Multiple Fistula Formation in the Gingiva Caused by Cytomegaloviral Infection Associated with Malignant Lymphoma: Report of a case

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A relative rare case of a cytomegalovirus (CMV) infectious disease is reported. Recently, CMV infection has attracted increasing clinical attention due to an increase in susceptible hosts, and CMV infections are usually manifested by serious symptoms. This patient showed multiple fistulae in the lower gingiva and the enlargements of gingiva and submandibular lymph nodes, but no other serious systemic complications. Cytomegaloviral infection caused intractable fistula formation in an immunocompromised host.

Key words: cytomegaloviral infection, oral symptoms, malignant lymphoma

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Introduction

Cytomegalovirus (CMV) is a linear DNA virus that is a member of the family of herpes viruses. CMV infection commonly occurs during the postnatal period and remains asymptomatic without serious presentation (1). However, recent reports have suggested that this virus may become activated due to immunosuppression in patients undergoing organ transplantation, a higher dose of chemotherapy or who suffer from AIDS (2,3). Most CMV infections manifest severe systemic symptoms and are sometimes lethal (4). Here we discuss a patient with malignant lymphoma who developed relatively indurative, local enlargement with multiple fistulae in the gingiva and was diagnosed as having a CMV infectious disease.

Case report

A 53-year-old Japanese man first visited the Department of Dentistry and Oral Surgery at Jichi Medical School Hospital complaining of pus discharge from the gingiva on the 27th of February, 1996.

The patient’s medical history included an appendectomy when he was 25 years old and surgical treatment of a duodenal ulcer at the age of 37 years. In 1986, at the age of 43 years, he noticed the indolent swelling of the right cervical lymph node but did not receive medical treatment at that time. In April 1989, he noted more widespread enlargement of the lymph nodes all over his body. At that time, he visited a local clinic where he underwent a biopsy of the right axillary lymph node and was diagnosed as having non-Hodgkin’s lymphoma (NHL, follicular mixed cell type). He was admitted to the Department of Hematology at Jichi Medical School Hospital on the 2nd of the June, 1989. The admission examination revealed the enlargement of both the right and left cervical, axillary and inguinal lymph nodes, periaortia tumors, invasion of the pararectal lymph nodes and prostate, and invasion of bone marrow. Based on these findings, he was diagnosed with Stage IVA NHL. He received treatment consisting of one course of CHOP therapy (Cyclophosphamide + Adriamycin + Vincristine + Predonisone), 6 courses of COD-BLAM IV therapy (Cyclophosphamide + Adriamycin + Vincristine + Bleomycin + Dexamethasone + Procarbazone) and 3 courses of MACE therapy (Methotrexate + Cytosine arabinoside + Etoposide + Leucovorin) and the treatment effect was Partial Response (PR). He then underwent treatment on an outpatient basis.

Follow-up analysis in April 1991 revealed the swelling of the left mandibular gingiva and the enlargement of the left submandibular lymph node. NHL re-proliferation and invasion of the gingiva were suspected, and thus he underwent chemotherapy (Cyclophosphamide + Etoposide + Vincristine + Methotrexate + Predonisolone). However, in June 1991, the enlargement of the right inguinal lymph nodes was detected, and he was treated with Ifosfamide + Vincristine therapy. The swelling of the lymph nodes and gingiva decreased.
However, the swelling of the gingiva and the multiple enlargement of the right and left cervical and submandibular lymph nodes were observed periodically every one to two months. As a result, he underwent chemotherapy (Vincristine + Etoposide) in June 1994. Despite the reduction in the swelling of the lymph nodes, multiple fistulae accompanied by discharge of yellow viscous pus were observed in the buccal gingiva from lower right canine to second premolar and indurations were palpable around the fistulae (Fig. 1). The patient complained of no spontaneous pain or tenderness.

Panoramic radiograph revealed a semicircular light radiopacity with an unclear border in the area corresponding to the root apex of the canine (Fig. 2).

Examination of the hematological parameters revealed mild anemia, a mild decrease in total protein and Na, and elevation of serum C-reactive protein (CRP). Atypical lymphocytes, toxic granules and Dohle bodies were also observed.

As NHL invasion of the gingiva was suspected, a biopsy was promptly performed. However, histopathological examination revealed no neoplastic cells, although inflammatory granulation cells, and some endothelial cells with distinct enlarged nucleus were observed (Fig. 3). The anti-CMV antibody reacted positively with the nuclear chromatin of swelled endothelial cells with enlarged nucleus (Fig. 4). The pathological diagnosis was inflammatory granulation tissue.

Fig. 3: Photomicrograph of the biopsy specimen. Inflammatory granulation cells and some endothelial cells with distinct enlarged nucleus, but no neoplastic cells were observed.

Fig. 4: Immunohistochemistry of the biopsy specimen. Anti-CMV antibody positive cells were detected.

The patient was admitted to the Division of Hematology on April 2nd. Hematological examination upon admission revealed him to be CMV-positive (5/150,000) based on results of the CMV antigenemia assay. In addition, the CMV IgG antibody level was 14000 IU/ml and the CMV IgM antibody was negative.

