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Plasma Cell Granuloma in Cyclosporine-Induced Gingival Overgrowth : A Report of Two Cases with Immunohistochemical Positivity of Interleukin-6 and Phospholipase C-γ1

We report two cases of gingival plasma cell granuloma in a 34-yr-old and 40-yr-old two male renal transplant recipients with cyclosporine A (CsA)-induced gingival overgrowth (GO). Histologically, these lesions were composed of mature plasma cells, showing polyclonality for both lambda and kappa light chains and fibrovascular connective tissue stroma. In addition to the fact that CsA-induced plasma cell granuloma is rare, the salient features of our cases were the secretion of interleukin-6 and overexpression of phospholipase C-γ1 of the tumor cells, which may explain the mechanisms of CsA- induced GO.

Key Words : *Cycosporin; Side Effect; Gingival Overgrowth; Plasma Cells; Interleukin-6; Phospholipase C*

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INTRODUCTION

Cyclosporine A (CsA) is a widely used immunosuppressant, with clinical applications ranging from organ transplants to chronic inflammatory diseases. One of the major side effects associated with CsA treatment is the development of gingival overgrowth (GO) (1-3). Regarding the histology of CsA-induced GO, the exuberant growth of connective tissue by active fibroblasts within the periodontium is the most common feature, and a case of extramedullary plasmacytoma as well as squamous cell carcinoma and Kaposi's sarcoma has been previously reported (4). To our knowledge, there has been no case of gingival plasma cell granuloma in renal transplant recipients treated with CsA as one of immunosuppressive agents.

Several studies have suggested that one of the pathogenic mechanisms underlying drug-induced GO may be the enhanced secretion of interleukin-6 (IL-6) in response to the immunosuppressive medications, such as CsA (5, 6). A recent report demonstrated that CsA upregulated phospholipase C-β1 (PLC-β1) in fibroblasts from GO (7). However, data concerning the molecular mechanisms involved in the pathologic connective tissue proliferation are as yet preliminary in nature.

We here report two patients who developed plasma cell granuloma of the gingiva 12 months and 8 yr after combined treatment with CsA and prednisolone for renal transplantation with immunohistochemical studies for IL-6 and PLC-γ1.

CASE REPORT

Clinical history

Case 1: A 62-yr-old male patient with an end stage renal disease due to diabetic nephropathy underwent renal transplantation in July 1998 and then was treated with CsA and prednisolone. One year later, he complained of gingival enlargement with bleeding.

Case 2: A 59-yr-old female patient presented with a diffuse gingival swelling, which had gradually increased for two years. She complained of difficulty in mastication, which was associated with gingival hyperplasia. She had underwent renal transplantation in April 1990 and was treated with CsA and prednisolone. She had one episode of acute rejection in 1991, which was treated with a high dose of CsA and prednisolone.

Pathologic findings

On dental examination, two patients were revealed to have marked generalized GO and underwent gingivectomy with gingivoplasty. The gross specimen from the gingiva consisted of a pinkish yellow fibro-connective tissue covered with mucosal epithelium, measuring 3.5 cm in its greatest dimension. Cut-section showed a homogeneous and granular surface.

Tissue sections showed hypertrophic squamous epithelium and underlying cellular lesion composed mostly of mature plasma cells and intervening fibrous connective tissue with

