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Pyogenic Granuloma of the Tongue Early after Allogeneic Bone Marrow Transplantation for Multiple Myeloma

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Oral complications occur frequently after bone marrow transplantation (BMT). Some of them are caused by regimen-related toxicity of the preparative regimen, and others by infections. In addition, oral tissues are targets of graft-versus-host disease (GVHD). Oral granulomatous lesions are not a common complication after BMT, and are especially rare on the tongue. Such rare lesions reported in the literature, developed late after BMT with oral chronic GVHD. We present here a patient who developed pyogenic granuloma of the tongue early after allogeneic BMT done for multiple myeloma. Regimen-related mucositis, oral acute GVHD, the administration of cyclosporine A, and the preexisting macroglossia might be responsible for the formation of granuloma.

Keywords: pyogenic granuloma, tongue, bone marrow transplantation, multiple myeloma, graft-versus-host disease

INTRODUCTION

Oral complications occur frequently after bone marrow transplantation (BMT). Some of them are caused by regimen-related toxicity of the preparative regimen, others by viral, fungal and bacterial infections. The intensity and severity of oral complications decrease three to four weeks after BMT, because oral tissues recover from regimen-related toxicity and neutrophils of donor-origin increase in peripheral blood (1). However, oral tissues are targets of chronic graft-versus-host disease (GVHD), nevertheless oral granulomatous lesions are not a common complication after BMT (2). Only eleven cases have been reported and all developed these lesions late after BMT (7 months to 12 years) with oral chronic GVHD, only four of which were on the tongue (2 – 5). We present here a patient who developed pyogenic granuloma of the tongue early after BMT performed for multiple myeloma.

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CASE REPORT

A 52-year-old woman underwent routine medical examination which revealed monoclonal hypergammaglobulinemia (IgG 8650 mg/dl). Bone marrow aspirate showed an increase in atypical plasma cells and accordingly the diagnosis of multiple myeloma was established. Her monoclonal component protein was IgG λ type and the disease stage was IIIB according to Durie and Salmon (6). After a single course of combined chemotherapy using melphalan, vincristine, ranimustine and dexamethasone, she was referred to our department. At this time, amyloidosis secondary to MM was suspected, because mild orthostatic hypotention and macroglossia were observed. Three courses of MCNU-VMP therapy (a combination of ranimustine, vindesine, melphalan and prednisolone) were added and partial remission was obtained (7).

She received a bone marrow transplantation from an HLA-identical sister on July 14, 1998. The preparative regimen comprised 140 mg/m^2 of melphalan and 12 Gy of TBI. TBI was given in six fractions of 2 Gy in three days (day −7, −6, −5) with 17% lung shielding. Melphalan was given in a single dose on day −4. Prophylaxis for graft-versus-host disease (GVHD) with cyclosporin A and a short course methotrexate was given. Aciclovir, levofloxacin, and fluconazole were also given orally through the neutropenic period. Donor bone marrow cells were collected under general anesthesia and 1.5×10^8 nucleated cells per patient body weight were infused via a central venous catheter after the removal of red blood cells.

Regimen-related mucosal toxicity was prominent. She complained of diarrhea and severe oral pain from day 3, which needed intravenous analgesia. On the sixth day after BMT, a skin rash developed on her extremities and trunk. Regimen-related skin toxicity was considered, but we started 2 mg/kg/day methylprednisolone (mPSL) after a skin biopsy, was performed because we could not exclude acute GVHD of the skin. The skin region responded to steroids and diminished in several days. The mPSL was tapered and eventually censored on day 37.

The peripheral blood leukocyte count reached more than 1.0×10^9 /l on day 29 post BMT and the reticulocyte count exceeded more than 1.0 % on day 37. However, she still required platelet transfusion consistently after BMT. Bone marrow aspirate on day 43 showed an almost normal bone marrow, with a plasma cell count less than 1 %.

On day + 45, she developed stage 3 skin GVHD, which was confirmed by skin-biopsy. Prednisolone given at the dose of 1 mg/kg/day improved the skin lesion within a few days. CMV antigenemia assay turned positive (30 cells positive per 50000 cells analyzed) on day 48, which was cleared by preemptive therapy with ganciclovir. On day + 55, the monoclonal protein was undetectable, thus, complete remission of multiple myeloma had been achieved.

