

[CASE REPORT]

Ramucirumab-related Oral Pyogenic Granuloma: A Report of Two Cases

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Abstract:

Pyogenic granuloma (PG) is a granulomatous elevated lesion that occurs on the skin and mucous membranes. We herein report two cases of intra-oral PG that developed during the administration of ramucirumab for gastric cancer. Case 1 involved a 55-year-old man with a 6-mm tumor on the right tongue, and case 2 involved a 67-year-old man with a 5-mm tumor on the upper lip. The imbalance in angiogenesis caused by ramucirumab and the deterioration in the local oral environment were suggested to have caused the PG. Medical and dental collaboration is essential during the administration of ramucirumab.

Key words: ramucirumab, pyogenic granuloma, VEGFR2, oral management, medical and dental collaboration

(Intern Med 60: 2601-2605, 2021)

(DOI: 10.2169/internalmedicine.6650-20)

Introduction

Pyogenic granuloma (PG) is a granulomatous, elevated lesion that occurs on the skin and mucous membranes (1). Clinically, this lesion grows without pain, and frequently appears as a hemorrhagic, red-purple, venous or perforating tumor mass (2). It may grow rapidly, and needs to be differentiated from malignant tumors. PGs are commonly found in the face and limbs. In the oral region, the gingiva, lip, and tongue are common sites (1, 3).

PG arises from various stimuli, including chronic low-grade irritation, traumatic injury, hormones, and drugs (1). The pathogenesis of pyogenic granuloma at the molecular level is unclear, but may be considered as resulting from the imbalance of angiogenesis enhancers and inhibitors (4).

It has been reported that PG and angioma can develop during the administration of ramucirumab, an angiogenesis inhibitor (5-7). Most of these reports describe skin lesions, and to our knowledge, no detailed studies have been pub-

lished on oral lesions, especially from the point of view of histopathology. Therefore, in this study, we report two cases of PG that occurred in the oral cavity during the administration of ramucirumab. The study protocol adhered to the recommendations in the Declaration of Helsinki and the study was approved by the regional Ethical Review Board of our Institution.

Case Report

Case 1

A 55-year-old man presented to our department with swelling of the right tongue. He was diagnosed with stage IV (T4aN2M1) gastric cardia cancer. Combination chemotherapy with capecitabine+cisplatinum+trastuzumab therapy was started; owing to tumor growth, however, chemotherapy was stopped after eight courses, and new combination chemotherapy with ramucirumab+weekly paclitaxel was initiated. In each four-week course, ramucirumab was adminis-

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Received: November 5, 2020; Accepted: January 13, 2021; Advance Publication by J-STAGE: March 8, 2021

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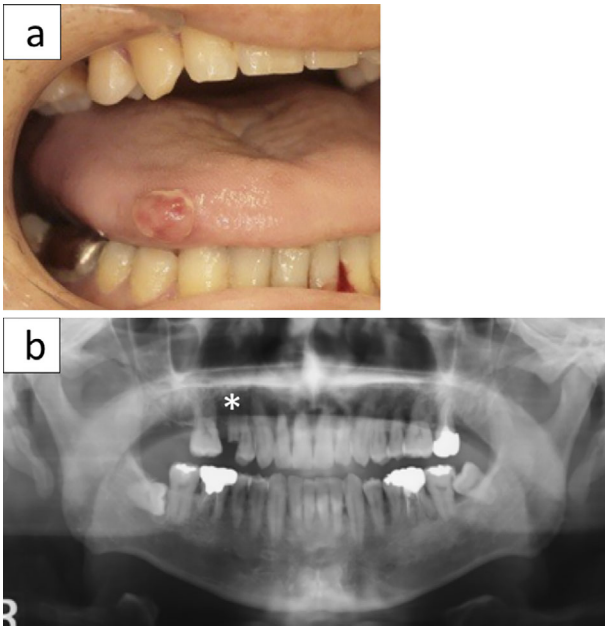


Figure 1. Clinical and imaging characteristics of case 1. (a) Macroscopic findings. A pedunculated tumor of approximately 6 mm can be seen on the right side of the tongue. Slight bleeding is seen from the left lower anterior gingiva. (b) Panoramic image: Moderate marginal alveolar bone resorption is seen. The upper right maxillary second molar had a residual root (*).

tered once every two weeks with paclitaxel for three consecutive weeks, with a one-week break. After four courses of treatment, computed tomography (CT) showed that the tumor had shrunk by more than 30%; this indicated a partial response (PR) to treatment according to the Response Evaluation Criteria in Solid Tumors.

