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Up-to Date Review And Case Report

Lymphoma of the lip after kidney transplantation: a case report

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Abstract – Introduction: In transplant recipients, the risk to develop cancer increases 4 fold compared to general population due to the immunosuppressive treatment. **Observation:** A 68 years old woman, kidney transplanted four years ago, presented with a slowly growing swelling over her left lip since six weeks. The histopathological analyses showed a non Hodgkin lymphoma. **Comment:** Post-transplant lymphoproliferative disorders (PTLD) is a complication developing after solid organ transplantation or allogenic hematopoietic stem cell transplantation. Immunosuppression due to the immunosuppressives drugs is considered as the most important risk factor and the incidence rate depends of transplant type, age and risk of primary Epstein-Barr virus infection. **Conclusion:** PTLD is a rare but serious complication. It must be suspected in all cases of intra-oral mass for a transplanted patient and requires a histopathological analysis for early diagnosis and appropriate treatment.

Introduction

Among malignant lesions of the head and neck, lymphomas are the second most common lesion [1], with an incidence rate of 0.1–5% [2]. They form a heterogeneous group of malignant haematology pathology. Lymphomas are more likely to develop in immunosuppressed patients like transplant recipients forming the post-transplant lymphoproliferative disorders (PTLD). These are a well-recognized complication of solid organ transplantation and need to be found out during the tracking of patients in order to be cured prematurely [3]. Lesions affect commonly the vestibule, gingival, or posterior hard palate and develop slowly as non-tender swellings, mimicking a dental abscess of endodontic or periodontal origin [4].

Observation

A 68 years-old woman was referred to the unit of the oral medicine of the Hospital University Center of Nice with growing swelling over her left lip since six weeks. She was toothless and she initially thought this swelling was due to an accidental blow. Before the persistence, she consulted her dentist, who prescribed antibiotics (amoxicillin/clavulanic acid) without any improvement. The patient did not report any systemic symptoms including weight loss or fever. She gave history of kidney transplantation 4 years ago, with tacrolimus 6 mg/day like treatment.

The extraoral examination disclosed a firm, painful swelling that is fixed into superficial and deep tissue. It was an unique homogeneous subcutaneous mass, measuring $5 \times 5 \times 3$ cm. The overlaying mucosa was smooth and slightly erythematous (Fig. 1). There was no lymph node enlargement. Contrast computed tomography (CT) confirmed the presence of the enlarged mass in left lip, without bone lesion and without involvement of nasal cavity and metastasis, just a submandibular lymph node aspecific (Fig. 2). Punch biopsy was performed under local anaesthesia and histopathological analyses showed diffuse infiltrate by atypical lymphoid cells (Fig. 3). Immunohistochemical staining was positive for CD20 and CD79a, and negative for CD3, CD5 and CD138. Fluorescence *in situ* hybridization depicted an absence of rearrangement of loci MYC and BCL6. The proliferative rate by Ki-67 was superior to 95% (Fig. 4). The laboratory investigation revealed a normal hemogram and a positive serology for Epstein-Barr Virus (EBV). A diagnosis of non-Hodgkin lymphoma (diffuse large B-cell lymphoma) was rendered.

The patient received one cycle concurrent chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), at the same time nephrologists switched PROGRAFT by EVEROLIMUS. Unfortunately a week later, she died of a pulmonary embolism due to pro-thrombotic treatments such as EVEROLIMUS, hematopoietic growth factors and the absence of antithrombotic prophylaxis, which was impossible in her case on account of her renal deficiency.

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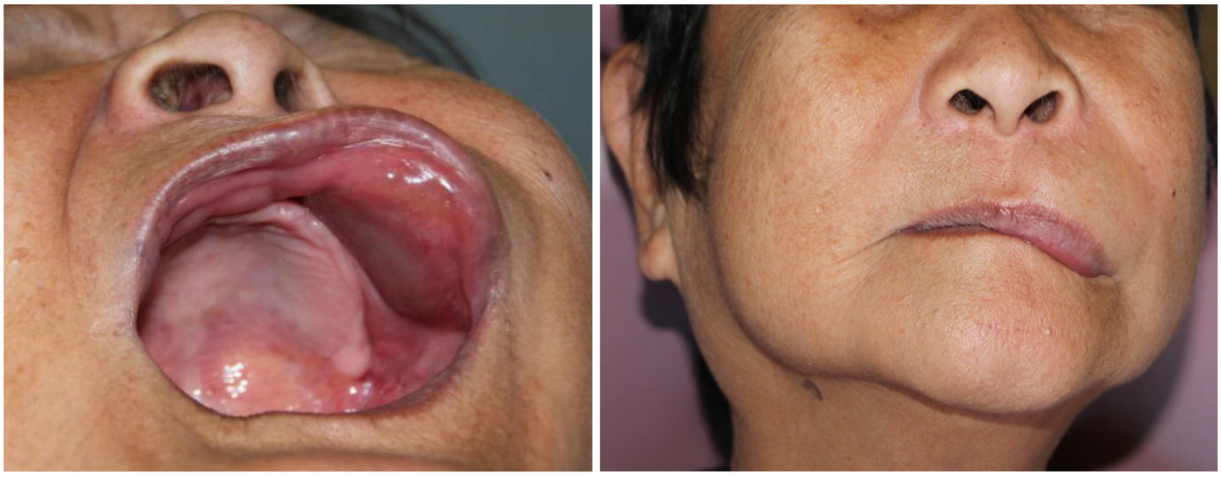

Fig. 1. Local examination on the lymphoma of the left lip.

