Squamous Cell Carcinoma of Maxillary Gingiva Progressing to Disseminated Carcinomatosis of Bone Marrow

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Abstract

Disseminated carcinomatosis of the bone marrow (DCBM) is characterized by diffuse metastasis to bone marrow and sudden mortality. To the best of our knowledge, no studies to date have reported progression of oral squamous cell carcinoma to DCBM. Herein, we report a case of squamous cell carcinoma in the maxillary gingiva suspected of progressing to DCBM. A 64-year-old woman presented with white lesions on the left maxillary gingiva. The lesions were diagnosed as squamous cell carcinoma (T2, N0, M0), and partial maxillectomy performed. Two years and 5 months after surgery, metastasis was noted in the left cervical lymph node and left radical neck dissection carried out. The subsequent diagnosis was right cervical lymph node metastasis and multiple bone metastases. The patient also presented with thrombocytopenia, anemia, and elevated levels of alkaline phosphatase, probably due to metastatic bone disease. Although various antitumor therapies were administered, the patient died 6 months after diagnosis of multiple bone metastases.

Key words: Oral squamous cell carcinoma — Disseminated carcinomatosis of the bone marrow — Multiple bone metastases — Thrombocytopenia — Alkaline phosphatase
**Introduction**

First reported by Hayashi et al. in 1979, disseminated carcinomatosis of the bone marrow (DCBM) is characterized by diffuse bone marrow metastases, and subsequent studies have described its clinical course. Patients typically receive symptomatic treatment due to the poor prognosis of this disease. It is not widely recognized outside of Japan, and is often considered as a type of advanced cancer with multiple bone metastases. A MEDLINE search using “DCBM” as the key word identified many related articles. The authors were all Japanese, however, and the majority of the papers were written in Japanese. The characteristics of DCBM, which include sudden mortality and coincidental hematological abnormalities, such as disseminated intravascular coagulation (DIC) and microangiopathic hemolytic anemia, thus constitute a significant area of research in Japan. Although DCBM is considered a subtype of solid tumor bone metastasis, a recent report has suggested that it may be a distinct clinical entity. Therefore, it is important for clinicians to better understand the etiology of this disease. Herein, we report a case of squamous cell carcinoma of the maxillary gingiva suspected of progressing to DCBM.

**Case Presentation**

The patient was a 64-year-old woman who had visited the Department of Otolaryngology at her local hospital after noticing white lesions on the left maxillary gingiva, for which she was given treatment. Approximately one year later, however, she was referred to our hospital for further examination and follow-up care. The patient had a history of atomic bomb exposure during the neonatal period. Her current history revealed pollinosis, but no other significant family history, or history of smoking or alcohol consumption. During her first visit to our hospital, a 10-mm mass painful to the touch was observed on the buccal side of the left maxillary premolar. White lesions were also observed on the buccal mucosa. Cytology performed at the initial examination revealed no malignant findings (class I).

The patient’s previous physician was then contacted to confirm her clinical history. Two months later, the patient visited our hospital again with a letter of introduction from her previous doctor. Following a biopsy, a diagnosis of leukoplakia with severe dysplasia was confirmed, and follow-up care provided by the patient’s previous physician. Although no change had occurred in the clinical findings since her first visit to our hospital, we also continued to provide follow-up care.

Three months later, the lesion had enlarged and presented as an ulcer with white and red distal lesions (Fig. 1). The tumor showed a maximum dimension of 38-mm. A subsequent biopsy resulted in a diagnosis of well-differentiated squamous cell carcinoma. No evidence of metastasis was evident on head/neck and chest computed tomography (CT), and the diagnosis of squamous cell carcinoma in the left maxillary gingiva (T2, N0, M0) was confirmed. The following month, a partial maxillectomy was performed (Fig. 2). The tumor was resected from the leading edge of pterygoid process to the distal side of the left canine. One course of adjuvant chemotherapy with oral tegafur/gimeracil/oteracil potassium (2 weeks of treatment followed by one week of rest) was administered preoperatively, and the same adjuvant chemotherapy was continued for one year postoperatively after consultation with the patient and her family.

One year and 10 months postoperatively, an enlarged level Ib lymph node was palpable on the left side of the neck, but CT findings remained unchanged and revealed no lymph node metastasis. This was followed up with further regular CT, but no MRI or ultrasonography. Erythema, including on the face, neck, arms, showed a pattern of repeated occurrence and remission. Two years and 5 months postoperatively, rapid enlargement was observed of the left cervical lymph node (Fig. 3), and left radical neck dissection (RND) was
performed within the same month. Metastatic lymph nodes with extranodal invasion were observed at levels IB and III, and the tumor cells exhibited sarcomatous change (Fig. 4). Radiotherapy (exposure dose of 62 Gy) was applied to the left side of the neck, and cisplatin (3 doses of 100 mg/m$^2$) administered postoperatively.