After seven courses, a tumor was found on the right tongue. An initial physical examination revealed a 6-mm ex-troverted, elastic, soft mass (Fig. 1a). The mass was painless and involved the upper and lower canines and premolars. Hemorrhaging was also observed from the gingiva of the lower anterior region, and the crown of the right upper second molar was missing. On panoramic imaging, the upper right maxillary second molar had a residual root (Fig. 1b). The patient had no family dentist and had not received dental care for more than three years. Daily prevention at home was performed only once a day.

The tumor showed rapid growth and was therefore resected under local anesthesia; no abnormal bleeding was observed. Histopathological findings of oral specimens obtained from the tongue tumor revealed local proliferation of vascular endothelial cells in the connective tissue (Fig. 2a). Expanded capillaries and surrounding endothelial cells were also observed (Fig. 2b). For immunostaining, heat-induced antigen retrieval was performed by incubating the sections

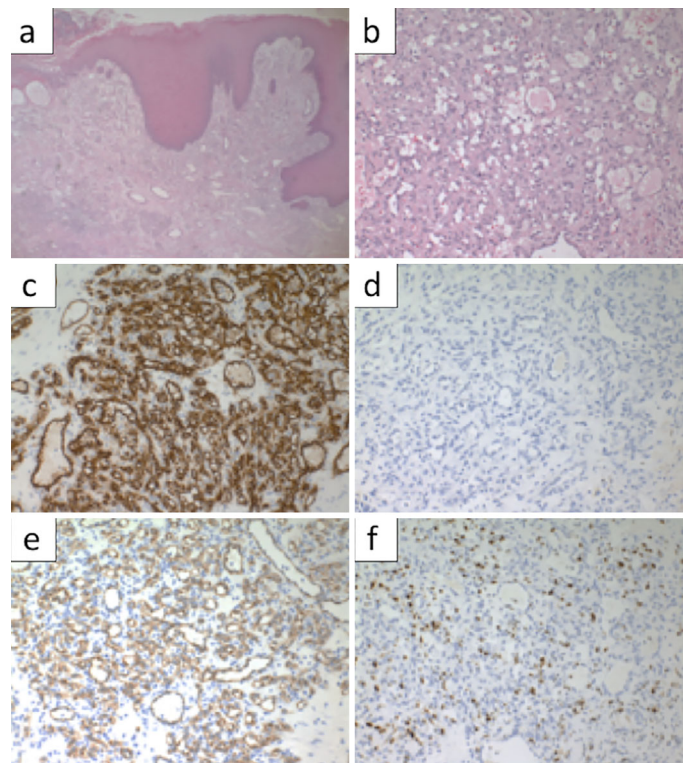


Figure 2. Histopathological characteristics of case 1. (a, b) Hematoxylin and Eosin staining. a: $\times 100$, b: $\times 400$. A large number of capillaries showing foliar compaction can be seen beneath the mucous membrane. Hemorrhaging and slight inflammatory cell infiltration can be seen in the stroma. No malignant cells are observed; the findings are consistent with those of pyogenic granuloma. (c, d) Endothelial cells positive for CD31 (c) and negative for D2-40 (d) can be seen. (e) Strong immunostaining for vascular endothelial growth factor receptor-2 (VEGFR2) can be seen in almost all vascular endothelial cells. (f) Cell proliferation marker Ki-67 is also frequently detected.

