OBSERVATIONS

Association Among Sarcoidosis, Type 1 Diabetes, and Charcot Neuro-Osteoarthropathy

Sarcoidosis is a multisystemic inflammatory disease. The association between sarcoidosis and type 1 diabetes is rare. We report two cases of sarcoidosis associated with type 1 diabetes complicated by Charcot neuro-osteoarthropathy (CN).

A subject with type 1 diabetes complicated by peripheral and autonomic neuropathy presented cough and cervical lymphadenopathy. The chest computed tomography (CT) scan revealed bilateral hilar lymphadenopathy. A mediastinal lymph node biopsy showed noncaseating giant epithelioid cell granulomas. The immunohistological examination of a follicle showed the prevalence of T-cells. The result of a Mantoux test was negative. Bronchoalveolar lavage was sterile. ACE was absent from bronchoalveolar lavage fluid and increased to 40 UI/l (normal <20 UI/l; colorimetric enzymatic assay) in serum. Through these tests, sarcoidosis was diagnosed. Ten years later, the subject developed CN (5).

A second subject with type 1 diabetes and neuropathy, after presenting with abdominal pain, diarrhea, and vomiting, underwent an abdomen-pelvis CT (adenopathy and parenchymal liver alterations). The CT-guided biopsy revealed omental lymph nodes of 1 cm (nonnecrotizing reactive lymphadenitis with chronic granulomatosis and epithelioid giant cells) and liver granulomatosis with the presence of intracellular Schaumann's asteroid bodies, indicative of sarcoidosis. This subject developed CN 5 years after diagnosis of sarcoidosis.

Cytokines regulate bone metabolism (2); interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-α, IL-17, and receptor activator of nuclear factor-κB (NF-κB) (RANK) ligand (RANKL) enhance bone resorption, whereas osteoprotegerin (a soluble receptor decoy for RANKL), IL-4, IL-10, IL-12, IL-13, IL-23, IL-18, leptin, and interferon-γ and -β have opposite effects. Therefore, inflammatory conditions are able to modulate local and/or systemic levels of cytokines and are implicated in bone metabolism. A key mechanism involved in CN pathogenesis is increased bone resorption, to which the RANKL/RANK/osteoprotegerin axis is undoubtedly relevant.

The local stromal cells are the major source of RANKL; recruitment and activation of macrophages and T-cells enhance the production of proinflammatory cytokines (TNF-α, IL-1, and IL-6) that stimulate RANKL expression in stromal cells, reducing bone mineral density. This "metabolic inflammatory" interplay allows to provide an explanation of the frequent presence of inflammatory stimuli (i.e., accidental trauma, local surgery, revascularization, orthopedic procedures, neuropathic ulcers, and infections) as trigger factors of acute CN. Several studies have shown the central role of inflammation in diabetes.

Hyperglycemia increases intracellular diacylglycerol content, which activates protein kinase C, which, through NF-κB, increases the expression of multiple inflammatory genes (i.e., *IL-6*, *IL-1*, and *TNF-α*) (3). Furthermore, autonomic dysfunction could disrupt the negative feedback control of inflammation by the autonomic nervous system ("the inflammatory reflex"), exacerbating inflammation (4). Regarding sarcoidosis, several studies have shown high levels of TNF-α secretion from alveolar macrophages of patients with active diseases, and TNF-α inhibitors have been used in the treatment of sarcoidosis, suggesting the relevance of inflammation (5). Furthermore, high levels of parathyroid hormone–related peptide (PTHrP), linked to an alteration of calcium metabolism, have been shown in sarcoidosis. The high inflammatory milieu of such an association between diseases (diabetes and sarcoidosis) could interfere with the metabolic inflammatory balance in bone, enhancing the development of CN, whereas in other circumstances it represents a very rare complication of diabetes.

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