Comment on: Evidence of lifetime susceptibility to Tropheryma whipplei in patients with Whipple’s disease

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Sir,

Rather than a primary immune genetic defect (e.g. chronic granulomatous disease) causing life-long susceptibility to Tropheryma whipplei infection suspected by Lagier et al., the acquisition of tolerance due to systemic antigenaemia and lack of induction of delayed-type hypersensitivity (DTH) caused by lymphatic failure, denoted by lymphangiectasia, can explain the absence of T. whipplei specific immunity.

One of the clinical and histological characteristics of Whipple’s disease (WD) is the co-existence of dilated lacteals (lymphangiectasia) with periodic acid-Schiff (PAS)-positive macrophages. Indeed, small intestinal lymphangiectasia in adults is an important, albeit not specific, clue to WD. See Figure 1. The main, suspected cause of dilated lacteals in WD is the obstruction of intra-abdominal lymph nodes due to effacement of the normal lymph node architecture by fatty deposits, granulomas and fibrosis. In successfully treated intestinal WD, PAS-positive macrophages slowly decrease in number and form over time, attesting to the reversal of the obstructed lymphatic flow.

Besides the important function of clearing protein, particulate matter (including bacteria like T. whipplei) and excess fluid from the interstitial spaces, lymphatic vessels are crucial for the induction of appropriate immune responses by channelling antigens, macrophages, lymphocytes and Langerhans cells to regional lymph nodes. Bypassing lymphatic pathways by direct haematogenous drainage and reduction or blockage of lymphatic flow to regional lymph nodes can induce tolerance and impair the development of DTH, respectively. The level of the DTH to T. whipplei is probably the predictive factor for the manifestations and course of WD, the absence of DTH explains the persistence and massive accumulation of T. whipplei in affected organs seen as sheets of PAS-positive macrophages. The induction of DTH to organisms within infected macrophages activates macrophages and leads to clearance of the organisms.

Antigen is suspected to be the principal regulator of the immune response. Specifically, the antigen dose, the time period during which it is available to interact with immune cells and its anatomic distribution in the host govern the immune response against it. Low levels of antigen are ignored. Adequate, transient levels induce adaptive immunity. A large, persistent antigen dose can elicit two distinct responses based on antigen distribution. High, persistent levels of systemic antigen produce T cell tolerance. In contrast, high, persistent localized antigenic challenge produces immunopathology seen as an excessive, persistent inflammatory response with granulomatous inflammation, tissue destruction and the formation of secondary lymphoid organs. These two latter pathways are equally applicable in WD.

The steady-state stage of classic WD is a systemic, multiorgan infection that exhibits PCR-detectable T. whipplei DNA in the blood, lower serological reactions to T. whipplei, the absence of a Th1 inflammatory response against T. whipplei and alternative rather than classic Th1 activation of macrophages leading to a permissive state for bacterial replication. At the local tissue level, particularly during the prodrome of WD, the affected organs can display a spectrum of immunopathology similar to that of leprosy, ranging from tuberculoid and sarcoid granulomas with few organisms to massive accumulations of macrophages replete with insufficiently degraded T. whipplei antigens and the absence of a T cell inflammatory component. Interference with immune cell trafficking (T cell – macrophage interactions), because of disrupted lymphatic flow, can explain the lack of activated macrophages, and persistence of T. whipplei and its antigens in WD. Indeed, direct injection of immune contact sensitizers, such as chrome, into the bloodstream, bypassing the lymphatics, produces immune tolerance, and both sensitization and the elicitation of allergic contact dermatitis (DTH) are dramatically impaired in lymphoedematous limbs.

Causes of lymphostasis include high-input failure due to inflammation and low-output failure due to blockage or destruction of the lymphatic vessels, the causes of which include infection, chronic inflammatory disorders (e.g. Crohn’s disease), parasitic infestations, trauma (including surgery), radiation therapy and neoplastic disease. What are the origins of lymphostasis in WD? T. whipplei is a ubiquitous organism associated with asymptomatic carriage, but it is also considered to be a cause of bacteraemia and gastroenteritis. Local injury from an infectious or inflammatory insult to intestinal lymphatics could be the predisposing factor that initiates and promotes WD, causing either a chronic inflammatory state and/or a region of decreased immunity where T. whipplei can multiply...
and, via leaky lymphatics, disseminate throughout the body. Depending on local, environmental factors, such as lymphatic drainage, other organs can show symptomatic disease. It is probably more than coincidence that WD and lepromatous leprosy both show lymphangiectasia. T. whipplei and Mycobacteria leprae have much in common: they belong to the Actinobacteria class; ostensibly show tropism for macrophages; neither disease is associated with increased susceptibility to other pathogens; and the level of activation of macrophages (the DTH response) predicts the disease course and clinical manifestations, ranging from focal inflammatory disorders with few detectable organisms (high activation) to widespread, multiorgan infiltrates with abundant organisms (no activation). While an intrinsic defect in macrophage or lymphocyte function cannot be excluded as the underlying cause of WD, the consequences of systemic antigenaemia and lymphatic failure readily explain the absence of specific immunity and life-long susceptibility to T. whipplei.

Transparency declarations
None to declare.

References

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Comment on: Outpatient parenteral antibiotic therapy (OPAT) for bone and joint infections: experience from a UK teaching hospital-based service

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Sir,
We read with interest the article by Mackintosh et al.1 about the role of teicoplanin for outpatient parenteral antibiotic therapy (OPAT) for bone and joint infections (BJIs), considering the high rate of methicillin-resistant Staphylococcus aureus (MRSA) as the responsible pathogen and the increased risk of treatment failure associated with MRSA infections.