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Case Report

Multifocal oral squamous cell carcinoma post haematopoietic stem cell transplantation: A case report

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الملخص

يعتبر تطور سرطان الخلايا الحرشفية عن طريق الفم من المضاعفات النادرة لزراعة الخلايا الجذعية المكونة للدم. الكشف المبكر عن هذا الاختلال أصبح أكثر تعقيدا من خلال مظهرها السريري المتداخل وعرضها مع الآفات المرتبطة بالأمراض المصاحبة لرفض زراعة الأعضاء. يصف هذا المقال تقرير حالة لرجل يبلغ من العمر 33 عاما لديه حالة معروفة بسرطان الدم الليمفاوي الحاد الذي ظهر مع ألم شديد داخل الفم في الجانب الأيسر السفلي من الخد والفك بعد تسعة عشر شهرا من عملية الزرع. لقد عولج سابقا باستخدام سيكلوفسفومايد في الوريد كنظام تكييف لعملية زرع الخلايا الجذعية المكونة للدم ثم طور لاحقا لرفض زراعة الأعضاء للكبد والعينين والأمعاء ولكن تم حله بالعلاج. كشف الفحص داخل الفم عن اختلاليين منفصلين. ظهر الاختلال الأول على شكل انتفاخ عقدي بيضاوي مرتفع مع حافة مقيدة جيدا وسطح غير منتظم على الغشاء المخاطي الشدق الأيسر. لوحظ وجود اختلال مماثل، ولكن أكثر اتساعا على اللثة اللسانية اليسرى وترافق مع نزيف تلقائي. كشفت الخزعة عن كل من الاختلالين وكذلك سرطان الخلايا الحرشفية المتمايزة وكانت إيجابية للبروتين 16 (ب16). خضع للعلاج الإشعاعي الملطف لكنه استسلم لمرضه بعد ثلاثة أشهر من بدء العلاج.

الكلمات المفتاحية: سرطان الخلايا الحرشفية الفموي؛ زراعة الخلايا الجذعية المكونة للدم؛ العلاج متعدد البؤر؛ العلاج المثبط للمناعة؛ المضاعفات

Abstract

Oral squamous cell carcinoma is considered a rare complication of post-haematopoietic stem cell transplantation (HSCT). Early detection of these lesions is further complicated by the overlapping clinical appearance and presentation of lesions associated with chronic graft versus host disease (cGVHD). We report a case of oral squamous cell carcinoma in a 33 year-old man who presented with severe intraoral pain on the lower left side of the cheek and jaw 19 months after undergoing HSCT for the treatment of underlying acute lymphoblastic leukaemia. He was previously treated with intravenous cyclophosphamide as a conditioning regimen for HSCT and later developed cGVHD of the liver, eyes, and gut, which resolved with treatment. Intraoral examination revealed two separate lesions. The first lesion presented as a raised oval nodular swelling with a well-circumscribed margin and irregular surface on the left buccal mucosa. A similar, but more extensive, lesion was noted on the left lingual gingiva and was associated with spontaneous bleeding. Biopsy revealed that both lesions were well-differentiated squamous cell carcinomas and were p16 positive. He underwent palliative radiotherapy but succumbed to his disease 3 months after initiation of treatment.

Keywords: Complication; Haematopoietic stem cell transplantation; Immunosuppressive therapy; Multifocal; Oral squamous cell carcinoma

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Introduction

For the past 30 years, haematopoietic stem cell transplantation (HSCT) has been widely used as curative therapy for various haematological malignancies.[1] Indications for treatment mainly involve conditions such as myeloma, leukaemia, and lymphoma. Previously, this procedure was known as bone marrow transplantation and divided into two categories: autologous and allogeneic. In an autologous transplant, the patient's own normal stem cells were collected prior to high dose chemotherapy, followed by the reinfusion of collected stem cells after treatment. In an allogeneic transplant, normal stem cells are collected from a 'matched' donor and infused in the patient for the purpose of immune response development against the growing malignancies in the new 'host'. Problems arise when this 'foreign' immune response, growing and developing in the new host, also mounts a similar response toward the normal organs of the host. This phenomenon is known as graft versus host disease (GVHD), and it frequently affects the skin, lung, liver, and gastrointestinal tract.[2] Another rare complication associated with allogeneic transplant is the development of post-treatment oral squamous cell carcinoma (OSCC).[3,4]