The pain in the tongue persisted even after other manifestations of regimen-related mucosal toxicity, such as diarrhea or buccal mucosal damage resolved. She had ulcers and areas of desquamation on the dorsal tongue (Figure 1A). Thorough microbiological studies were performed, but no pathogens were detected. Biopsy of the tongue was performed on day + 65 after BMT. The pathological examination showed liquefactive degeneration of the basal cell layer, infiltration with lymphocytes, and apoptosis of the prickle cells, which were consistent with the diagnosis of GVHD (Figure 1B) (8). No microbiological pathogens were observed. Because skin GVHD had improved with the administration of prednisolone at the time, we did not add treatment for the tongue lesion. However, two weeks later, a white nodule appeared on the dorsal tongue, which enlarged to several millimeters in size within a week (Figure 2A). The lesion was biopsied on day 86. It was covered by a pseudomembranous fibrin exudate, under which a nodule of granulation and fibrous tissue was seen (Figure 2B). No infectious organisms were identified. After the removal of the nodule, it never recurred until she died on day + 123 after BMT because of idiopathic interstitial pneumonitis.

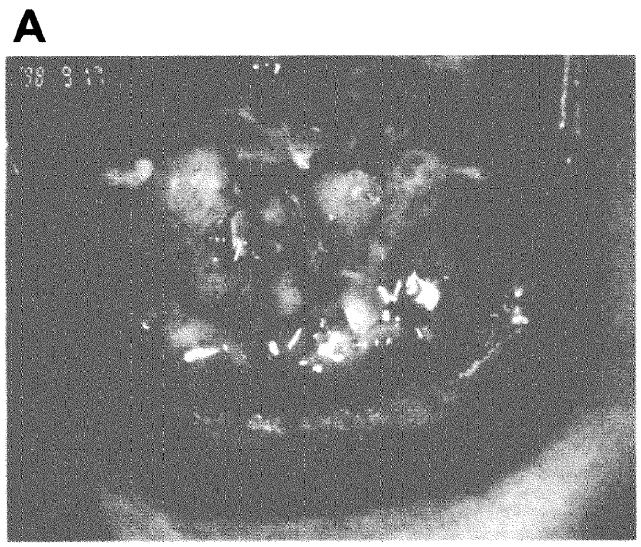

FIGURE 1 A. The patient had ulcers and areas of desquamation on the dorsal tongue

FIGURE 1 B. The biopsy of the tongue was performed on day 65 after BMT. The pathological examinations showed liquefactive degeneration of the basal cell layer, infiltration of lymphocytes, and apoptosis of prickle cells. H&E, orig. mag. x200

DISCUSSION

We present here a patient with pyogenic granuloma of the tongue after BMT for multiple myeloma. The development of oral pyogenic granuloma, and reactive proliferations of fibrous and granulation tissue, are not common complications after BMT. There have been a few case reports in the literature (2 – 5) and it seems that only four patients developed such lesions on the tongue (2,4,5).

Oral complications cause significant problems for patients after BMT. Regimen-related mucositis is observed in most of the BMT recipients, while oral mucosal involvement of chronic GVHD is also well known. However, there has been only one report which described oral involvement of acute GVHD until Barrett *et al.* reported five recipients with acute oral GVHD (9,10). The clinical onset of oral manifestations was between 3 and 31 days after the development of dermal manifestations (10). The reason why acute oral GVHD has been less described might relate to the difficulty in differential diagnosis between oral GVHD and regimen-related toxicity or viral infections. In the present case, oral infection was excluded by thorough screening for microorganisms. The pathological examination on day + 65 showed active mucosal damage. The direct toxic effect of preparative regimen occurs in the first three weeks after BMT and produces epidermal damage overlapping that of GVHD, but the effects usually wear off in three to four weeks (11). Taking into consideration these findings and the existence of systemic acute GVHD together, it was reasonable to diagnose oral acute GVHD. In this respect Lloid *et al.* performed tongue biopsy in seven BMT recipients with tongue ulcerations and systemic GVHD (12). Cytomegalovirus (CMV) infection was detected in five patients and GVHD in only one. These lesions could not be distin-

