THE RELATIONSHIP OF VEGF AND PGE2 EXPRESSION TO EXTRACELLULAR MATRIX REMODELING OF THE TENOSYNOVIAL IN THE CARPAL TUNNEL SYNDROME

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Introduction

Recent studies using MRI have clearly demonstrated that flexor tenosynovial swelling is the most often encountered abnormality in CTS. However, histological findings of the flexor tenosynovium confirm that the involvement of inflammation is very rare and that oedema, angiogenesis, vascular stenosis, and fibrosis with collagen degeneration are the most common features. The purpose of the present study is to analyze the expression of prostaglandin E2 (PGE2) and vascular endothelial growth factor (VEGF), two representative angiogenic and vascular permeability factors to identify their roles in the tenosynovium pathology of CTS.

Materials and Methods

Subjects: All patients signed an informed consent document, and the study was approved by the institutional review board. The study group consisted of 40 patients (12 men and 28 women) who underwent open surgical treatment for CTS. The patients’ mean age was 53.18 years (range, 31 to 79 years). Patients with a history of diabetes mellitus, inflammatory arthritis, autoimmune disorders, thyroid abnormalities, or renal failure, were excluded. The patients were divided into 4 groups based on the duration of disease: group A (n=9; ≤3 months); group B (n=12; 4-6 months); group C (n=6; 7-12 months); and group D (n=13; ≥12 months). Most of the patients in group D had had mild numbness in the median nerve distribution for years, however, abrupt worsening of their symptoms had led them to choose surgery.

Histological analysis: The specimens were cut into 5μm-thick sections, and stained with hematoxylin & eosin (HE) and Sirius red. Immunohistochemical studies were performed with polyclonal rabbit anti-VEGF antibody (Santa Cruz Biotechnology, Santa Cruz, CA), monoclonal anti-proliferating cell nuclear antigen (PCNA) (Dako Japan, Kyoto, Japan) and monoclonal anti-type III collagen antibody (Daiichi Fine Chemical, Takaoka, Japan).

Biochemical analysis: The biopsy specimens were homogenized and subjected to enzyme-linked immunosorbent assay (ELISA).

Results

Immunolabelling of type III collagen clearly demonstrated extracellular matrix (ECM) changes in the tenosynovium. In group A, the oedema manifested with the characteristic findings of connective tissue separation and villous thickening of the tenosynovium. At this stage, type III collagen expression was weak. Specimens from group C generally showed disorganization of collagen bundles characterized by thickening, disruption, and hyaline degeneration. Both immunolabelling of type III collagen (Figure 1) and Sirius red staining demonstrated that drastic collagen remodelling took place insidiously between the early and late phases (Figure 2). Another conspicuous histological change in group C was severe stenosis of small arteries and angiogenesis in the fibrotic area. PCNA staining demonstrated that the cells within the vessels and synovial lining do proliferate (Figure 3). It is noteworthy that cell proliferation was observed only in group B when the histology of the flexor tenosynovium changes from oedematous to fibrotic. Immunohistochemical staining localized VEGF to the synovial lining, pericytes, vascular smooth muscle, and endothelium (Figure 4). Furthermore, the areas with distinct VEGF expression were closely matched with the areas of cell proliferation. Figure 5 shows the results of quantitative analysis of VEGF and PGE2. Both molecules were expressed at significantly higher levels in group B as compared to group A or C. Interestingly, group D also showed higher expression than groups A and C. It is noteworthy that there was a significant correlation between VEGF and PGE2 levels.

Discussion

VEGF and prostaglandins as well as various cytokines are all present in the synovial tissue and interact cooperatively in the pathogenesis. Tucci et al. speculated that PGE2 was induced by ischemia in the carpal tunnel, which in turn causes oedema by increasing vascular permeability1. If his hypothesis is true, PGE2 would have to be induced during the early phase. However, the present study has demonstrated that PGE2 production increases temporarily only in the intermediate phase. This result strongly indicates that neither PGE2 nor VEGF contribute to oedema formation or onset of CTS. Because PGE2 expression level was correlated well with that of VEGF, they cooperatively involves in vascular stenosis and angiogenesis. Since collagen degeneration and fibrosis proceeds during intermediate phase, circulatory disturbances from stenotic vascular lesion may induce drastic ECM alteration. The molecules were expressed at significantly high levels in group D, too. Patients in group D had a unique clinical history in that most them had complained mild symptoms for years and sudden exacerbation of pain led them take surgery. Therefore, vascular lesions induced by the molecules may affect pain severity.

Figure 1: Immunolabeling for type III collagen in group C

Figure 2: Sirius red staining (red; type I, green; type III collagen)

Figure 3: PCNA staining

Figure 4: Immunolabeling for VEGF

Figure 5: Quantitative analysis with ELISA

References