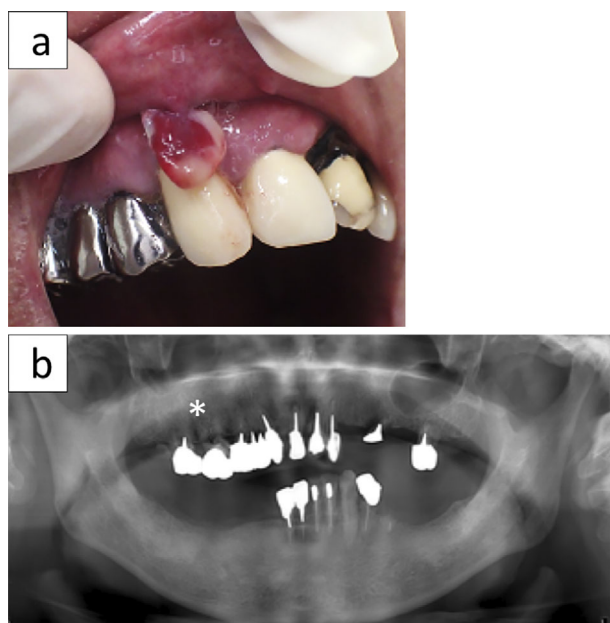


Figure 3. Clinical and imaging characteristics of case 2. (a) Macroscopic findings: a 5-mm extroverted, elastic, soft mass can be seen on the upper right lip. (b) Panoramic image: Moderate to high marginal alveolar bone resorption can be seen. A horizontal root fracture can be seen in the upper first molar (*); both maxillary sinuses are deformed.

with 10 mM Tris base containing 1 mM ethylenediaminetetraacetic acid (pH 9.0). In order to detect vascular endothelial growth factor receptor-2 (VEGFR2), CD31, D2-40, and Ki-67, a section was incubated with anti-VEGFR2 rabbit monoclonal antibody (clone 55B11; Cell Signaling Technology, Danvers, USA), anti-CD31 (clone 1aA10; Novocastrolaboratories, Newcastle upon Tyne, UK), anti D2-40 (clone D2-40; Nichirei Bioscience, Tokyo, Japan), and Ki-67 (MIB-1; Dako, Glostrup, Denmark), followed by incubation with an anti-rabbit peroxidase polymer (Nichirei Bioscience). Based on the immunostaining results, most blood vessels were considered to be CD31- and VEGFR2-positive and D2-40-negative; Ki-67, a proliferation marker, was also found to be strongly expressed in the nuclei of endothelial cells (Fig. 2c-f). After treatment at our department, ramucirumab was discontinued due to cancer progression on CT. The patient subsequently received other drugs but died six months after visiting our department; the oral lesions did not recur after the discontinuation of ramucirumab.

Case 2

A 67-year-old man was admitted to our department owing to a tumor on the upper lip. He had been diagnosed with stage IIIB (cT3N3aM0) gastric cancer six years previously, and distal gastrectomy had been performed at the gastrointestinal surgery department of our hospital; S-1 was administered for 1 year as postoperative adjuvant chemotherapy. Four years later, magnetic resonance imaging showed cancerous peritonitis; S-1 was therefore restarted. Owing to the

evidence of lesions on a CT examination three months later, XELOX therapy was started. Since disease progression was observed after 22 courses, combination chemotherapy was started with ramucirumab+nab-paclitaxel. In each four-week course, ramucirumab was administered once every two weeks along with nab-paclitaxel for three consecutive weeks and a one-week break. At the end of six courses, CT showed no obvious change in the tumor size and increased ascites; this indicated stable disease (SD) according to the Response Evaluation Criteria in Solid Tumors.

During the fifth course, a tumor appeared on the upper lip. The lip tumor fell off spontaneously but subsequently recurred and increased in size; the patient was therefore referred to our department during the seventh course. On an initial physical examination, a 5-mm elastic soft mass was observed on the right upper lip. In addition, the crown of the upper left central incisor was fractured (Fig. 3a). Oral care was found to be poor, and the periodontal pocket was deep overall, reaching 6 mm at the right maxillary canine. The left maxillary central incisor and lateral incisors showed moderate instability; the mandibular partial denture was not sufficiently stable. Panoramic imaging showed multiple residual roots, with a fracture at the upper right first molar (Fig. 3b). The patient's family had a dental clinic, but he had not undergone intensive treatment after the initiation of anticancer drug therapy. A benign tumor was diagnosed at the upper lip and was excised under local anesthesia; the fractured piece of the upper left central incisor was also removed simultaneously. No abnormal bleeding was observed from the sutures nine days later.

The histopathological findings of the oral specimens obtained from the lip tumor revealed local proliferation of vascular endothelial cells in the connective tissue (Fig. 4a). Expanded capillaries and surrounding endothelial cells were also observed (Fig. 4b). Based on the immunostaining results, most blood vessels were considered to be CD31- and VEGFR2-positive and D2-40-negative; Ki-67, a proliferation marker, was also found to be strongly expressed in the nuclei of endothelial cells (Fig. 4c-f).