Case presentation

A 33 year-old Malay male patient, with a history of T cell acute lymphoblastic leukaemia 19 months after allogeneic HSCT, presented with severe pain on the lower left side of the cheek and jaw area. The pain started approximately 1 month prior and was scored as an 8 out of 10. The patient denied tobacco or alcohol consumption. He had previously been treated with intravenous cyclophosphamide as a conditioning regimen for HSCT. After the transplant, the patient was diagnosed with GVHD of the liver, eyes, and gut, which resolved upon treatment. The patient subsequently developed a generalised painful skin lesion and was diagnosed with GVHD of the skin. His medications included Tab. Prednisolone (10 mg od), Tab. Mycophenolate mofetil (750 mg bd), Tab. Aciclovir (800 mg bd), Tab. Bactrim (11/11 bd 2 × /week), and Tab. Itraconazole (100 mg od).

Upon intraoral examination, two separate lesions were noted. The first lesion presented as a raised nodular swelling with a well-circumscribed margin, and an irregular ulcerated surface was observed on the left buccal mucosa. A similar, but more extensive, lesion was noted on the left lingual gingiva of teeth 37, 36, and 35 and was associated with spontaneous bleeding (Figure 1). The right buccal mucosa, lingual gingiva, and surrounding area were within normal limits. The tongue appeared slightly atrophic, and erosion was noted on both sides.

The initial clinical impression was medication-related osteonecrosis of the jaw, and panoramic imaging and cone-beam computed tomography (CBCT) were requested to assess the possibility of underlying bone involvement. CBCT revealed lilingual alveolar bone resorption involving teeth 36 and 37 (Figure 2). The patient was discharged, prescribed with Tab. Celecoxib (200 mg od for 5 days), and asked to return for a follow-up in 1 week.

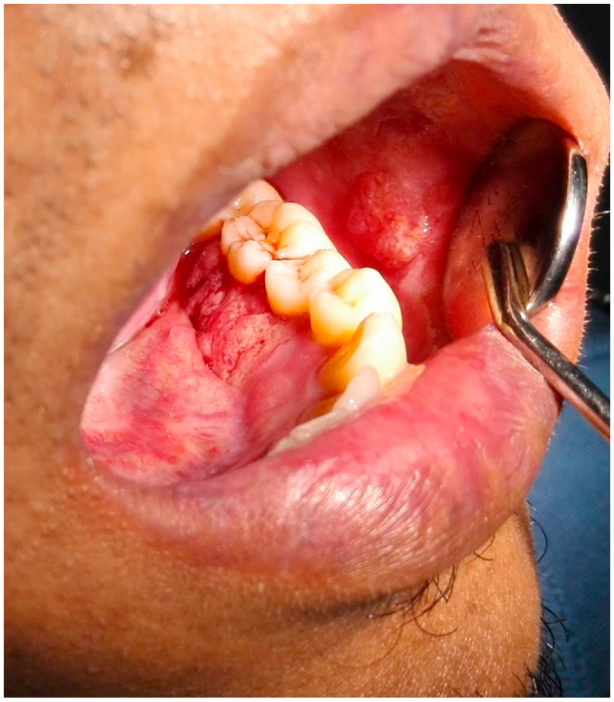

Figure 1: Intraoral photograph showing presence of a discrete, oval swelling with irregular surface on the left buccal mucosa, similar lesion seen on the posterior lingual gingiva of the second premolar and molars with bleeding.

On the second visit, based on the peculiar appearance and presentation of the lesions and the presence of spontaneous bleeding from the gingival lesion, a differential diagnosis of OSCC was made. Incisional biopsies were performed under local anaesthesia at three different sites: left buccal mucosa, left lingual gingiva, and left lateral tongue.