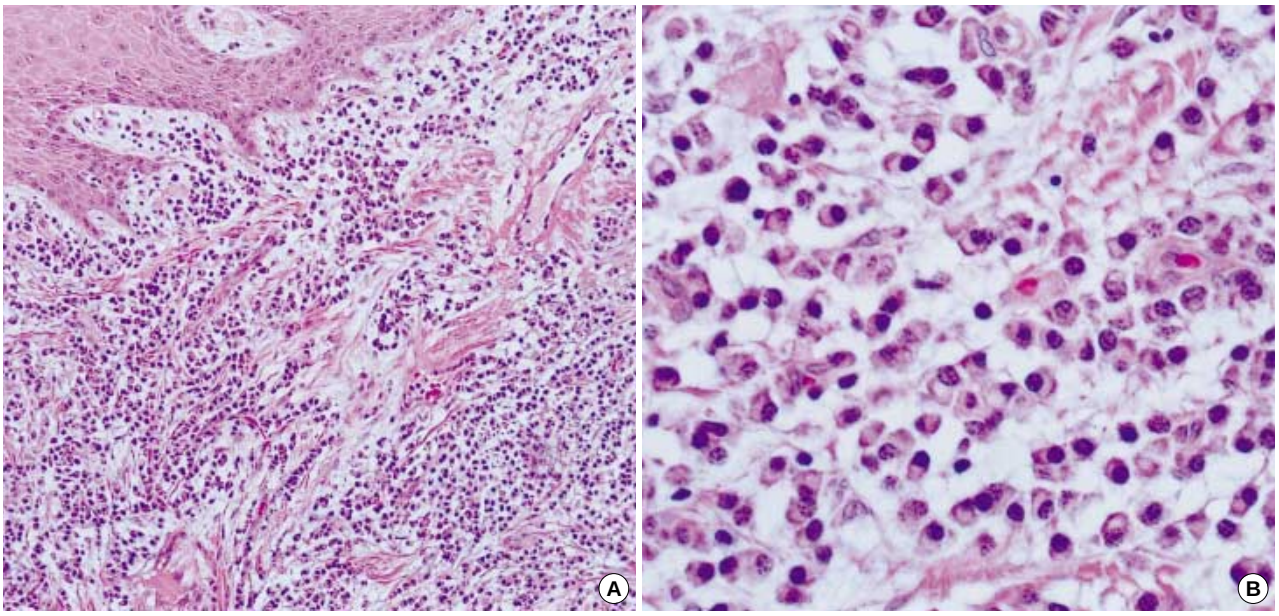

Fig. 1. Microscopic findings. (A) a low power view of gingival biopsy specimen shows diffuse infiltration of plasma cells in fibrotic stroma with overlying squamous epithelium (H&E, × 100). (B) a high power view of Fig. 1A reveals that the infiltrating plasma cells are all mature forms and do not show any pleomorphism (H&E, × 400).

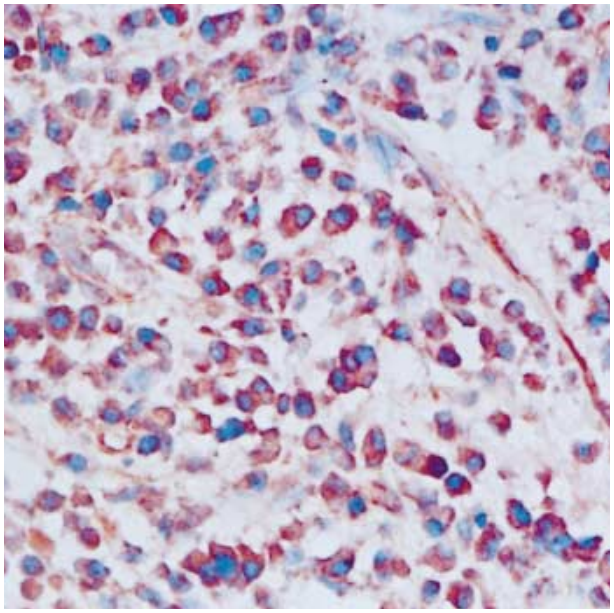

Fig. 2. Immunhistochemistry for IL-6 demonstrated that plasma cells, endothelial cells, and fibroblasts are diffusely positive in their cytoplasms (× 200).

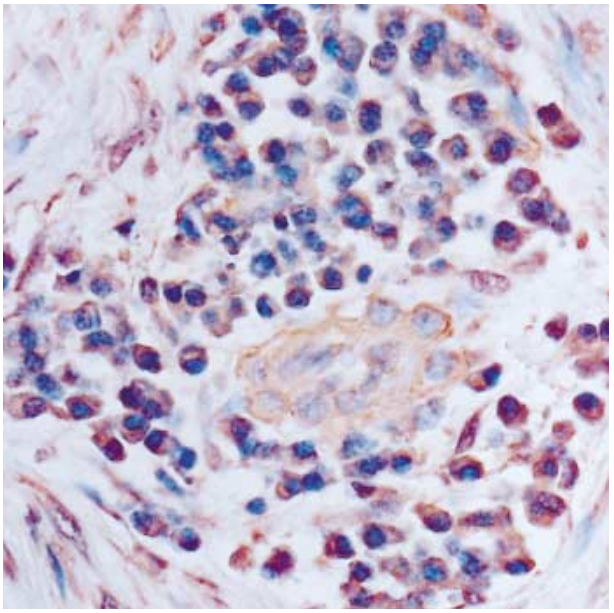

Fig. 3. PLC-γ1 immunoreactivity is positive in the cytoplasms of most plasma cells (immunostain for PLC-γ1, × 200) and smooth muscle cells of the vascular wall (internal staining).

blood vessels (Fig. 1A). The individual plasma cells had eccentric round nuclei with cartwheel chromatin pattern and abundant cytoplasm (Fig. 1B). There was no nuclear atypia or pleomorphism. Mitotic figures were not observed. Cytoplasms of some plasma cells contained immunoglobulin-like globules. The covering epithelium showed slight hyperplasia. Neither ulceration nor atypical proliferation was observed. Increased fibrosis with fibroblast activation was not remarkable. Immunophenotyping revealed polyclonality for both lambda and kappa light chains (data not shown). Stainings of these cells for panT, panB, CD68, CD15, and CD30 were negative. These immunohenotyping findings confirmed the light microscopic interpretation of plasma cell granuloma composed of mature plasma cells. Cytokeratin staining showed strong positivity on the squamous epithelium.

