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Letter to the Editor

Listeria infection in patients using anti-TNFα treatment: Should there be preventive strategies?

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Recently, one of our patients was admitted to the Intensive Care Unit with a severe listeria sepsis while using adalimumab, an anti-TNFα biological. It is a 50-year old man of Moroccan descent with Behçet's disease who was being treated with adalimumab for a year when he presented with fever and hypotension without any other focal symptoms. When blood cultures revealed *Listeria monocytogenes*, he was treated with amoxicillin and recovered uneventfully. No cause for the Listeria infection could be identified.

Listeria infections are rare but are associated with high mortality rates and predominantly present as meningitis, septic arthritis, or sepsis with unknown cause. [1] *Listeria monocytogenes* is an aerobic gram positive intracellular bacillus. Transmission predominantly occurs via contaminated food products [2]. Pregnant women, elderly and immunocompromised patients are susceptible for severe listeria infections [3]. For this reason, preventive food recommendations are given to pregnant women, as well as to patients using immunosuppressive drugs after organ transplantation. These recommendations are not common practice for patients starting with anti-TNFα treatment for rheumatic diseases. However, several studies suggest an important role of TNFα in the human host defense against listeria and therefore, one could suspect an increased risk for listeria infections also in these patients. Here, we present data on listeriosis in our own center, followed by an overview of the current evidence on the risk of listeria infections among anti-TNFα users and the value of preventive strategies.

We collected information of all patients with listeria infections at the Erasmus Medical Center, from January 2008 to December2018. In this period, 28 patients with positive listeria cultures were identified (Table 1). Only one patient used anti-TNFα at the time of infection. Since the introduction of anti – TNFα agents, the Erasmus MC has been one of the leading centers in the Netherlands prescribing these drugs. Similar to the data from the FDA adverse events reporting system, this suggests that the absolute risk for listeria infections in patient using anti-TNF is low. These data might be biased by underreporting since only positive cultures in our center were included, and patients may have been admitted with a listeria infection in other centers.

Several studies on the risk of listeriosis during the use of TNFα blockers have been published. Previous animal studies investigated the role of TNFα in the host defense against listeria infections. Nakane et al. showed that mice who received anti-TNFα therapy had increased growth of listeria cultures in spleen and liver after an induced infection, and there was a dose dependent increased mortality compared to mice who received placebo. [4] Furthermore, in TNFα deficient knock-out mice, increased growth of listeria was measured after induced infection [5]. More importantly, all knock-out mice died after 7 days while all wild type mice survived, suggesting a crucial role of TNF in host defense against listeria infections [5].

Several case reports and case series have been published reporting listeria infections in patients on anti-TNFα treatment. These include patients with various indications for anti- TNFα therapy including inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis and Still's disease [6]. The presentation varied from meningitis, septic arthritis, brain abscess, peritonitis to endophthalmitis. Based on data from the Food- and Drug Administration (FDA), Slifman et al. estimated that the incidence of listeria infections in patient using anti-TNFα treatment was higher compared to the general population [7]. The absolute risk remained low (43 per million person years versus 3 per million respectively) but the authors suggest that this might represent an underestimation due to underreporting. Based on these studies, the FDA added a boxed warning about the risk of listeriosis for the entire class of TNFα inhibitors in 2011.

It is not known whether interventions aiming to avoid listeria infections are effective. Patients starting anti –TNFα therapy in the UK are given food recommendations to avoid listeria infections since 2006. Davies et al. indeed showed a decreased incidence of listeria infections among anti-TNFα users after 2006 [8]. This study is however limited by the inability of the investigators to compare patient characteristics of patients starting anti –TNFα before and after 2006.

In conclusion, there might be an association between anti-TNFα treatment and listeria infections, although the absolute risk of listeriosis appears to be low. Furthermore, there is very little evidence that specific food recommendations are effective in reducing the risk of listeria infections. We think that until further evidence is available, clinicians should be aware of the association, but there is currently not enough evidence for food recommendations to prevent for listeria infections in patients using anti-TNFα treatment.

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Table 1
Overview of patients with positive listeria cultures.

Culture site	Use of anti-TNFα (other immune suppressive agent)	Outcome	Age (years)	Sex	(co)morbidity
Aortic wall	No	Recovered	81	M	Aortic aneurysm
Blood	No (Mycophenolate mofetil)	Recovered	62	F	Microscopic polyangiitis
Blood	No (Solumedrol)	Recovered	36	M	Sarcoidosis
Blood	No	Recovered	52	M	Hemodialysis
Blood	No (Mycophenolate mofetil + prednisone)	Died	67	M	Kidney transplantation
Blood	No	Recovered	64	M	Heart failure
Blood	Unknown	Unknown	94	F	Unknown
Blood	Unknown	Unknown	94	F	Unknown
Blood	No	Recovered	29	F	–
Blood	No	Recovered	66	F	Melanoma
Blood	No	Recovered	59	F	Chronic lymphatic leukemia
Blood	No	Recovered	65	M	Hemochromatosis
Blood	No (Mycophenolate mofetil + tacrolimus)	Recovered	66	M	Liver transplantation
Blood	No	Died	84	F	Meningeoma
Blood	No	Recovered	73	M	Aortic valve replacement
Blood	No	Recovered	77	M	Coloncarcinoma
Blood	No	Died	68	F	–
Blood	No	Recovered	55	F	Atrial fibrillation, gout
Blood	No	Recovered	54	M	Allogenic stem cell replacement
Blood and ascites	No	Died	56	F	Livercirrosis
Blood and liquor	No (Prednisone)	Recovered	51	F	Broncholitis obliterans
Blood and liquor	No	Died	69	M	Livercirrosis, laryngeal carcinoma
Brainabscess	No (Methotrexate)	Recovered	52	F	Psoriasis
Joint	Yes (infliximab)	Recovered	64	F	Rheumatoid arthritis
Liquor	No (Mycophenolate mofetil)	Recovered	58	M	Morbus Waldenstrom
Liquor	No	Recovered	57	F	–
Pleural effusion	No	Recovered	76	M	Oropharynxcarcinoma
Vitrael	No	Recovered	83	M	Diabetes Mellitus

Declaration of Competing Interest

The authors have declared no conflicts of interest.

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