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SPECIAL ARTICLE

Inflammatory Bowel Disease: Joint Management in Gastroenterology and Dermatology☆

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Abstract Inflammatory bowel disease (IBD) is a complex entity that includes Crohn disease and ulcerative colitis. It is characterized by a chronic proinflammatory state of varying intensity that often leads to considerable morbidity. In the last decade, several therapeutic targets have been identified that are susceptible to the use of biological agents, including anti-tumor necrosis factor alpha antibodies, which are associated with paradoxical psoriasiform reactions in 5% of patients. Decision-making in the management of these cases requires close collaboration between the dermatologist and gastroenterologist. Inflammatory bowel disease is also associated with various other dermatologic and rheumatologic manifestations, and presents a genetic and pathogenic association with psoriasis that justifies both the interdisciplinary approach to these patients and the present review.

PALABRAS CLAVE
Enfermedad inflamatoria intestinal;
Reacción paradójica;
Antifactor de necrosis tumoral

Enfermedad inflamatoria intestinal: abordaje conjunto digestivo-dermatológico

Resumen La enfermedad inflamatoria intestinal es una entidad compleja que incluye la enfermedad de Crohn y la colitis ulcerosa, y se caracteriza por un estado proinflamatorio crónico con un curso oscilante y que en muchas ocasiones conlleva una gran morbilidad a estos pacientes. En la última década se han identificado distintas dianas terapéuticas que permiten el uso de fármacos biológicos, en particular los anticuerpos dirigidos contra el factor de necrosis tumoral alfa, que se asocian en un 5% de los casos con reacciones paradójicas psoriasiformes, que requieren una estrecha colaboración entre el dermatólogo y el gastroenterólogo en la toma de

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decisiones. La enfermedad inflamatoria intestinal se asocia, asimismo, a otras diversas manifestaciones dermatológicas y reumatológicas, y presenta una asociación genética y patogénica con la psoriasis, que justifica tanto el abordaje interdisciplinario de estos pacientes como la presente revisión.

Introduction

The term immune-mediated inflammatory disease (IMID) refers to entities that share common pathogenic pathways. Although the organs involved may differ, these diseases are characterized by chronic inflammation and also by response to treatment with anti-tumor necrosis factor (TNF) agents. IMIDs include skin conditions such as psoriasis, rheumatic conditions such as rheumatoid arthritis and a range of spondyloarthropathies, and digestive diseases such as inflammatory bowel disease (IBD), a term which encompasses both Crohn disease (CD) and ulcerative colitis (UC). Taken together, IMIDs affect between 5% and 7% of the population in western countries. These diseases share a genetic predisposition, and so more than one may occur in the same patient.

Psoriatic arthritis and the appearance of paradoxical reactions to anti-TNF treatment provide grounds for collaboration between dermatologists and rheumatologists, as well as for integrated care for more complex patients. In the case of CD and UC, given the frequent occurrence of skin manifestations (erythema nodosum, neutrophilic dermatoses, and hidradenitis, for example) and paradoxical reactions, along with the possible development of rheumatological manifestations, close collaboration is also justified between specialists in dermatology, rheumatology, and digestive diseases, with particular dedication to these diseases and experience in the use of immunosuppressants and biologic agents.

On November 21, 2014, in the Hospital de la Santa Creu i Sant Pau, Spain, the first meeting of gastroenterologists, rheumatologists, and dermatologists experienced in IMIDs took place. The different specialists, from leading hospitals in Aragon, the Balearic Isles, and Catalonia met with the aim of discussing topics of common interest. Topics debated in a workshop format included common and differential pathogenetic aspects of IBD and psoriasis; management of other inflammatory manifestations generally associated with IBD activity (erythema nodosum, pyoderma gangrenosum, arthritis); paradoxical manifestations of anti-TNF treatment; and current and future strategies in the treatment of IBD. We considered it of interest to publish the content of these discussions, given the limited literature on the topic.

Etiopathogenesis, Genetics, and Comorbidities: Parallels Between the Gastrointestinal Tract and the Skin

There is a marked parallel between the digestive tract and the skin, as both structures have extensive interfaces in permanent contact with different antigens and an individual microbiome whose disturbances may have pathogenic implications. Both systems also have a complex associated immune system in which both innate and adaptive immunity play important roles.

The pathogenesis of IBD can be explained by the interaction between environmental factors and gastrointestinal flora in a genetically susceptible individual. In IBD, 163 susceptibility loci have been identified, the majority of which are common to CD and UC.[1] Many of the polymorphisms and mutations identified play a potential pathogenetic role as the corresponding proteins are implicated in lymphocyte activation pathways, adaptive immunity, intestinal barrier function, intestinal epithelial barrier repair, and immune tolerance.[1]

Traditionally, CD is considered to be characterized by T-helper (Th) 1 polarization while CU is characterized by Th2 polarization associated with decreased lymphocyte apoptosis.[2,3] Currently, innate immunity is thought to predominate initially with disturbance in intestinal mucosa, secretion of antimicrobial peptides such as defensins, and activation of bacterial antigen recognition in the intestinal lumen. Bacterial antigens are captured by presenting cells, which migrate to the secondary lymphoid organs (Peyer patches) for presentation to naive T lymphocytes. Depending on the phenotype and the cytokines present in the medium, these lymphocytes differentiate to Th1, Th2, Th17, and regulatory T lymphocytes, which modulate response to these antigens.[3] When certain cytokines such as TNF, interleukin (IL) 12, or IL2 are present, clonal expansion of the T lymphocytes occurs with recruitment of circulating T lymphocytes towards the lamina propria, leading to perpetuation of inflammation. The trigger has not yet, however, been identified. Studies have shown that Th1 response predominates in the early phase of CD,[4] with increased IL2 or IL12, whereas in advanced CD, an exaggerated Th17 response may predominate.[5] These observations may have implications for the most appropriate therapeutic strategy according to the stage of disease. Mutation of the IL10 receptor has been reported in early CD.[6] While this may have pathogenic implications, the therapeutic approach, which depends on phenotype and not genotype, is unaffected. In addition, only one third of patients with IBD have one of the polymorphisms described to date.[6] This suggests that the environmental component is much more important than the genetic one and that development of CD is due to interaction between genetic load, the environment, the microbiome, and the genes themselves (Figure 1).

Psoriasis also has a genetic base, attributable in 30% to 50% to the susceptibility locus PSORS1, located on chromosome 6,[7] although in some patient subgroups, the genetic load is even greater (100% in the case of guttate psoriasis).[3] More than 40 susceptibility loci have been identified, and their gene products are related to synthesis of epidermal proteins, innate and acquired immunity, and intracellular transcription processes.[8]