Histopathological findings of the left buccal mucosa and lingual gingiva biopsies revealed specimens covered with parakeratinised stratified squamous epithelium with evidence of cellular atypia and keratin pearl formation. There was an invasion of the epithelial rete ridges into the underlying fibrous connective tissue. Numerous malignant epithelial tumours were observed in large islands and smaller groups of two to three individual cells. The tumour cells exhibited nuclear hyperchromatism, an increased nuclear cytoplasmic ratio, and bizarre mitotic figures with more than 10 per high-power field. Most part of the tumours exhibit well-formed keratin pearls. Subjacent to the invading fronds of the tumour, dense and severe chronic lymphocytic infiltrates were observed within the stroma. Tumour invasion was observed throughout the thickness of the section and extended into the muscle layers and at the specimen margin (Figure 3). Both lesions on the left buccal mucosa and left lingual gingiva were reported as well-differentiated squamous cell carcinomas, whereas the biopsy on the left tongue was negative for the tumour.

Subsequent panoramic imaging revealed a rapidly enlarging mass on the left mandible three months post biopsy (Figure 4). Computed tomography findings showed the presence of a soft tissue mass at the lower alveolar process, measuring 4.8 cm × 3.5 cm × 4.3 cm and involving the buccal mucosa and base of the tongue. The lesion extended

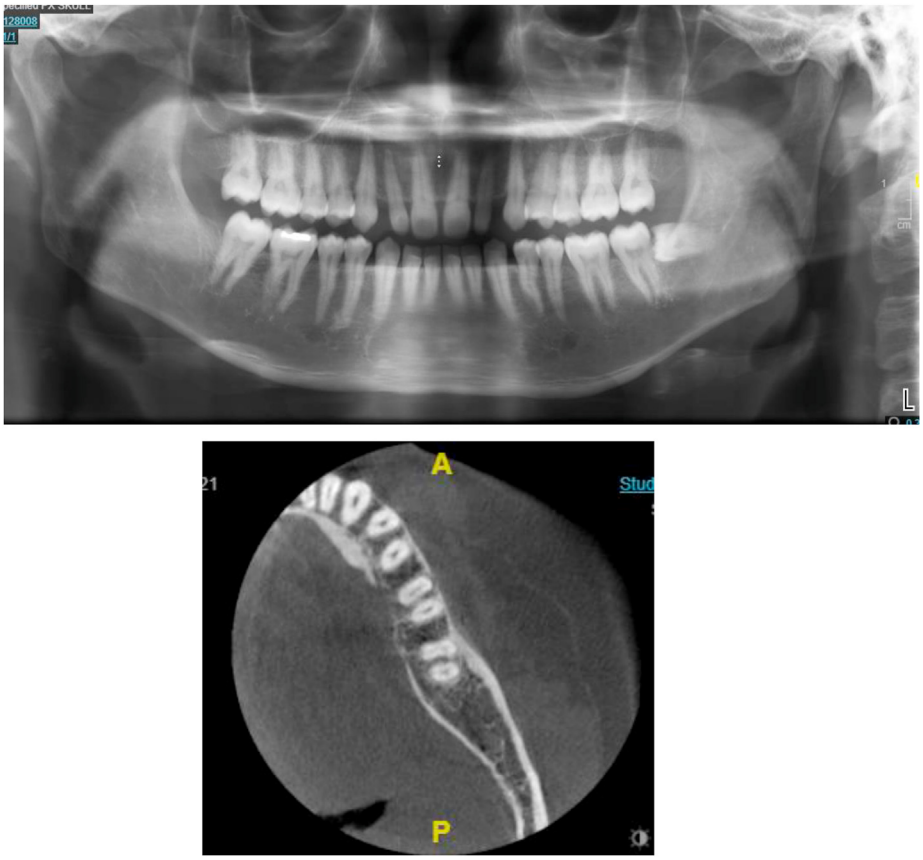

Figure 2: Panoramic imaging did not reveal any bony abnormalities, however cone beam tomography (axial view) revealed lingual bone discontinuity consistent with bone resorption.

