



Tick-borne co-infections in Europe: Clinical conundrums

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The most widespread European tick species, *Ixodes ricinus*, can transmit several bacterial, viral, and protozoan infectious agents to humans and animals. The differential diagnosis can be difficult since many tick-borne infections have overlapping geographical distributions and share similar vectors and clinical manifestations. Furthermore, the transmission to and outcome of infection in humans can be affected by co-infection of pathogens in ticks. Co-infections in humans can range from seropositivity without clinical symptoms to co-disease, where two or more pathogens cause symptomatic disease. A further challenge is the lack of general guidelines regarding clinical and laboratory recommendations for possible co-infections.

The current study from Kosak et al. [1] suggests that tick-borne infections with Spotted Fever Group (SFG) Rickettsiae and *Anaplasma phagocytophilum* are more widespread than previously considered in Switzerland. Among 121 individuals who were seropositive for *B. burgdorferi*, 65 (53.7%) were seropositive for SFG rickettsiae IgG, 15 (12.4%) were seropositive for SFG rickettsiae IgM and 12 (9.9%) were seropositive for *A. phagocytophilum* IgG. No *A. phagocytophilum* IgM antibodies were found. The authors conclude that infections with SFG Rickettsiae and *A. phagocytophilum* are underdiagnosed and should be ruled out after a tick bite. More specifically, it is advised that treatment with tetracycline should be first-line therapy in patients with early Lyme disease, in whom antibody testing for SFG rickettsiae and *A. phagocytophilum* is not performed. While this might be relevant in the studied context, these recommendations need to be adapted to the local/regional/national epidemiology, since prevalences can vary geographically. Today, when prudent use of antibiotics is called for, phenoxymethylpenicillin might still be a valid treatment option in areas where co-infections are less common [2,3]. Nevertheless, clinicians should pay close attention to accompanying symptoms in patients with early Lyme disease, since these can indicate a symptomatic co-infection. This is corroborated by the present study, in which *B. burgdorferi* seropositive patients with myalgia, headache, and fatigue more frequently had IgG antibodies to SFG rickettsiae than if those symptoms were absent.

Ticks collected from Swiss vegetation have shown somewhat higher prevalences of *Neoehrlichia mikurensis* than of *A. phagocytophilum* [4]. Serological cross reactivity between *N. mikurensis* and *A. phagocytophilum*

has been reported, and the positive IgG response in the studied population might at least partly be elicited by *N. mikurensis* [5]. This is worth considering, since the recommended treatment for neoehrlichiosis is doxycycline 100 mg bid orally for three weeks, which is slightly longer than the recommended duration of treatment for anaplasmosis.

The finding that SFG rickettsiae IgG titres were significantly higher in patients with acrodermatitis chronica atroficans (ACA) is well worth highlighting. Early inflammatory stages of ACA show vasculitis and perivasculitis, and the authors suggest that this may be caused by a concomitant infection with SFG rickettsiae, who have a tropism for microvascular endothelium and can cause rickettsial vasculitis. Furthermore, the authors speculate that ACA could be more common in Europe due to SFG rickettsiae. A more feasible explanation would be that ACA is predominantly caused by *Borrelia afzelii*, which is the most common of the *B. burgdorferi* sensu lato genospecies in Europe, whereas this genospecies is absent in North America [6]. Nevertheless, the idea that a concomitant infection with SFG rickettsiae and borrelia can cause ACA is not far-fetched. Rickettsial vasculitis is well known in Rocky Mountain Spotted fever with its characteristic petechial skin lesions. Furthermore, *N. mikurensis*, which also targets the vascular endothelium, can cause both vasculitis and thromboembolic events and has been observed in patients with erythema migrans [7]. The key to successful treatment in vasculitides caused by infectious agents is an awareness of the diagnosis and targeted antimicrobial therapy, which is usually not included in the standard treatment panel.

The field of co-infections in tick-borne diseases continues to pose a challenge for clinicians. The recent study sheds some light on the prevalence and symptomatology of SFG rickettsiae and *A. phagocytophilum* in Switzerland and the observation that rickettsial vasculitis can play a role in ACA needs to be further investigated.

Declaration of competing interest

LLS has no COI. HHA is currently local PI for the VALOR Borrelia vaccine phase 3-study in Stockholm, sponsored by Pfizer, but not receiving any personal benefits or compensation.

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