INFLAMMATORY SKIN DISEASES (OTHER THAN ATOPIC DERMATITIS & PSORIASIS)

PYODERMA GANGRENOSUM AND OTHER RARER NEUTROPHILIC DERMATOSES AS PARADIGM OF AUTOINFLAMMATION

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Autoinflammatory diseases are an emerging group of diseases distinct from autoimmune, allergic and infectious disorders, that classically comprises genetically determined forms due to mutations of genes regulating the innate immunity. They are clinically characterized by recurrent episodes of sterile inflammation in the affected organs, in the absence of high titers of circulating autoantibodies and autoreactive T cells. Recently, neutrophilic dermatoses (ND), which are inflammatory skin disorders caused by the accumulation of neutrophils in the skin and rarely in internal organs, have been included among the autoinflammatory diseases. Pyoderma gangrenosum (PG), the main ND that usually presents with deep erythematous-to-violaceous painful ulcers with undermined borders, was the first to be regarded as an autoinflammatory disease when occurring in the context of the so-called pyogenic arthritis, PG and acne (PAPA) syndrome. In PAPA syndrome, different mutations involving the proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) gene, via an increased binding affinity to pyrin, induce the assembly of inflammasomes. These are molecular platforms responsible for the activation of the caspase 1, a protease cleaving the pro-interleukin (IL)-1β to functionally active IL-1β. The overproduction of IL-1β triggers the release of several proinflammatory cytokines and chemokines, inducing the recruitment and activation of neutrophils; the result is a neutrophil-mediated inflammation that is the pathophysiological hallmark of ND. Recently, it has been demonstrated that a missense mutation of SHP-1 induces in a mouse model severe cutaneous inflammation mimicking human ND that is driven by overexpression of IL-1α, suggesting an important role also of this isoform of IL-1 in the pathogenesis of ND. Deletion in CARD9 significantly dampens this IL1-mediated inflammation. Thus, aberrant signaling involving SHP-1 and CARD9 can lead to neutrophil-mediated autoinflammation driven by IL-1α overproduction. PG is also a feature of a new disease entity within the spectrum of autoinflammatory syndromes, PASH syndrome, characterized by the clinical triad of PG, acne and hidradenitis suppurativa. Moreover, PG is present in the so-called synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. SAPHO syndrome is a rare autoinflammatory disease in which osteoarthropathy is associated with various dermatological manifestations in different degrees, such as acne, palmoplantar pustulosis and, more rarely PG, hidradenitis suppurativa and Sweet's syndrome. PAPA, PASH and SAPHO are variants belonging to a single clinicopathological spectrum having abnormal

activation of innate immunity as the crucial pathogenetic event.