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Human cytomegalovirus in peripheral giant cell granuloma

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Background: The peripheral giant cell granuloma is a relatively common non-neoplastic inflammatory lesion of gingiva, but the etiopathogeny remains unknown. This study aimed to evaluate the importance of human cytomegalovirus and Epstein–Barr virus in a peripheral giant cell granuloma of a 47-year-old female.
Methods: The lesion was studied clinically, histopathologically, immunologically and virologically using established procedures.
Results: The gingival growth was located at the mesial surface of the maxillary left canine having a vital pulp. The mass was 12 × 21 mm in size and exhibited a smooth surface with no evidence of fluctuation on palpation. An excisional biopsy revealed giant cells in a fibrohistiocytic stroma with areas of haemorrhage. Serum protein levels and lymphocyte subsets were within normal limits, except $CD3^+$ and $CD4^+$ cells were below normal ranges. Polymorphonuclear leukocytes expressed p150,95 (CD11c/CD18) and CXCR-2 receptors within normal ranges, but the CXCR1 receptor showed decreased density, and CD15 were below normal range. A virological sample of the tooth surface adjacent to the gingival swelling yielded 7.6×10^3 copy-counts of cytomegalovirus and 4.3×10^3 copy-counts of Epstein–Barr virus.
Conclusions: The clinical and histological findings were consistent with the diagnosis of peripheral giant cell granuloma. Cytomegalovirus has the potential to induce multinucleated giant cells, and the possibility that the virus contribute to the development of peripheral giant cell granuloma merits further study.

Key words: cytomegalovirus; Epstein–Barr virus; peripheral giant cell granuloma; periodontal disease

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The peripheral giant cell granuloma of the oral cavity (giant cell epulis) is a relatively common non-neoplastic lesion of middle-aged individuals (13). The lesion is located at the gingival margin as an exophytic growth with a diameter of usually 1–2 cm. Peripheral giant cell granuloma can also develop adjacent to dental implants (21). The giant cell granuloma lesion typically appears as an irregular, smooth, glossy mass of a bluish-purple color, which may ulcerate and occasionally invade the underlying bone. Histologically, peripheral giant cell granuloma is characterized by proliferation of fibrohistiocytic cells and numerous multinucleated giant cells separated by a vascularized stroma.

The oral peripheral giant cell granuloma is generally considered to be a response to injury and is commonly associated with persistent gingival inflammation but the etiopathogeny of the granuloma remains enigmatic. It is of interest that cytomegalovirus has been linked to several different proliferative lesions in various parts of the body, such as Wegener's granulomatosis with progressive palatal ulceration and osseous destruction (2), exophytic lesions of the airways (9), granuloma formation in the lungs (16), granulomatous cutaneous lesions (3) and fibrin-ring granulomas of the bone (28) and the liver (7). Epstein–Barr virus has been related to rare cases of oral plasma cell granuloma (4), post-transplantation lymphoproliferative disorders of gingiva (18), lymphomatoid granulomatosis (14) and systemic granulomatous arteritis (5). As herpesviruses have been associated with a variety of granulomas, though with histopathologies quite different from that of giant cell granuloma, and because large quantities of herpesviruses can exist in periodontal lesions (20, 24), this study sought to determine if cytomegalovirus or Epstein–Barr virus were connected to gingival peripheral giant cell granuloma.

Material and methods

A 47-year-old female presented with a gingival growth of inflamed tissue at the

mesial surface of the maxillary left canine. The lesion reappeared at 6 months following the initial excision, and the data included here pertain to the recurrent lesion. The patient was generally healthy, except for dryness of both eyes.

Peripheral blood was collected for evaluation of immunoglobulins (IgA, IgG, IgM), complements (C3, C4), C-reactive protein and rheumatoid factor (Behring Diagnostics GmbH, Marburg, Germany). Immunophenotyping of leukocyte subsets was carried out by two-color and three-color flow cytometry using panels of conjugated monoclonal antibodies (BD Biosciences, San Jose, CA). Antinuclear antibody (ANA) and autoantibodies against ssA/Ro, ssB/La, Sm-RNP, Scl-70, centromere, mitochondrial and neutrophil antigens were assessed by enzyme-linked immunoassay (Orgentec Diagnostika GmbH, Mainz, Germany).

