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Letters to the Editor

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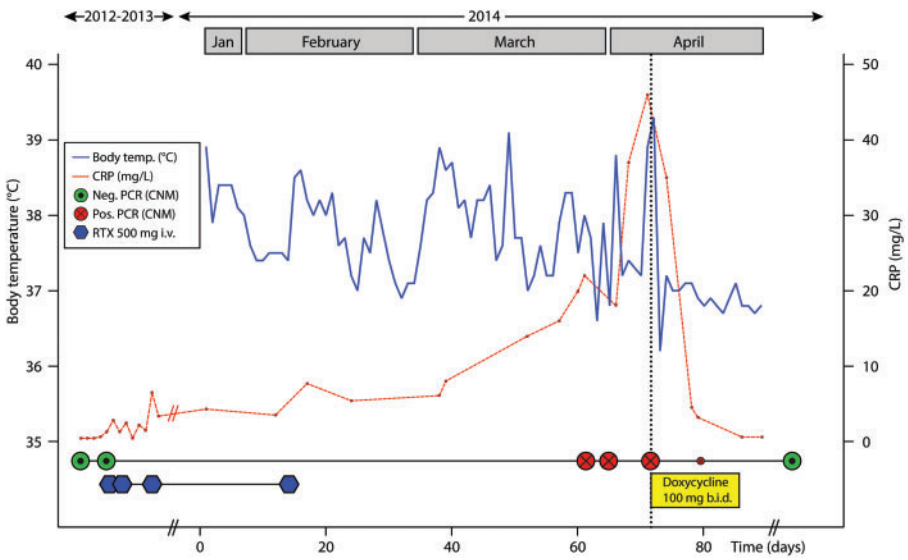
Recurrent fever caused by *Candidatus Neoehrlichia mikurensis* in a rheumatoid arthritis patient treated with rituximab

Sir, It has been reported that RA can be successfully treated using rituximab (RTX) without an increased risk of serious infections [1]. *Candidatus Neoehrlichia mikurensis* (CNM) is a tick-borne bacterium that has recently been described as causing serious infections in immunocompromised humans [2]. We report a case of recurrent fever caused by CNM infection in a patient suffering from RA treated with RTX.

A 71-year-old woman with a history of mammary cancer was diagnosed with ACPA-positive RA in November 2011 and was started on MTX in January 2012. As the patient only responded partially, RTX therapy was initiated in January 2013, with additional infusions in July 2013 and February 2014. During 2013, the patient experienced nausea and weight loss. In December 2013, MTX was discontinued but symptoms progressed and in January 2014, she developed recurring fever (Fig. 1) and dyspnoea. On 19 March, she was admitted to the Rheumatology clinic in Lund, displaying anaemia, tachycardia, fever, slightly elevated aminotransferases and raised CRP, with a weight loss from 65 to 55 kg in 12 months. She was extensively investigated for malignancies, infections and thromboembolism. The patient enjoys hiking in the woods and recalled several tick-bites in July–August 2013, but serological tests for *Borrelia*, *Rickettsia* and for *Anaplasma* were all negative in the face of normal IgA, IgM and IgG levels. The spleen was slightly enlarged, but bone marrow examination including immunophenotyping did not show neoplastic pathology. Treatment with doxycycline 100 mg twice daily for 2 weeks was initiated *ex juvantibus* on 8 April. Shortly thereafter, the fever subsided, CRP and haemoglobin levels normalized, and the patient recovered. Retrospective PCR analysis (both specific PCR and pan-bacterial PCR [2]) of stored sera identified CNM in samples from March to April 2014, but not in samples from late 2012 or July 2014.

CNM is an intracellular bacterium that as yet has not been possible to cultivate. It is commonly found in ticks and rodents (which appear to be the healthy reservoir hosts for the bacterium) in parts of Africa, Asia and Europe, including the southernmost part of Sweden where this patient resides [3]. Phylogenetic analyses have suggested CNM to be a new species within the family Anaplasmataceae, which comprises bacteria giving rise to human ehrlichiosis and anaplasmosis with

Fig. 1 Body temperature and evolution of CRP levels in a CNM-infected RA patient treated with RTX



The patient received RTX twice in January 2013, followed by infusions in July 2013 and February 2014. She developed recurrent fever in January 2014, which she carefully registered. Doxycycline 100 mg twice daily was started on 8 April 2014. *Neoehrlichia*-specific PCR analyses of stored patient sera were retrospectively performed. Sera from 27 March and 8 April showed CNM at >1 million copies/ml, while corresponding levels were 1200 copies/ml on 15 April. CNM infection could not be detected in July 2014. CNM: *Candidatus Neoehrlichia mikurensis*; RTX: rituximab.

clinical manifestations ranging from mild febrile illness to severe disease with multi-organ failure [4].