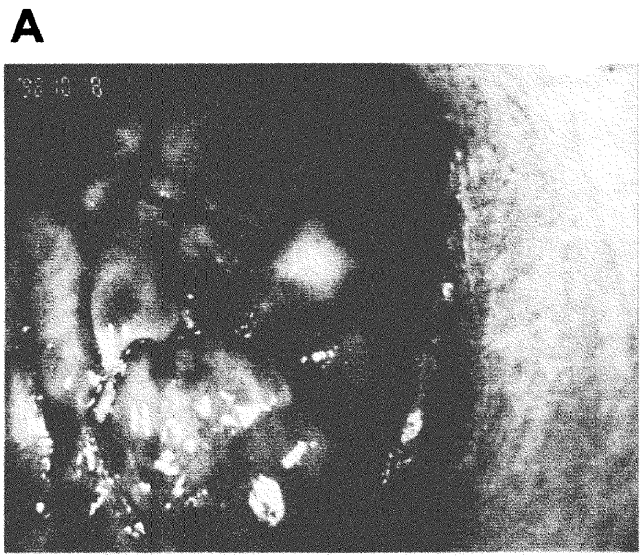

FIGURE 2 A. A white nodule appeared on the dorsal tongue, which enlarged to several millimeters in length in a week

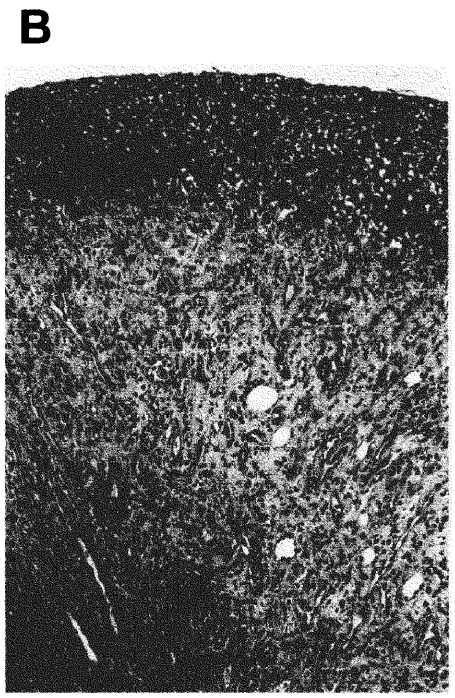

FIGURE 2 B. The lesion was biopsied on day 86. It was covered by a pseudomembranous fibrin exudate, under which nodule of granulation and fibrous tissue existed. H&E, orig. mag. x100

guished by thair clinical appearance. Therefore, some of the oral lesions which had been diagnosed before as oral acute GVHD might have been caused by CMV infections. However, a CMV-associated tongue lesion was not considered in the present case, because viral inclusion was not detected in pathological examinations and the tongue lesion did not respond to intravenous ganciclovir. In the patients with oral CMV infections reported by Lloid *et al.* (12), the tongue ulcerations all resolved on intravenous ganciclovir.

Chronic mucosal injury and irritation predisposes to the development of pyogenic granuloma (2). Chronic GVHD has been the major cause of mucosal injury reported patients in the past (2 – 5). In the present case, pyogenic granuloma developed much earlier than in those patients and acute GVHD may have been responsible for the mucosal damage. Cyclosporine A had been used in each patient during the time of presentation of pyogenic granuloma. Cyclosporine A is known to have on hyperplastic effect on gingival tissues (13 – 14), and might trigger an exaggerated proliferative response of the connecting tissue, resulting in the formation of pyogenic granuloma (2). Treatment of the granuloma is usually successfully performed by surgical removal (1).

To ourknowledge, this is the first description of a patient who developed pyogenic granuloma of the tongue early after BMT. The characteristic issue in the patient was the existence of macroglossia before BMT, probably due to amyloidosis, although this was not proven histologically. The regimen-related mucositis and the subsequent oral acute GVHD were severe, which resulted in the formation of pyogenic granuloma. These oral complications damaged her quality of life after BMT. Approaches to decrease regimen-related mucositis, such as oral cryotherapy during the preparative regimen. should be investigated in BMT recipients with preexisting macroglossia (15, 16).

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