An excisional biopsy specimen was fixed in 10% neutral phosphate-buffered formaldehyde, and serial sections of 5-μm thickness were cut from paraffin-embedded tissue blocks and placed on poly-L-lysine-treated slides. Specimens were stained with hematoxylin & eosin for histological examination.

A virological sample was obtained using a periodontal scaler from the mesial pocket of the affected canine. A 5′-nuclease (TaqMan) real-time polymerase chain reaction (PCR) assay was used to determine the genomic copy-counts of cytomegalovirus and Epstein–Barr virus (11). Sample DNA was extracted using an alkali phenol–chloroform–isoamyl alcohol procedure (19) and then dissolved in 100 μl distilled water. Previously described PCR primers and probes were employed in the study (20).

Results

A painful pathological growth 12 × 21 mm in size was observed at the labial–mesial aspect of the maxillary left canine, extending anteriorly onto the edentulous ridge, but not crossing the midline (Fig. 1). The maxillary canine showed no discoloration, was non-tender on percussion, and revealed a vital pulp on vitality testing. The patient did not report a history of trauma of the anterior teeth. Most teeth showed moderate periodontitis.

The gingival growth exhibited a smooth surface and demonstrated no evidence of fluctuation on palpation. Orthopantomogram and periapical radiographs revealed little or no radiolucency of the alveolar bone around the canine. The excisional

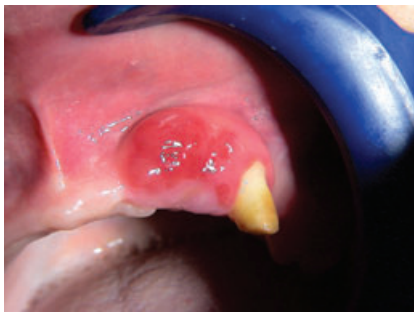

Fig. 1. Clinical photograph of the gingival growth.

biopsy showed giant cells in a fibrohistiocytic stroma with areas of hemorrhage (Fig. 2). The lesion was covered with squamous epithelium. The histopathological findings were consistent with the diagnosis of peripheral giant cell granuloma.

Serum protein levels (IgG, IgA, IgM, C3, C4, C-reactive protein, rheumatoid factor) and lymphocyte subsets (CD8, CD14, CD19, $CD3^{-}$ $CD16^{+}$ 56^{+}, CD45, CD4/CD8) were within normal limits. $CD3^{+}$ and $CD4^{+}$ cells were below normal ranges. The percentage of polymorphonuclear leukocytes expressing p150,95 (CD11c/CD18), CXCR1 and CXCR-2 receptors were within normal ranges, but the CXCR1 receptor (interleukin-8 receptor) showed decreased density. The percentage of polymorphonuclear leukocytes expressing CD15 (sLeX) and the membrane density of this adhesion molecule were below normal ranges. ANA were strongly positive by both enzyme immunoassay and indirect immunofluorescence tests, and anti-ssA antibody was detected by enzyme immunoassay. The ANA results led us to consider Sjögren syndrome, but the patient did not exhibit xerostomia.

The virological examination revealed cytomegalovirus in a quantity of 7.6×10^3/ml and Epstein–Barr virus in a quantity of 4.3×10^3/ml.

