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LETTER TO THE EDITOR

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Consecutive occurrence of rhinoconjunctivitis, seronegative spondyloarthritis and pyoderma gangrenosum in a patient with ulcerative colitis

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Dear Editor:

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon with a clinical course characterized by periods of exacerbation and remission. Its aetiology is unknown, although genetic, environmental, infectious and immunological factors are thought to be involved. In UC, data seem insufficient to characterize the T-helper (Th) cell cytokine phenotype as either Th1 or Th2, even though there is more evidence of antibody-mediated hypersensitivity in tissue damaging, and less evidence of Th1 cell responses. UC is associated with a variety of extraintestinal manifestations (EIMs) and up to one-third of patients experience at least one in their lifetime. The most frequent EIM in UC is an arthritis included among the seronegative spondyloarthropathies (SpA), which is characterized by inflammatory axial spine disease, asymmetric peripheral arthritis and enthesopathy. Few studies have been performed to establish the profile of pro-inflammatory cytokines in SpA, and a Th predominance has not yet been demonstrated, even though the efficacy of anti-TNF-alpha treatment and other indirect evidence suggest a Th1 implication. Pyoderma gangrenosum (PG) is a dermatologic manifestation seen in about 0.5–5% of UC patients. There are four prototypic forms of PG (ulcerative, pustular, bullous and vegetative), but even in PG the Th profile has not yet been clarified. In this report, we describe the case of a UC patient who showed the consecutive occurrence of allergic rhinoconjunctivitis, SpA and PG over a period of 10 years.

A 14-year-old boy presented to the Gastroenterology Unit in November 1991 with a 1-year history of UC. He had been subjected to tonsillectomy and adenoidectomy at the age of 6 years. The pan-colonoscopy showed an active pancolitis and biopsy confirmed the diagnosis. Over the next 4 years he was admitted to the hospital on four occasions for moderate to severe activity of the intestinal disease. The therapy was established according to the clinical course of UC and was based on chronic administration of mesalazine. Corticosteroids were added to aminosalicylates when needed. At the age of 16, he started to smoke regularly 10 cigarettes per day. In 1993 he underwent an allergologic evaluation for the presence of an increasing perennial rhinoconjunctivitis that had started at the age of 12 with a mild, intermittent clinical profile. He was subjected to skin prick testing (SPT) with a panel of common, local allergens. The patient showed a more intense positive SPT response to mites than to histamine (positive control). Total serum IgE levels were 452 μg/l (normal range 12–240 μg/l), and the circulating eosinophil count was 220 cells/μl (normal count

<500 cells/μl). Allergic rhinoconjunctivitis was confirmed after a challenge test and treated with antihistamine drugs, topical corticosteroid and ophthalmic preparations. No injection immunotherapy was planned. Over the next 6 years we noted an improvement in the allergic symptoms, which gradually disappeared, together with a slow improvement in the intestinal disease in both severity and number of flare-ups. An allergologic evaluation made in June 1998 showed negative skin reaction to the same SPT panel in the presence of normal reactivity to histamine. Total serum IgE levels fell within the normal range (194 μg/l). Eosinophil count was 140 cells/μl. The allergologic status remained unmodified during subsequent follow-ups, and the pan-colonoscopy with biopsy confirmed the remission of UC. In October 1999, the patient was observed at the Rheumatology Unit with severe inflammatory polyarthritis. A bone scintiscan examination was performed after i.v. administration of ^{99m}Tc methylene diphosphonate (555 MBq), using a large-field gamma camera (Starport 400 AT, General Electric, Milwaukee, WI, USA), to determine the distribution and activity of the disease. The sacroiliac involvement was defined on the basis of the sacroiliac/sacrum uptake ratio as suggested by Percy and Lentle [1]. The search for serum rheumatoid factor was negative. Arthritis was classified as seronegative spondyloarthropathy, based on the European Spondyloarthropathy Study Group criteria, and required treatment with methotrexate (10 mg/week). The human leukocyte antigen (HLA) haplotypes, tested with a microlymphocytotoxicity technique, showed no particular rheumatologic susceptibilities (A24, A28, B62, BW4, BW6, CW3, CW7, DR11, DR13, DR52, DQ7). In February 2000, the patient was admitted to the Dermatologic Unit with a large ulcerative pyoderma gangrenosum in the left leg, which required a systemic treatment with prednisone (40 mg/day) and a local therapeutic option with Castellani's paint. At the same time, there appeared in the right leg a small follicular-based pustule (initial lesion of PG) that did not break down and rapidly disappeared.

The patient's history showed the occurrence of UC together with IgE-mediated allergic disease. During the course of UC, symptoms of atopy disappeared at the same time as an improvement in the intestinal disease, while SpA and PG emerged. T-helper lymphocytes have been shown to play an important role in immune responses, and at least three functional subsets of Th cells have been distinguished according to their cytokine secretion profiles. Each subset regulates the others in a dynamic process. A prominence of one or other of the Th1 and Th2 phenotypes is described in several diseases, and cross-regulation of the Th1 immune response to suppress Th2 disease, or vice versa, has been established in human and animal models. Recently, we have shown that UC atopic diseases and SpA, as well as atopic diseases and allergic contact dermatitis (ACD), are strongly polarized immunological conditions tending to mutual exclusion, while SpA and ACD may coexist. To explain the mutual exclusion of atopic diseases and SpA or ACD, and the coexistence of SpA and ACD, we have postulated that the diseases might lie at opposite or equal ends of the immunological spectrum according to T-helper cell responses. It should be noted that atopy is a well-known Th2 condition, while in ACD the Th1 subtype predominates.

The clinical course shown by our patient seems to indicate high Th2 activity at the beginning of his medical history. In contrast, the late onset of SpA and PG, together with a better course of intestinal disease and the disappearance of atopy symptoms, suggests that immunological changes, promoting Th1 manifestations, occurred later in the course of UC. These results clearly indicate dynamic changes in the immune response in our patient. From a dynamic point of view, the immune system could express over time, at the individual level, different responses according to the prevalent Th profile, as found in a patient with rheumatoid arthritis. In particular, our case possibly represents the clinical expression of the linear differentiation model postulated for lymphocyte development. In this model, Th2 represents an immature pattern that, through a Th0 stadium, terminally differentiates along type-1 effector cells. In fact, our patient, after developing UC together with rhinoconjunctivitis, and after a period of remission of both diseases, showed arthritis and PG. Unfortunately, the stimuli promoting the Th1/Th2 balancing or alternation of different Th1/Th2 polarized diseases in vivo remain far from clear. Recently, we have demonstrated that cigarette smoking and appendectomy are risk factors for the development of EIMs in patients with UC. In our case, the patient was exposed to both risk factors, which may have contributed to a T-helper profile modification over time.

The development of these concepts will not only allow a better understanding of the mechanisms involved in the pathogenesis and course of UC, but will also provide the basis for the development of novel strategies for its treatment.

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