After starting treatment, the patient presented with a generalized pruritic skin rash; difluprednate ointment was prescribed. At the same time as the visit to our department, pruritus was observed on the back; a 1-cm tumor also appeared, which required resection at a nearby dermatology clinic. A histopathological examination showed capillary lobular growth with vascular endothelial cell proliferation, suggestive of a pyogenic granuloma. Since exacerbation of the cancerous peritonitis was confirmed on CT after 12 courses, ramucirumab+paclitaxel therapy was discontinued at 6 months after the initial visit to our department, and nivolumab therapy was started. After resection, there was no evidence of recurrence of the oral or skin tumors.

Discussion

To our knowledge, this is the first report concerning the

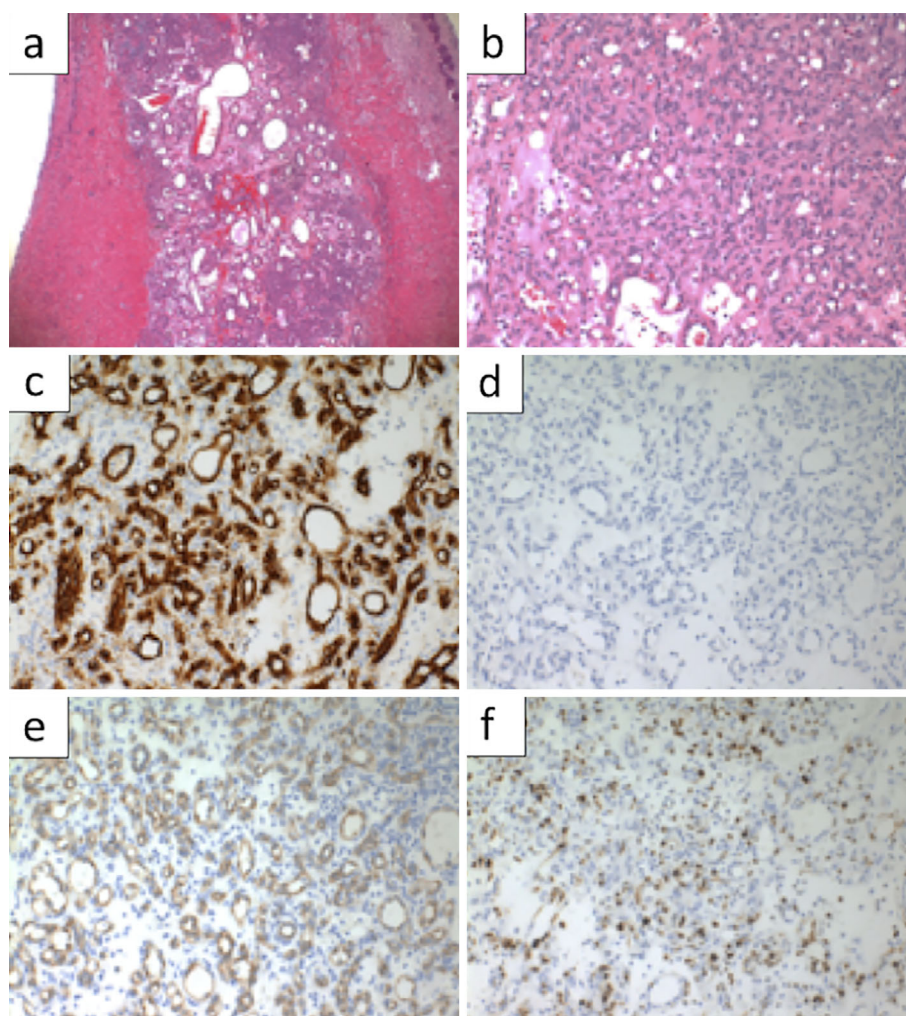


Figure 4. Histopathological characteristics of case 2. (a, b) Hematoxylin and Eosin staining. a: $\times 100$, b: $\times 400$. A large number of capillaries showing foliar compaction can be seen beneath the mucous membrane. Hemorrhaging and slight inflammatory cell infiltration can be seen in the stroma. No malignant cells are observed; the findings are consistent with those of pyogenic granuloma. (c, d) CD31 (c) and D2-40 (d) immunostaining: endothelial cells are positive for CD31 and negative for D2-40. (e) Vascular endothelial growth factor receptor-2 (VEGFR2) immunostaining. Strong staining can be seen in almost all vascular endothelial cells. (f) The Ki-67 cell proliferation marker is also frequently detected in vascular endothelial cells.