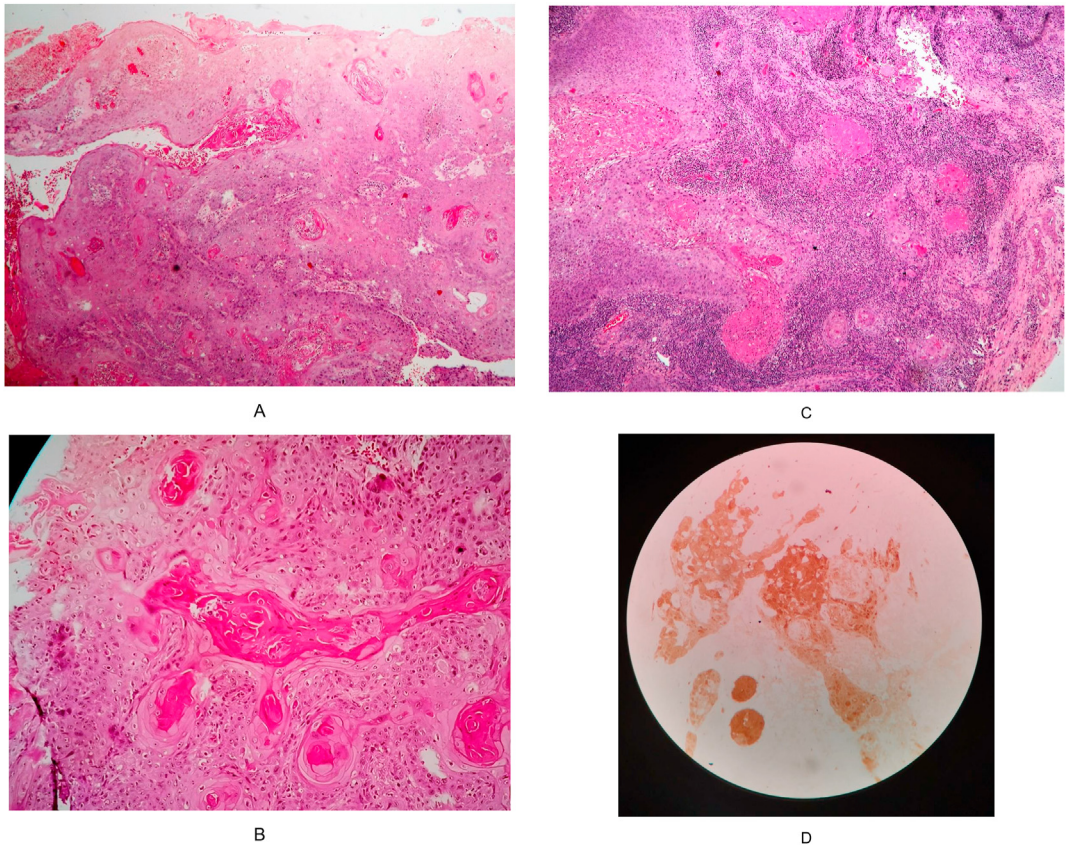

Figure 3: HPE revealed proliferation of squamous epithelial islands with central keratin pearls and cellular atypia (A; specimen from left lingual gingiva, 100x, B; same specimen, 200x), C; specimen from left buccal mucosa, 100x, D; p16 IHC revealed strong positivity).

