morbidity and mortality. Serology for *Rickettsia* is frequently negative at presentation,[2] but in our case IgM for this agent was positive. Additionally, given the epidemiological context and the anamnesis (namely the classic triad of rash involving palms and soles, eschar and fever) the diagnosis of MSF, an infection endemic in European southern countries like Portugal, must be assumed promptly, especially in the summer when tick bites are much more common. It is important to notice that the triad is not always present, and the eschar may not be observed in up to 40% of the cases.[3] Blood analysis is unspecific; usually inflammatory markers are elevated, and leucopenia or thrombocytopenia may occur in nearly 20% of the patients.

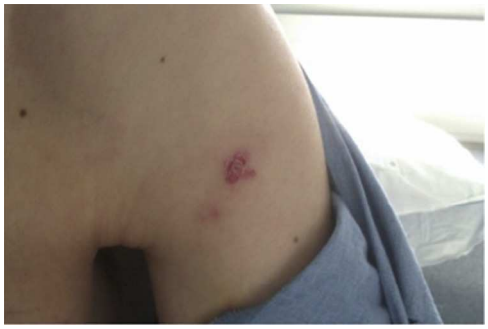

Figure 1 Eschar of the tick bite on the left shoulder.

Little is known concerning this type of infections, namely regarding more serious outcomes and treatment implications, in patients with inflammatory bowel disease (IBD), since there are no reported cases. Furthermore, the clinical course and outcome of MSF (and other tick-borne illnesses) in patients under anti-TNF agents is unknown. TNF is a key cytokine in the defense against intracellular pathogens, as *Rickettsia conorii*,[4] so one could anticipate a more serious disease. The only reported case of a rickettsiosis in this context is a Rocky Mountain spotted fever (by *Rickettsia ricketsii*) in a patient with rheumatoid arthritis under adalimumab (with prior exposure to etanercept), with good outcome.[5]

Crohn's disease and the immunosuppressive treatments that are commonly applied in these patients raise the risk for opportunistic infections and can contribute to a poorer outcome of infectious diseases in general. The authors present a very unusual case of a zoonosis in a context of anti-TNF-alpha therapy for Crohn's disease. This is the first report of a MSF in a patient under adalimumab. In an era in which immunosuppressants and biologics are the mainstay of Crohn's disease therapy, it is expected that this type of drugs will been increasingly applied in patients living in

rural areas. Therefore, zoonotic illnesses in patients under anti-TNF therapies may become more frequent, and it is very important to know how to manage them. The clinical challenge is to know whether these patients could have a worse outcome than general population, requiring different therapeutic strategies. It is unknown if adalimumab must be stopped and for how long, since there are no guidelines for this kind of infections in the context of IBD. We think that anti-TNF agents must be temporarily suspended because TNF is important in the defense from these intracellular organisms. In our case, we chose to prescribe standard antibiotic treatment and stop adalimumab until one week after concluding the antibiotic regimen. Promptly recognition and treatment without delays was decisive for this excellent outcome.

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João Santos-Antunes[a,b], Amadeu C.R. Nunes[a], Guilherme Macedo[a]

[a] *Gastroenterology Department, Faculty of Medicine, Hospital de São João, Porto, Portugal*
[b] *Department of Biochemistry (U38-FCT), Faculty of Medicine, University of Porto, Portugal*
E-mail address: joao.claudio.antunes@gmail.com (J. Santos-Antunes).

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Síndrome de Budd-Chiari como expresión clínica de un síndrome de POEMS

Budd-Chiari syndrome as clinical expression of POEMS syndrome

El síndrome de POEMS[1] (polineuropatía, organomegalia, endocrinopatía, proteína monoclonal y cambios en la piel) se caracteriza por la presencia de un trastorno en las células plasmáticas monoclonales, neuropatía periférica y una o más de las siguientes características: mieloma osteosclerótico, enfermedad de Castleman, elevación del factor de crecimiento vascular endotelial (VEGF), organomegalia, endocrinopatía, edema, cambios típicos de la piel y papiledema[2]. Presentamos el caso de una paciente con polineuropatía asociada a un síndrome de Budd-Chiari resultante de una presentación inusual de síndrome de POEMS.

Se trata de una mujer de 44 años de edad, afecta de hipotiroidismo, en estudio por parestesias y debilidad de ambos pies por el que se realizó el diagnóstico de polineuropatía desmielinizante inflamatoria crónica. La exploración física mostró hiperpigmentación de la piel y hepatomegalia. Los análisis séricos fueron normales, salvo la detección de anti-HBs y anti-HBc (IgG). La ecografía reveló esplenomegalia, discreta ascitis y circulación portal y hepática patentes. Dado que presentaba mínima ascitis en este momento no se realizó paracentesis. En una primera evaluación se realizó una medición del gradiente de presión venosa hepática, siendo la presión hepática enclavada de 15,5 mmHg, la presión hepática libre de 9,67 mmHg, la presión en la cava de 8,39 mmHg y la biopsia hepática transyugular normal. Además se realizó estudio ecocardiográfico que no mostró alteraciones de la función cardiaca. Debido a la polineuropatía se inició tratamiento con inmunoglobulina intravenosa. Diez meses más tarde, la ascitis se había incrementado hasta hacerse casi a tensión, y la paciente fue hospitalizada de nuevo. Se realizó angio-TAC hepático objetivando hepatomegalia heterogénea a expensas del lóbulo caudado (fig. 1), ascitis y trombosis parcial de las venas hepáticas (fig. 2). Se calculó el gradiente de albúmina: 1,7 (albúmina sérica 3,1 g/dl y albúmina en líquido ascítico 1,4 g/dl). Se realizó de nuevo una medición de la presión venosa hepática, siendo la presión 'enclavada' de 20,31 mmHg y la «libre» de 15,58 mmHg, por lo que el gradiente de presión venoso hepático resultó en ese momento normal. Se realizó nueva biopsia hepática, que en esta ocasión reveló dilatación sinusoidal, congestión vascular y necrosis de la zona[3]. Mediante inmunofijación se detectó una paraproteína monoclonal IgA lambda en suero (1,06 g/dl). Posteriormente, la paciente presentó episodios de visión borrosa mostrando el estudio oftalmológico edema de papila bilateral; la RMN craneal evidenció trombosis parcial de la arteria carótida interna derecha y se inició tratamiento anticoagulante. Ante la sospecha diagnóstica de un síndrome de POEMS se procedió a la biopsia de médula ósea y al estudio de la misma mediante citometría de flujo, identificando menos del 2% de células plasmáticas atípicas. Los niveles de VEGF en plasma fueron de 1.951 pg/ml. En esos momentos la paciente presentaba: Cr 1,11 mg/dl, Na 130 mmol/l, bilirrubina 0,69 mg/dl, colinesterasa 3.300 U/l, albúmina 3.100 g/dl, plaquetas 148.000 y Quick 74%. Ante estos hallazgos, la paciente fue diagnosticada del síndrome de POEMS, complicado con un síndrome de Budd-Chiari. Se