CNM was first reported to be a human pathogen in 2010, and recently a series of all 11 known cases among immunocompromised patients diagnosed in Europe 2010–13 was published [2]: 8 out of 11 displayed a triad of immunosuppressive treatment, haematological malignancy and asplenia. All cases had fever, and the majority experienced thromboembolic complications, indicating a potential fatal outcome. On the other hand, healthy individuals can be asymptomatically infected with CNM and clear the infection spontaneously, as shown in a recent report on 316 asymptomatic northern European foresters [5]. Finally, it is yet to be explored to what degree rheumatic patients with various immunosuppressants are capable of handling this infection. We report the first case of CNM in a rheumatic patient without a haematological malignancy or spleen deficiency. Interestingly, however, similarly to 5 out of 11 of the previously described subjects, our patient was treated with RTX. The dominating symptoms in our patient were recurrent fever and weight loss. These symptoms are non-specific and may potentially be mistaken for disease activity in RA and SLE. CNM appears to lack serological cross-reactivity with other Anaplasmataceae; hence, diagnosis of CNM must currently be sought by PCR analysis.

RTX targets CD20 expressed on B cells and was originally developed against B-cell lymphomas, but it has also been shown to be effective in patients with autoimmune diseases, including RA. RTX depletes most B cells, which is related to a reduction in pathogenic antibody production. In addition, RTX modulates T-cell function in several ways, which could explain its efficacy in RA [6]. This may also be relevant for our case, since cellular immune responses are critical for the clearance of intracellular pathogens such as CNM. In contrast to the haematological context, randomized controlled trials and meta-analyses have not shown any significantly increased infection rates in RTX-treated RA patients [1]. It is possible that CNM infection is an exception. Of interest, reactivation of another intracellular pathogen, JC polyomavirus, causing progressive multifocal leucoencephalopathy, has also been associated with RTX therapy [7]. Human ehrlichiosis may present with neurological symptoms. Interestingly, our patient had increased serum levels of the CNS damage biomarker S100B (0.38 μg/l), which were normalized (<0.1 μg/l) after doxycycline treatment [8].

In summary, we report a case of symptomatic CNM infection in a RTX-treated RA patient that was successfully treated with doxycycline. Hence, when encountering unexplained fever in an immunocompromised patient, we recommend that CNM infection (a potentially fatal, yet completely curable condition) is considered.

Rheumatology key message

- Rituximab may facilitate serious infectious disease caused by *Neoehrlichia*, a novel and elusive tick-borne bacterium.

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Treatment of systemic sclerosis with tocilizumab

Sir, SSc has a highly variable clinical picture and different levels of severity. Despite innumerable attempts to identify potential drugs, there is a lack of effective immunomodulatory therapies [1, 2]. IL-6 overexpression and pathogenicity in SSc have been demonstrated [3], and the effects of IL-6 in the SSc fibrotic response *in vitro* are concentration dependent [4], thus providing the rationale for its antagonization with tocilizumab (TCZ) [5]. Two cases of SSc treated with TCZ have been published [6]. In addition, TCZ has been demonstrated to be effective in SSc-polyarthritis in a trial that enrolled 15 patients treated with TCZ [7]. We report a mini-series of three patients with refractory SSc (patients 1, 2 and 3), treated with TCZ (8 mg/kg every 4 weeks). They were all female, and age at the time of SSc diagnosis was 52 (patient 1), 34 (patient 2) and 53 (patient 3) years old. The time lapse since diagnosis was 3 years, 8 years and 1 year, respectively. At baseline, the manifestations were as follows: skin thickening in face, hands (patients 1, 2 and 3), forearms, trunk (patients 1 and 2) and lower legs (patient 2); facial telangiectasias (patients 1–3); RP (patients 1, 2 and 3); digital ulcers in PIP joints (patient 1 with three ulcers and patient 2 with eight ulcers); arthralgias of PIP joints, wrists, elbows (patients 1 and 2), shoulders (patients 2 and 3) and MCP joints (patient 3), with synovitis only in PIPs and MCPs of patient 3; gastro-oesophageal reflux (patients 1 and 2), malabsorption syndrome (patient 1); intestinal infarction (patient 2); non-specific interstitial pneumonia, according to the scoring system proposed by Wells [8] (patient 1 with

Table 1 Evaluated parameters at baseline and after the first tocilizumab infusion

Parameter	Patient	Baseline	6 months	9 months
mRSS	1	17	11	–
	2	41	25	–
	3	7	5	–
Digital ulcers, *n*	1	3	0	–
	2	8	0	–
	3	0	0	–
Weight, kg	1	35	47	–
	2	49	57	–
	3	70	62	–
Patient global assessment (0–100)	1	70	40	–
	2	70	30	–
	3	60	10	–
Haemoglobin, g/dl	1	9.5	11.5	–
	2	11.8	13.3	–
	3	14.2	14.7	–
ESR, mm/h	1	86	55	–
	2	46	5	–
	3	3	3	–
CRP, mg/dl	1	8.1	1.9	–
	2	1.75	0	–
	3	0	0	–
DLCO, %	1	47.8	50	–
	2	72.1	75	–
	3	78	63	–
Chest CT (Wells' score)	1	Global disease extent 40% Reticular 40% Ground glass 60%	–	No change
	2	Global disease extent 15% Reticular 20% Ground glass 80%	–	No change
	3	Global disease extent 20% Reticular 10% Ground glass 60%	–	Global disease extent 25% Reticular 15% Ground glass 85%

mRSS: modified Rodnan Skin Score; DLCO: diffusing capacity for carbon monoxide.