Sarcoid-like granulomatosis in a patient treated by interleukin-1 receptor antagonist for TNF-receptor-associated periodic syndrome

Sir, Recombinant IL-1 receptor antagonist (IL-1ra; anakinra) is being increasingly used in the treatment of diseases such as RA, autoimmune disorders, particularly cryopyrin-associated periodic syndromes, and acute gout. We report the first case of sarcoidosis occurring in a woman treated with anakinra for TNF-receptor-associated periodic syndrome (TRAPS).

A 32-year-old woman was followed up for recurrent fever with persistent subcutaneous inflammation of the trunk and limbs. The onset of disease was noted at the age of 3 years. The diagnosis of TRAPS was made at the age of 19 years when a missense mutation was characterized in the first extracellular N-terminal cysteine-rich domain (CRD1) of the 55 kDa TNF receptor superfamily 1A (C30S TNFRSF1A mutation) [1].

A long-term oral prednisone regimen, etanercept, infliximab and AZA all failed to achieve clinical and biological remission. Treatment with daily s.c. injections of 100 mg anakinra was initiated in November 2006. From the day anakinra was started, clinical symptoms disappeared. CRP decreased to normal baseline values within 3 weeks and remained in the normal range. Prednisone could be definitively stopped in February 2007, 3 months after anakinra was started. Anakinra was well tolerated apart from minor injection site reactions [2]. Unfortunately, anakinra produced only the suspension of inflammatory pro-inflammatory effects of IL-1. Anakinra is well tolerated and reported adverse events are usually mild to moderate, consisting mostly of an inflammatory reaction at injection sites [3]. To our knowledge, sarcoid-like granulomatosis occurring in the setting of anakinra treatment has never been reported.

The diagnosis of sarcoidosis was established on the basis of compatible clinical (anterior uveitis, arthralgia, cutaneous involvement), biological (hypergammaglobulinaemia), radiological (mediastinal lymphadenopathy, pulmonary infiltrates, splenic lesions) and therapeutic (response to steroids) findings and supported by histological evidence in two organs of non-caseating granulomas in the absence of organisms or particles.

Because of the severity of TRAPS and the lack of alternative therapy in our patient, anakinra could not be stopped. However, the compatible chronology between anti-IL-1 therapy and granulomatous disease, the lack of known TRAPS-associated granulomatosis features and the potential implication of IL-1ra in granuloma formation support a causal link between anakinra and sarcoidosis.

IL-1 is a pro-inflammatory cytokine with a variety of both local and systemic effects but it is not recognized as a key cytokine involved in granuloma formation. However, IL-1 takes part in the early macrophage-dependent phase of granuloma responses [4] and may have granuloma-inducing activity [5] in murine models. In sarcoidosis, granulomas not only contain IL-1β but also macrophages that express IL-1ra. Interestingly, tissue staining reveals a stronger IL-1ra expression as compared with IL-1β [6], suggesting that excessive production of IL-1 inhibitors may contribute to granuloma formation. Moreover, injection of monoclonal antibody against type 1 IL-1 receptor in mice inhibits the ability to eliminate Mycobacterium paratuberculosis and promotes extensive formation of well-defined granuloma in the liver [7]. Anakinra may induce the failure of immune regulatory mechanisms to limit the duration of the inflammatory process. Alternatively, by being immunosuppressant, it could also favor infection with an unidentified microorganism suggested as a possible aetiological agent in sarcoidosis (such as Propionibacterium acnes or Propionibacterium granulosum [8]. Of note, other biotherapies such as IFN-γ [9] and anti-TNF-α [10] have been implicated in...
sarcoid-like systemic reactions. In conclusion, recombinant IL-1ra anakinra may induce systemic sarcoidosis.

Rheumatology key message

- Recombinant IL-1ra anakinra may induce systemic sarcoidosis.

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