Findings obtained at 4 months after the RND suggested right cervical lymph node metastasis. Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) revealed abnormal FDG accumulation in the right cervical lymph node, around the right sternoclavicular joint, and in the left scapula, left ribs, thoracic spine, left ilium, and both pubic bones. The diagnosis was right cervical lymph node metastasis and multiple bone metastases. Further invasive procedures, such as bone marrow biopsy, were declined. The following month, bone scintigraphy revealed femoral and skull metastases, and the patient reported metastasis-associated lower back pain. Radiotherapy was administered to the thoracic spine and sacrum, and zoledronic acid hydrate initiated to prevent fracture due to loading. The metastatic right cervical lymph node was also irra-
diated, and dendritic cell vaccine immuno-
therapy administered simultaneously at
another hospital. After consultation with
physicians at another hospital, celecoxib was
also administered to induce tumor dormancy.
The lesions progressed continuously thereaf-
her, however, and bone scintigraphy revealed
exacerbation of bone metastases (Fig. 5a).
Magnetic resonance findings showed that
almost all areas of the lumbar spine, ilium,
sacrum, pubic bones, and femur were replete
with tumors (Fig. 5b). Liver metastases were
also reported, and the patient’s thrombocyto-
penia and anemia were attributed to the pres-
ence of multiple bone metastases (Fig. 6). No
tendency toward bleeding was observed. Pal-
liative chemotherapy was considered but
rejected as the patient was deemed too ill to
receive it. Six months after the diagnosis of
multiple bone metastases, the patient received
outpatient blood transfusion therapy when
required. Other blood tests revealed elevated
levels of alkaline phosphatase (ALP), but little
change in those of lactate dehydrogenase
(LDH) (Fig. 6). When the pain, which was
mainly in her back, became severe, she was
admitted to our hospital for pain manage-
ment. The patient died, however, of multiple
organ failure with carcinomatous peritonitis 7
days after admission.

**Discussion**

Progression to DCBM typically occurs more
in women, and the disease exhibits a bimodal

![Fig. 4 Histopathological findings from serial sections of metastatic lymph node](image)

(a) Low-power field, H&E staining. (b) Low-power field, immunohistochemical staining of AE1/AE3. (c) High-power field, H&E staining. (d) High-power field, immunohistochemical staining of AE1/AE3.

Tumor cells with diffuse extranodal invasion were observed in low-power field. In high-power field, these tumor cells were poorly differentiated, showed sarcomatous change, and differed from tumor cells found at primary site. Tumor cell nests were observed more clearly by immunohisto-
chemical staining of AE1/AE3.
Oral Cancer Progressing to Carcinomatosis

distribution with respect to age (early- and late-onset). An earlier study noted that more than 90% of the 40 patients addressed had presented with primary gastric cancer, and this high rate of progression from gastric cancer to DCBM has been supported by subsequent studies. Although the clinicopathological characteristics of carcinomas exhibiting a tendency to progress to DCBM remain to be clarified, those commonly reported include poorly differentiated, mucin-producing, and diffusely infiltrative carcinomas. Hematogenous metastasis is the primary pathway by which solid carcinomas metastasize to the bone marrow. Specifically, in the absence of pulmonary and hepatic metastasis, metastasis.

Fig. 5 Bone scintigraphy findings
(a) shows multiple bone metastases. (b) shows magnetic resonance images of femur. Almost all areas of femur bone marrow were replete with tumors, as indicated by low signal intensity on T1-weighted images (allows).

Fig. 6 Laboratory data indicating diagnosis of multiple bone metastases
Horizontal axis indicates elapsed time. WBC: leukocyte count, Hb: hemoglobin, Plt: blood platelet count, ALP: alkaline phosphatase, and LDH: lactate dehydrogenase.
sis via the vertebral vein is the primary route by which cancer spreads to the vertebrae, ribs, and skull. Given that the rate of vertebral vein metastasis in gastric cancer is low, however, the specific metastatic pathway of DCBM with respect to this cancer type remains to be determined. Several common clinical findings of DCBM have been reported. Three cardinal symptoms include lower back pain, anemia, and a tendency toward bleeding. Elevated DIC and LDH levels, as well as those of DIC are also observed at a high frequency.

Disseminated carcinomatosis of the bone marrow results in sudden death, with a mean survival of a few months after onset.

At the time of this report, we were not aware of any cases of oral squamous cell carcinoma progressing to DCBM. The patient in the present report presented with sarcomatous tumor cells diffusely infiltrating lymph nodes of the neck. No tumor mucus production was observed in this case, however. Thrombocytopenia was first observed at 2 months after diagnosis of multiple bone metastases, and the platelet count continued to show a gradual decrease. The patient also exhibited a gradual course of anemia, but blood transfusion was needed. In addition, biochemical test results revealed an increase in ALP. Furthermore, fibrinogen levels and prothrombin time were generally normal, and the respective criteria for DIC were not met at any time. Ultimately, fibrin degradation product levels showed a slight elevation, suggesting progression to DIC. Additional clinical symptoms included lower back pain and sudden death, which are suggestive of DCBM.