Immunohistochemistry for IL-6 and PLC-γ1

Antibodies for IL-6 (8) and PLC-γ1 (9) used in this study. Most infiltrating plasma cells showed strong expression of IL-6 in their cytoplasms (Fig. 2). Beside the tumor cells, endothelial cells and fibroblasts were also positive for IL-6, even if less intense. The PLC-γ1 was diffusely positive in plasma cells and stromal cells (Fig. 3). We also did an immunohistochemical study for PLC-β1, but the plasma cells and fibroblasts were negative for this isozyme in tissue section (data not shown).

DISCUSSION

Gingival overgrowth is a well-documented unwanted side effect associated with phenytoin, cyclosporine, and the calcium channel blockers (1-3). The present cases showed profound and diffuse mature plasma cell infiltration in addition to the fibroblast proliferation with fibrosis, which was rather less prominent. Even if CsA-induced GO is almost always associated with acute or chronic inflammation due to plaque accumulation, triggering the secretion of inflammatory cytokines (5, 6) and mediators, the present case showed unique findings. Among the previous reports of CsA-induced GO, only one case reported the primary extramedullary plasmacytoma with favorable prognosis. Therefore, it seems that a careful differential diagnosis from malignant plasmacytoma was needed in our cases (4). However, as described in microscopic findings, the infiltrating plasma cells were almost fully mature and showed obvious polyclonality for lambda and kappa light chains by immunohistochemistry, which could differentiate the plasma cells from these of malignant plasmacytoma.

Although the pathogenesis of drug-induced GO is uncertain, it has been postulated that CsA alters the fibroblast activity through effects on various growth factors and cytokines, such as PDGF-β (platelet-derived growth factor -β) (10, 11) and IL-6 (5, 6). IL-6 is known to not only mediate important signals in the nonspecific gingival inflammation, but also play an important role in the pathogenesis of CsA-induced GO. Both the present two cases revealed strong immunoreactivity for IL-6 in the cytoplasms of plasma cells, as well as endothelial cells and fibroblasts. This finding suggests that CsA does regulate the cytokine expression in gingival tissue, and this effect may play an important role in the pathogenesis of CsA-induced GO, along with its well-established effect on T cells (4). Considering that multiple myelomas are associated with high levels of IL-6, IL-6 plays an important role in the differentiation and activation of plasma cells as well as other stages of B cells (8). IL-6, secreted by gingival tissue due to CsA stimulation, may induce heavy plasma cell infiltration, as in our cases and in the previously documented case of plasmacytoma (5).

One of the interesting findings in our cases is the overexpression of PLC-γ1 in plasma cells of the gingival tissues. PLC-γ1 is involved in cell proliferation via various growth factors, signaling pathways, including that of PDGF (12) as has been, demonstrated in several cancer tissues. Plemons et al. (10) demonstrated CsA-induced GO is associated with the enhanced expression of the macrophage PDGF-β gene. The fact that PDGF is related with PLC-γ1 signaling pathway may support our hypothesis that PLC-γ1 is involved in CsA-induced GO. Although a previous study suggested that cAMP/protein kinase A might be involved in IL-6 production by human gingival fibroblasts (5), recent observation showed that tyrosine phosphorylation of PLC-γ1 is induced by IL-6 in PC 12 cells (13). The elucidation of exact role of and relation between IL-6 and PLC-γ1 needs further experiments. A recent report demonstrated that CsA upregulated nuclear PLC-β1 in fibroblasts from GO (7). In the present cases, neither plasma cells nor fibroblasts expressed PLC-β1. The possible explanations for the discrepancy between our result and that of Breschi et al. (7) include the differences of the materials (tissues vs cells) and antibodies used, and the major component (plasma cells vs fibroblasts).

Our observation suggests that IL-6 and PLC-γ1 may induce heavy plasma cells infiltration in CsA-induced GO. Considering the increased levels of IL-6 and PLC-γ1 in plasma cells, understanding of the roles of IL-6 and PLC-γ1 in CsA-induced GO can be of great implication in designing future therapies aimed at the prevention of GO after cyclosporine treatment for immune suppression in transplant recipients.

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