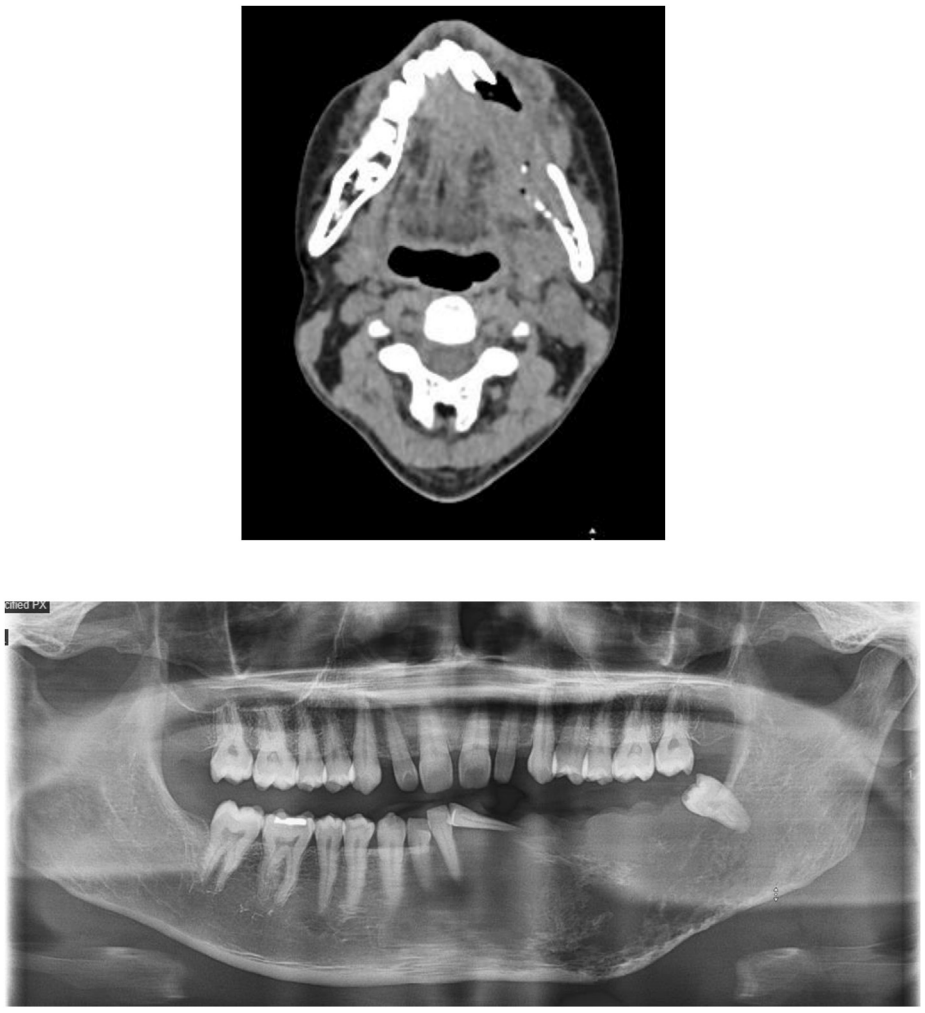

Figure 4: Axial view CT-scan revealed a rapidly enlarging lesion on left mandible with localized bone destruction at two months post biopsy, panoramic imaging revealed similar findings at three months post biopsy.

superiorly from the base of tongue into the oral cavity and inferiorly into the floor of the mouth. Laterally, it extended from the body of the left mandible and medially to the symphysis menti. Multiple necrotic nodes were observed at the left cervical level Ib, level ll, and level lll, with the largest measuring 2 cm × 1.6 cm. There was no evidence of distant metastasis.

For pain management, the patient was initially prescribed with Tab. Celecoxib (200 mg od), later combined with Sy. Morphine (2 mg/ml, 5 ml tds). After 3 days, the pain became unbearable, and the patient was administered intravenous morphine (1 mg STAT). The pain was controlled with a pain score of 3/10. The patient was only scheduled for radiotherapy because he was unfit for surgery due to his immunocompromised state. Additional p16 immunohistochemistry (IHC) was performed on the biopsied specimen, which showed strongly positive staining for the protein expression. The patient completed nine cycles of radiotherapy but succumbed to his disease 3 months later.

Discussion

The first case of successful allogeneic HSCT was reported more than 50 years ago[5] in a 5-month-old infant with sex-linked lymphopenic immunological deficiency. The reconstitution of both cellular and humoral immunity of the host was achieved by transplantation of a graft comprising immunologically competent cells derived from both the peripheral blood and bone marrow of a sibling donor. The donor cells were pre-determined to be HLA loci compatible with the patient's cells prior to the procedure to avoid any major GVHD complications. Currently, common strategies to prevent graft rejection or severe GVHD include infusion of large doses of intense T cell-depleted stem cells and cyclophosphamide administration post-HSCT, which effectively causes T cell depletion in HSCT recipients.[6]