One point of clinical interest is that some chemotherapy regimens are effective, particularly in the setting of DIC. For example, one earlier study reported the usefulness of chemotherapy following thrombomodulin preparation, the latter of which was administered based on the assumption that activation of the extrinsic coagulation cascade promotes DIC. Mucin activates factor X, which in turn may promote DIC in DCBM. Disseminated carcinomatosis of the bone marrow progresses rapidly, and chemotherapy cannot be performed in many cases. Where possible, however, chemotherapy improves DIC, and an improved prognosis has been emphasized by some researchers. The present patient did not develop marked DIC until approximately 6 months after diagnosis of multiple bone metastases, potentially due to the administration of various antitumor therapies. There have been few reports of bone metastases in patients with head and neck squamous cell carcinoma. In a single center in China, 116 of 221 patients receiving treatment for distantly metastatic nasopharyngeal carcinoma presented with bone metastases.

Chemoradiotherapy prolonged survival more effectively than chemotherapy alone in the low-risk group, which was defined according to prognostic factors (age >40 years, local recurrence, subsequent metastasis, and disease-free interval). However, in the high-risk group, no differences in survival were observed. Further studies with a larger number of patients are needed.

Disseminated carcinomatosis of the bone marrow is a pathogenetic concept. Although bone marrow carcinosis due to distant metastasis of head and neck squamous cell carcinoma has not been frequently reported, Frölich et al. and Mathew et al. described oral squamous cell carcinoma progressing to bone marrow carcinosis and coinciding with back pain. Interestingly, the patient described in the former report also died suddenly. Moreover, some cases of Yamamoto-Kohama grade 4D, as well as oral squamous cell carcinoma with sarcomatous change in patients with poor prognosis—such as in the present case—may indicate a diagnosis of DCBM. We hypothesize that cases of DCBM-progressing oral squamous cell carcinoma have been underreported. Accurate reporting of these cases is needed in order to provide better palliative care.

**Conflict of Interest**

The Oral Cancer Center (OCC) of Tokyo
Dental College received a research grant from Taiho Pharmaceutical Co., Ltd. [Tokyo, Japan]. Hirokazu Saito, Satoru Ogane, and Nobuo Takano are employees of OCC; while Kazumichi Sato and Takeshi Nomura are former OCC employees. Taiki Suzuki, Yusuke Sanjo, Takashi Ushioda, and Kazuhiko Hashimoto declare no conflict of interest regarding the publication of this paper.

**Ethical Approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**References**

1) Arakawa Y (2014) Malignant tumors and DIC. The Journal of Adult Diseases 44:933–936. (in Japanese)
2) Cao X, Han Y, He L, Xiang J, Wen Z (2011) Risk subset of the survival for nasopharyngeal carcinoma patients with bone metastases: Who will benefit from combined treatment? Oral Oncol 47:747–752.
3) Fröhlich K, Alzoubi A, Müller J, Kleinsasser N (2013) Bone marrow carcinosis in head and neck carcinoma in a young adult. J Oral Maxillofac Surg 71:e198–e202.
4) Hayashi H, Haruyama H, Emura Y, Kaizuka I, Ozeki T (1979) Disseminated carcinomatosis of the bone marrow—Study of a type of metastatic cancer and relationship of microangio-pathic hemolytic anemia or disseminated intravascular coagulation. Jpn J Cancer Clin 25:329–343. (in Japanese)
5) Iguchi H (2015) Recent aspects for disseminated carcinomatosis of the bone marrow associated with gastric cancer: What has been done for the past, and what will be needed in future? World J Gastroenterol 21:12249–12260.
6) Kawamoto H, Uchida Y, Ueda S, Yanagita S, Terajima H (2015) Case report of disseminated carcinomatosis of the bone marrow originating from gastric cancer with cancer-related disseminated intravascular coagulation successfully treated with recombinant human soluble thrombomodulin. Jpn J Cancer Chemother 42:363–365. (in Japanese)
7) Mathew BS, Jayasree K, Madhavan J, Nair MK, Rajan B (1997) Skeletal metastases and bone marrow infiltration from squamous cell carcinoma of the buccal mucosa. Oral Oncol 33:454–455.
8) Moriwaki S, Mandai K (2002) Postmortem pathological findings of bone marrow metastasis the via vertebral vein system. Jpn J Cancer Clin 48:499–508. (in Japanese)
9) Nakamura K, Takamori H, Nakahara O, Ikuta Y, Kuroki H, Nakagawa S, Mima K, Okabe H, Nitta H, Imai K, Chikamoto A, Doi K, Ishikawa T, Beppu T, Iyama K, Baba H (2012) A case of cancer of the pancreatic tail with disseminated carcinomatosis of the bone marrow. Jpn J Cancer Chemother 39:1275–1277. (in Japanese)
10) Okuno T, Yamaguchi H, Kitayama J, Ishigami H, Nishikawa T, Tanaka J, Tanaka T, Kiyomatsu T, Hata K, Nozawa H, Kawai K, Kazama S, Ishihara S, Sunami E, Watanabe T (2016) A case of disseminated carcinomatosis of the bone marrow originating from gastric cancer 3 years after intraperitoneal chemotherapy against peritoneal carcinomatosis. World J Surg Oncol 14:107. doi: 10.1186/s12957-016-0851-3.

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