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Persistent pain as an indicator of infection from low virulence organisms compared to serological inflammatory markers

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Acute pain as a protective mechanism is well understood by physicians across the world. The benefits of localizing the source of inflammation and restricting movement to prevent further injury are obvious. However, persistent pain, even if poorly localized, can be an indicator of chronic deep-seated infection. The most consistent symptom, in a systematic review of the atypical manifestations of chronic Q fever, was pain[1]. Among these manifestations, vascular infections were associated with significant mortality. However, their early detection was impeded by the non-specific nature of presentations and in many cases, normal inflammatory markers. How are these atypical manifestations hiding from early detection? The possible explanations are linked to the virulence of the organism and the level of activation of the immune system.

It is important to recognise that host damage can occur from either the infecting organism or the host immune system itself. Therefore, the virulence of an organism, or its relative capacity to cause damage depends not only on its own pathogenicity, but also the inflammatory response it triggers[2]. With chronic infections, the fine balance between the pathogenicity of the infecting organism and the tolerance of the host immune system can be disrupted simply by advancing age. The resultant low-grade inflammatory activity in tissues can cause progressive damage that is not easily detected by conventional serological tests like the C reactive protein (CRP). However, the chemokines secreted by stimulated immune cells sensitise nociceptors and the resultant pain can be a surrogate marker for this low-grade inflammatory activity[3]. Neuroinflammation is a rapidly evolving concept not only in regard to aging but also in its association with chronic infections.

Some bacterial infections alter the expression of endothelin-1(ET-1) which, not only maintains vascular homeostasis, but also acts as a pro-inflammatory cytokine[4]. Malaria, Rickettisal infection and Chagas disease have been associated with ET-1 hyperexpression[4]. This could be the mechanism with Coxiella infections as well, given its propensity to cause vascular infections. Alternatively, it has been shown that following an acute Q fever episode, there are transcriptional changes in the monocytes that lead to chronic proinflammatory activity. This has been proposed an explanation for the chronic fatigue syndrome associated with Q fever[5].

Retrospective studies[6,7] have observed that the CRP in synovial fluid specimens of prosthetic joint infections (PJI) was highly dependent on the virulence of the infecting organism. It had low sensitivity in organisms of low virulence. Another study mentions that

diagnostic criteria that mention ESR and CRP for chronic PJI are unreliable[8]. Given that Coxiella burnetii infections can have varying levels of virulence[9], the presentation of patients with underlying serious infections can be non-specific. Many case reports in our review[1] mentioned the absence of fever and raised inflammatory markers. It was only persistent pain that led to further investigation. Whilst osteomyelitis and abscess can commonly present with unrelenting pain, it is also important to consider endovascular infections as a possible cause, particularly in those with aortic grafts and positive Q fever serology. With endovascular infections, 63.2% of patients had pain as their presenting symptom while only 16.7% reported fatigue. Infected aortic grafts commonly cause spondylitis through contiguous spread and chronic back pain could be the only manifesting symptom[10]. A consensus group of experts[11] outlined the difficulty in establishing a case definition and guidelines for aortic graft infections. This is particularly the case for chronic infections of low virulence which are subtle in presentation.

Systematic reviews have demonstrated that inflammatory markers correlate poorly with chronic back pain[12,13]. This suggests that persistent back pain, even with normal inflammatory markers, in the context of positive Q fever serology, has to be further investigated with advanced imaging. As there is no ideal pain assessment tool available[14], physicians not formally trained in pain management may have difficulty in recognising serious underlying causes. This review demonstrated the increased morbidity and mortality that can result from ignoring persistent pain in those with positive Q fever serology. This chronic pain could be a reflection of the low-grade inflammation from Coxiella infection of low virulence.

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