Nevertheless, despite the reduction in major GVHD incidents and improvement in post-transplant outcomes over the past five decades, the development of secondary malignancies (SM) post-transplant has been increasingly reported.[7] After reviewing 2415 patients who underwent allogeneic post-HSCT, Michelis et al. observed SM in 209 patients. The cumulative incidence was 6.3% at 10 years and almost tripled (17.6%) at 30 years post-HSCT. Twenty-one patients (10%) had squamous cell carcinomas that arose primarily from the oral cavity. The median duration reported for OSCC development ranges from 1.2 to

19.8 years post-transplant. Twelve of these patients underwent surgery alone and seven received a combination treatment of surgery and chemoradiation. The treatment status remains unknown for two of these patients.

The early diagnosis of OSCC post-HSCT remains challenging because its subtle clinical appearance may mimic the oral manifestation of chronic GVHD lesion (cGVHD).[8] According to the American Academy of Oral Medicine,[9] the clinical presentation of cGVHD includes oral pain, hyperalgesia to normally tolerated foods and drinks, trismus, and xerostomia. Lesions commonly appear as reticular or lacy-like whitish striations on the buccal mucosa or dorsum of the tongue, mimicking oral lichen planus/lichenoid lesions. Other presentations include painful widespread erosions with raw, erythematous areas resembling oral mucositis, and prominent ulcerations resembling large canker sores. In the case presented here, the lesion appeared as a nodular swelling with an irregular surface, and the associated bleeding rendered the lesions suspicious for malignancy.

After 30 years of transplantation medicine (1978–2008), Kruse and Gratz (2009) highlighted the importance of early detection of oral carcinoma post-HSCT and proposed a new classification.[10] They found that 49 out of 64 cases (76.6%) of oral malignancies were preceded by oral cGVHD. Other proposed risk factors include male sex, young age, viruses, particularly Epstein Barr virus and high-risk human papilloma virus (HPV),[4,11–14] prior cyclophosphamide immunosuppressive therapy and conditioning radiation,[15] and chemotherapy such as prophylaxis or treatment of cGVHD with cyclosporin and/or methotrexate, prednisone, and rituximab.[8,15,16]

Previous studies have also shown that the rate of SM development was 3.8-fold to 8-fold higher than that in an age-matched control population.[16,17] The most frequent malignant disease is squamous cell carcinoma of the skin, followed by the oral cavity.[15,17] Patients who received allogeneic stem cell transplants were almost 14 times more likely to develop oral cavity squamous cell carcinoma than the general population.[8]

In the present case, predisposing factors for the development of OSCC were identified, as the patient was a young male with a recent history of immunosuppressive therapy (cyclophosphamide, mycolate mofetil, and prednisone) and cGVHD. The lesions were also positive for p16 by IHC, indicating high-risk HPV involvement. The multifocal presentation of lesions was previously reported by Mawardi et al., where multifocal OSCC was observed in four out of 15 cases, and localised recurrence was observed in six cases.[18]

As for the management of these cases, there was no standard guideline established due to the limited number and difficulty in the follow-up of reported cases. Management varies from one study to another, but mostly involves either surgery or surgery combined with chemoradiation. The 5-year overall survival rate is approximately 70%.[18] Nevertheless, the prognosis mainly depends on the fitness of individual patients to undergo treatment, as these patients are already immunocompromised when these lesions are discovered.

Conclusion

OSCC development is considered a rare complication post-HSCT. The early detection of these lesions is further complicated by the overlapping clinical appearance and presentation of lesions associated with cGVHD. Multifocal presentation, nodular swelling, and irregular surfaces which easily bleed were helpful clinical features in raising suspicion of the possibility of OSCC post-HSCT.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/18010043). This study conformed to the principles of the Helsinki Declaration of 1975 and 1983.

Consent

Informed consent was obtained from the patient prior to the preparation of the case report for the purpose of publication (including clinical photographs), and author/s endeavoured to ensure anonymity.

Authors contributions

NAR: Conceptualisation, data interpretation, writing the original and final drafts. NANNO: Data acquisition and interpretation. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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