Discussion

Herpesviruses participate in more types of oral pathosis than previously recognized (22), and may also play a role in the development of peripheral giant cell granuloma. The finding of cytomegalovirus at the granuloma lesion was of interest. Cytomegalovirus resides in periodontal macrophages (8), and so may be abundant in peripheral giant cell granuloma lesions containing fused monocytes/macrophages. Through specialized proteins, the cytomegalovirus infection could interfere with the production and action of cytokines, chemokines and growth factors (23), thereby giving rise to the mass of granulation tissue. Cytomegalovirus (10) and Epstein–Barr virus (15) have previously been associated with hyperplastic gingival tissue in immunocompromised individuals. Also, cytomegalovirus can inhibit the functions of polymorphonuclear leukocytes (1) which, together with the neutrophil dysfunctions observed in the blood tests, may result in a gingival population of impaired neutrophils.

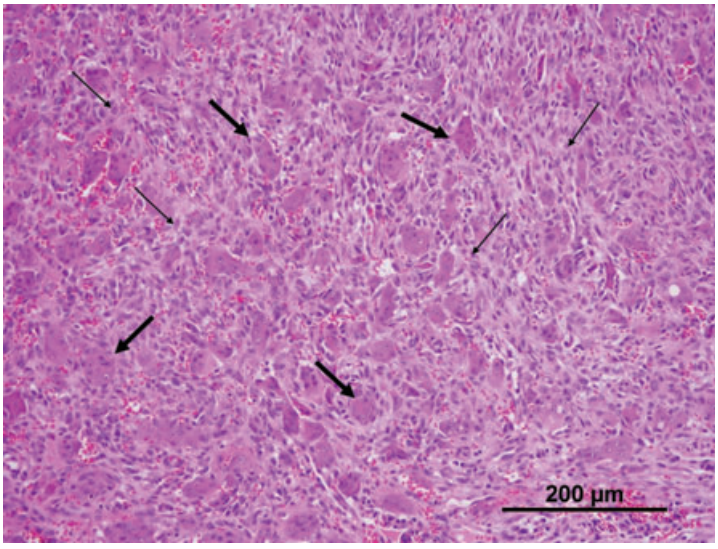

Fig. 2. Proliferative lesion showing multinucleated giant cells (thick arrow) and fibrohistiocytic stromal cells (thin arrow) within well-vascularized connective tissue (hematoxylin & eosin staining, 200 × magnification).

The cytopathological effects of herpesvirus infections are not completely known. Cytomegalovirus is able to induce a marked cellular aggregation and multinucleated giant cell formation in human embryo lung cell cultures (27), and in monocyte-derived macrophage/microglia cells in human brain cultures (17). Also, cytomegalovirus and human immunodeficiency virus, in cooperation at a single cell level, can produce multinucleated giant cells (6). Perhaps, in accordance with the model of Söderberg-Nauclér (25), the immune system would recognize the giant cells as 'altered self' and, in an attempt to eliminate them, sustain a local inflammation. Epstein–Barr virus infections may participate in the formation of Reed–Sternberg multinucleated cells in cases of Hodgkin's lymphoma (12) and in other types of multinucleated giant cell lesions (5). However, Epstein–Barr virus resides in periodontal B cells (8), which may not be directly involved in the formation of the gingival granuloma, although the Epstein–Barr virus may enhance the overall viral assault by transactivating a coexisting cytomegalovirus. The potential of herpesviruses to induce multinucleated giant cells is consistent with a viral role in the development of oral peripheral giant cell granuloma.

The present peripheral giant cell granuloma reappeared following the initial surgical excision. It may be of interest to study if relapse can be prevented by combining surgery with an antiviral medication. Sunde et al. (26) found that a 10-day course of Valtrex®, prescribed to a patient with recurrent periodontitis, was able to suppress high loads of subgingival Epstein–Barr virus to undetectable levels for at least one year.

The event that triggers a peripheral giant cell granuloma is unclear. If related to a foreign body insult or a local irritant, the injury may cause reactivation of a latent cytomegalovirus infection within periodontal macrophages. The active cytomegalovirus combined with certain host immune alterations may then give rise to the giant cell granuloma formation. However, additional patient cases are needed to incriminate cytomegalovirus or any other virus in the formation of the fibrohistiocytic cell proliferation and multinucleated giant cells and in the gingival growth characteristic of peripheral giant cell granuloma.

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