Administration of γ-globulin preparation (5g for 3 days) and ganciclovir (250mg for 14 days) did not stop the pus discharge from the gingiva. Consequently, peri-fistulae was curetted on April 24th. The buccal alveolar bone of the root apex of the canine was resorbed, and root apex of the canine was covered with granulation (Fig. 5). Following curettage, the surface of the root of the canine became irregularly resorbed and the tooth became frail. Therefore, the canine was extracted (Fig. 6) and the granulation around the fistulae was curetted. The tooth showed no decay.

Histopathologically, neither enlargement of the nucleus nor intranuclear inclusion were observed in the granulation (Fig. 6). However, the necrosis of the dental pulp in the canine was evident (Fig. 7).

Following curettage, the CMV antigenemia assay showed negative results, and CMV IgG antibody level
decreased to 720 IU/ml. In addition, the swelling of the cervical and axillary lymph nodes decreased. The swelling of left cervical lymph node was noted in February 1997 resulting in the diagnosis of recurrent NHL. He underwent radiotherapy of 40 Gy radiation, resulting in a reduction in the lymph node enlargement. No other abnormalities were observed in the oral cavity. The prognosis of this patient is good and there has been no recurrence to date.

Discussion

Cytomegalovirus (CMV) is a DNA virus that is a member of the herpes family of viruses (5). Ninety percent of Japanese adults are reportedly infected with CMV (6) and 96% of pregnant women were found to be CMV antibody positive (7). In most cases, infection is established postnatally. CMV may not be excreted completely, resulting in a latent silent infection (1). However, cytomegalic inclusion disease, systemic infection, pneumonia and CMV mononucleosis may be manifested depending on the time of infection. Recently, CMV infection has attracted increasing clinical attention due to an increase in susceptible hosts. CMV can become activated and pathogenic in patients undergoing tissue transplantation such as bone marrow transplantation, in cancer patients undergoing high-dose chemotherapy or in immunocompromised AIDS patients (8).

In susceptible hosts, CMV infections are usually manifested by interstitial pneumonia, hepatitis, encephalitis, retinitis and enteritis which are all serious symptoms (9). On the other hand, the symptoms of the present case were limited to the oral, submandibular and cervical lymph nodes. There have been some reports on the intraoral CMV infectious lesion of the patients with HIV and the patients receiving organ transplantation, cancer chemotherapy and steroid therapy (10, 11, 12). These reports have described that oral manifestations of CMV infection generally show painful erosions or ulcers, enlarged and painful salivary glands, and epiglottic or posterior pharyngeal ulcers, and these erosions or ulcers may be caused by CMV infection of epithelial cells, endothelial cells, myocytes and fibroblasts. Histopathologically, CMV infection produces a characteristic cytopathic effects: a large cell containing basophilic intranuclear inclusions sometimes surrounded by a clear halo and frequently associated with clusters of intracytoplasmic inclusions (12). However, there have been no reports of gingival multiple fistula formation associated with CMV infection. Previous reports have suggested that the severity of CMV infectious disease depends on immune condition (13, 14). The present patient underwent repeated high-dose chemotherapy as an inpatient as well as relatively weak chemotherapy as an outpatient. No abnormal hematological findings were observed at the initial visit to the Department of Dentistry and Oral Surgery. Therefore, as the suppression of immunity was relatively mild and long-lasting, CMV infection was manifested not by systemic symptoms but by local symptoms. Based on the time of manifestation, initial enlargement of the gingiva and lymph nodes cannot be considered to be due to CMV infection since chemotherapy was effective. Thus, because CMV was assumed to be reactivated during recurrence of the malignant lymphoma, the time of manifestation of CMV infection cannot be determined.

Detection of antibodies, viral antigens and viral nucleic acids, as well as isolation of the virus all provide
a promising means of accurate diagnosis of CMV infections (15–17). The present patient was diagnosed with CMV infection based on the presence of viral antigens detected by immunohistochemical examination of the biopsy. This diagnosis was subsequently confirmed by an elevated serum antibody level and CMV antigenemia.

Gancyclovir is an anti-CMV agent used to treat CMV infectious diseases (18, 19). Gancyclovir, a guanine derivative, is triphosphorated to an active form in CMV infected cells and delays replication of viral DNA, but the recurrence rate is high following cessation. Special attention should be paid to leukopenia, which is the main adverse effect (17). In addition to gancyclovir, immunoglobulin preparations with high antibody titers are also effective against CMV infection (20, 21). These two agents were used to treat of the present case. Following treatment, the CMV antibody level decreased and the patient became negative for antigenemia. However, due to continuing pus discharge from the fistulae, the lesion was curetted. Immunohistochemical examination of the curetted granulation indicated no CMV antigens. The granulation was localized from the gingiva to the root apex of the canine and necrosis of the pulp was observed. Because there was no decay in the canine, it was assumed that necrosis of the pulp was caused by ascending pulpitus.

The widespread use of chemotherapy for cancer and organ transplantation may lead to an increase in the number of CMV infectious disease patients who demonstrate systemic symptoms that are not characteristic of CMV infectious disease, as seen in the present case.

References


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