histopathological examination of oral PG in patients receiving ramucirumab. The causes of PG were considered to be the systemic deterioration of the angiogenic balance by ramucirumab and the locally deteriorated oral environment (4). Angiogenesis is an important characteristic of cancer; malignant tumors create new vascular networks to meet their increased demand for oxygen and nutrients and to achieve efficient removal of metabolic waste. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) have been identified as major regulators of angiogenesis (8, 9). VEGFR2 is a major mediator of VEGF-induced angiogenesis and exhibits the most potent tyrosine kinase activity; it is being investigated as a target of antiangiogenic therapy for cancer (10).

Ramucirumab is a fully human IgG1 monoclonal antibody that selectively binds to the extracellular domain of

VEGFR2 (9, 11). It is mainly used as a second-line treatment for advanced cancers, such as gastric, colorectal, and non-small-cell lung cancers (11). The Ramucirumab monotherapy for previously treated advanced gastric or gastro-esophageal junction adenocarcinoma trial, which was the first randomized phase III study on advanced gastric cancer, revealed that ramucirumab therapy was beneficial in terms of the overall survival compared with placebo in a second-line treatment setting (8, 12). The combination of ramucirumab with paclitaxel significantly increases the overall survival compared with placebo plus paclitaxel in advanced gastric or gastro-esophageal junction adenocarcinoma patients (11, 12). Various adverse events have been reported in relation to ramucirumab, including hypertension, deep vein thrombosis, headaches, anorexia, vomiting, and dyspnea (8, 11). Interestingly, there are several reports on PGs

and hemangiomas occurring in patients receiving ramucirumab. Lim et al. first reported the development of an angioma during the administration of ramucirumab in 2015 (5); several cases have been reported since then, including sporadic and multiple occurrences (5-7); tumors appeared at a minimum of two months and a maximum of six months after starting ramucirumab (5-7). The pathogenesis of ramucirumab-related PG remains unknown. Ibe et al. reported on a case of PG of the fingers, where strongly positive immunostaining was observed for VEGFR2; they hypothesized that following ramucirumab administration, a small wound triggered VEGFR2 overexpression owing to a mutation in KDR (p.T771R), which is a driver of vascular lesions (6).

PG in our two cases developed during the administration of ramucirumab. The tumor appeared during the fourth and sixth course in cases 1 and 2, respectively. From the clinical course, ramucirumab appeared to be involved in the formation of PG. The first case in the oral cavity was sporadic. However, in the second case, PG also developed in the skin of the back; it was therefore considered to be a case of multiple PG. On immunostaining, both cases tested positive for VEGFR2 and CD31, which are expressed in blood vessels; they tested negative for D2-40, which is expressed in lymphatic vessels. The expression of the growth factor Ki-67 was also observed. These results showed that the overexpression of VEGFR2 caused the excessive proliferation of small blood vessels, leading to PG.

The findings from these cases suggest that the oral environment was also involved in PG formation. The oral cavity is easily damaged by caries, periodontal disease, defective teeth or bite, food, and poor oral cleaning. In these two cases, the oral environment was poor, and dental care was insufficient. In addition to the administration of ramucirumab, intraoral stimulation by the residual roots and sharp edges of the dentures were also suspected of having induced the development of PGs.

A limitation of this study is that the frequency of ramucirumab-related PG and the difference in characteristics from other PGs were not determined. Further large-scale studies are needed to elucidate the characteristics and etiology of oral PG in patients treated with ramucirumab. Among the oral adverse events caused by specific drugs used in anticancer treatment, everolimus-related stomatitis and medication-related osteonecrosis of the jaw due to bone resorption inhibitors, such as bisphosphonates and denosumab, are well known. The frequency of ramucirumab-related PG is unknown, but the use of ramucirumab is increasing; the incidence of oral PG is therefore expected to increase in the future. Medical and dental interprofessional

collaboration is essential for investigating the possibility of oral PG development during the administration of ramucirumab.

In conclusion, we encountered two cases of ramucirumab-related oral PG. The deterioration in the local angiogenic balance caused by ramucirumab and the poor oral environment contributed to the formation of PG. Oncologists and dentists should carefully consider the development of oral symptoms and their management.

The authors state that they have no Conflict of Interest (COI).

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