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Letter to the Editor

Remembering visceral leishmaniasis as a potential trigger of haemophagocytic lymphohistiocytosis in individuals treated with anti-TNF-alpha therapy

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Dear Editor,

We have read with great interest the report given by Güven et al. (1) regarding haemophagocytic lymphohistiocytosis (HLH) after anti-tumor-necrosis-factor (TNF)-alpha treatment.

We recently reported the onset of HLH in a Scandinavian male 28 days after infliximab treatment Bukan et al. (2). In this report, a bone marrow examination not only verified the ongoing haemophagocytosis but also revealed the presence of Leishmania amastigotes. It is noteworthy that the patient did not have any recent travel history to leishmaniasis-endemic areas at the onset of the symptoms and had never traveled to any endemic areas outside of Europe. We concluded that a dormant visceral leishmaniasis (VL) infection was triggered by anti-TNF-alpha treatment, leading to HLH. The likely pathogenesis behind this is that TNF-alpha may have a protective effect against intracellular infections, such as VL (3). In the report given by Güven and colleagues, the patient had low-titred cytomegalovirus (CMV) viraemia. Similarly, the patient in our report also had low-titred Epstein-Barr virus (EBV) viraemia. CMV and EBV are the most common triggers of HLH (4). Nevertheless, we argue that the primary cause of the hyperinflammatory condition was VL infection and that viraemia was a secondary phenomenon.

As highlighted by Güven and colleagues, only few studies have described cases of anti-TNF-alpha triggered HLH driven by viral or bacterial co-infections. However, VL induced by anti-TNF-alpha treatment has been reported on several occasions (3). Furthermore, VL is a well-known HLH trigger (4, 5). The current standard therapy for HLH is associated with major side effects, and even with treatment, the prognosis of HLH is poor. VL and VL-induced HLH may be effectively treated with amphotericin B (5). Therefore, recognition of VL as the offending pathogen in VL-HLH is of major importance.

VL is a parasitic infection transmitted by Phlebotomine sand flies, and it should be considered in patients with pancytopenia, fever, weight loss, and splenomegaly (3). Although the majority of VL cases occur in the endemic areas of Nepal, India, Bangladesh, Sudan, and Brazil, most cases in northern Europe are imported from the Mediterranean region (6). Many people who are infected with VL only develop subclinical infections. Risk factors for the progression to clinical disease include immunosuppressive therapy, malnutrition, and HIV co-infection (6).

In conclusion, we agree with Güven and colleagues that clinicians should be aware of the possible complications due to anti-TNF-alpha therapy, and we must highlight the importance of testing for VL in patients who develop HLH following anti-TNF-alpha treatment. Considering the risk of VL activation, subclinical VL should be considered prior to the initiation of iatrogenic immunosuppression in patients who reside in, or have traveled to, VL endemic areas, including the Mediterranean region.

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