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【 EDITORIAL 】

The Relationship between Remitting Seronegative Symmetrical Synovitis with Pitting Edema and Vascular Endothelial Growth Factor and Matrix Metalloproteinase 3

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Key words: remitting seronegative symmetrical synovitis with pitting edema, RS3PE, vascular endothelial growth factor, VEGF, matrix metalloproteinase 3, MMP-3

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Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a syndrome that was initially reported by McCarty et al. (1) in 1985 in a study comprising 8 elderly men (age range, 59-82 years) and 2 elderly women (65 and 66 years old). This disease occurs in the elderly and is characterized by "remitting," "seronegative" [rheumatoid factor (RF) negative], "symmetrical," and "synovitis with pitting edema" (synovitis characterized by pitting edema on the dorsum of the hands and feet). The etiology of this condition is unknown, the patients test negative for autoantibodies, and there is no clear evidence of an autoimmune disease in such cases. Some reports have indicated the involvement of human leukocyte antigen (HLA)-B7, HLA-CW7, and HLA-DQW (1-3); furthermore, the involvement of the immune system is suspected. While rheumatoid arthritis (RA) and polymyalgia rheumatica have clear diagnostic criteria, there are no clear classification criteria for RS3PE, and patients with this syndrome are typically diagnosed when they present with the abovementioned features and when other diseases have been ruled out. Patients may also be diagnosed with RS3PE when they meet all of the diagnostic criteria proposed by Olive et al. (4) in 1997: 1) pitting edema in all 4 limbs, 2) an acute onset, 3) age ≥50 years, and 4) negative for RF.

Pitting edema that is symmetrical in the extremities of the four limbs-a characteristic feature of this disease-is attributed to tenosynovitis of the flexor and extensor tendons. In recent years, the role of vascular endothelial growth factor (VEGF) with its angiogenic and vascular permeability-enhancing activities that contribute to synovitis and edema has gained attention (2, 3, 5). The level of VEGF in the peripheral blood is notably higher in patients with RS3PE syndrome than in those with RA and healthy individuals. The expression of VEGF is inhibited by steroid treatment for RS3PE syndrome (2, 3, 5). Therefore, measuring the serum level of VEGF may aid in the diagnosis of RS3PE.

Patients with malignant tumors and POEMS syndrome are known to present with elevated VEGF levels (6). The complication rate of a malignant tumor in patients with RS3PE syndrome is high (31% to 54%); indeed, the incidence of malignant tumors in elderly patients with this syndrome is 7 times higher in men with RS3PE syndrome than in elderly men in the general population and 4 times higher in women with RS3PE syndrome than in young women (3). The incidences of gastric cancer, colorectal cancer, prostate cancer, and malignant lymphoma are the most common in patients with RS3PE, followed by lung cancer, ovarian cancer, bladder cancer, and chronic lymphocytic leukemia (3). These findings suggest the involvement of VEGF along with malignant tumors in RS3PE.

The presence of tuberculosis and parvovirus B19, *Streptobacillus moniliformis*, *Escherichia coli*, *Campylobacter jejuni*, and *Mycoplasma pneumoniae* infections has been reported in association with RS3PE syndrome (7-10). In addition, the onset of RS3PE syndrome in a patient with toxic shock syndrome (TSS) has been reported, indicating the role of elevated VEGF levels, which accompany TSS, in the onset of RS3PE syndrome (11). Recently, an association between RS3PE syndrome and organizing pneumonia was reported (12). VEGF levels have also been shown to be elevated in patients with organizing pneumonia (13). Such elevations were observed in a study conducted by Hosoda et al. (12).

Taken together, these findings indicate that malignant tu-

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mors, infections, and organizing pneumonia are all characterized by elevated levels of VEGF; therefore, the possibility of VEGF involvement in the pathology of RS3PE syndrome is extremely high.

Matrix metalloproteinase 3 (MMP-3) is a protease generated from synovial cells, chondrocytes, and fibroblasts owing to inflammatory cytokines and oxidative stress. The serum MMP-3 levels are elevated in patients with RS3PE syndrome due to inflammation of the synovial membrane (5, 14). Serum MMP-3 reportedly supports the diagnosis as well as reflects the state of the disease and may be more sensitive than C-reactive protein (15). MMP-3 also is known to be produced in breast cancer, gastric cancer, colorectal cancer, lung cancer, head and neck cancer, and basal cell carcinoma (14). Therefore, if the level of MMP-3 is elevated in RS3PE syndrome, complications associated with malignant tumors must be considered (16).

The pathogenesis of RS3PE syndrome remains unknown, and its diagnostic criteria have not yet been established. Therefore, in addition to the characteristic symptoms of RS3PE syndrome, the evaluation of HLA, VEGF, and MMP-3 levels may prove useful for diagnosing and determining the progression of this disease.

The author states that he has no Conflict of Interest (COI).

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