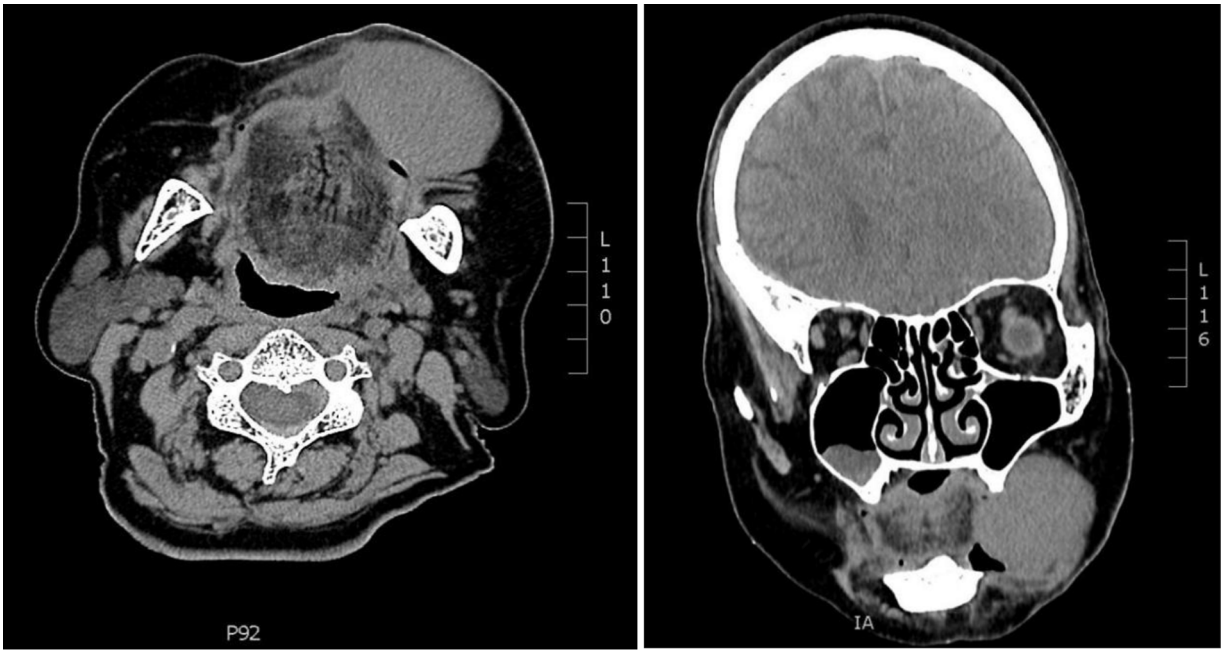

Fig. 2. CT scan of the face with lymphoma of the left lip without bone lesion (axial and coronal slices).

Comments

The PTLD is a heterogeneous group of diseases occurring after solid organ transplantation or allogenic hematopoietic stem cell transplantation. It may present various clinical manifestations, from non-specific mononucleosis-like syndrome to lymphomas. The first cases were reported in 1968 by DOAK and al. for kidney recipient [3]. This is a well-known complication for transplant recipient due to the immunosuppressive treatment used to prevent graft rejecting. In Kasisks study, they analysed rates of malignancies after kidney transplantation ($n = 35\ 765$), non-Hodgkin lymphoma is increased 20-fold compared to general population [5]. Post-transplant non-Hodgkin lymphomas differ from lymphomas of the general population with more aggressive clinical course, poorer response to conventional therapies and poorer outcomes. The most common malignant PTLD subtype is diffuse large B-cell lymphoma, with only 5% of T cell or T/NK cell origin [6].

Immunosuppression is considered as the most important risk factor, as it decreases the immunologic control of oncogenic viral infection and cancer immunosurveillance. The other risk factors of PTLD are EBV infections, age, transplant type and immunosuppressive therapy provided. The mean age correlated with diagnosis is about 46/48 years in many studies [3,7,8,9], but the risk is linked to the age at the moment of the transplantation: the younger the recipient is, the higher the risk gets. For the transplant type, PTLD prevails most often (20% of patients) for bowel recipients; less often for liver and kidney recipients 2.4–8% vs 1-10%, and even less for bone marrow recipients (1%) [10].

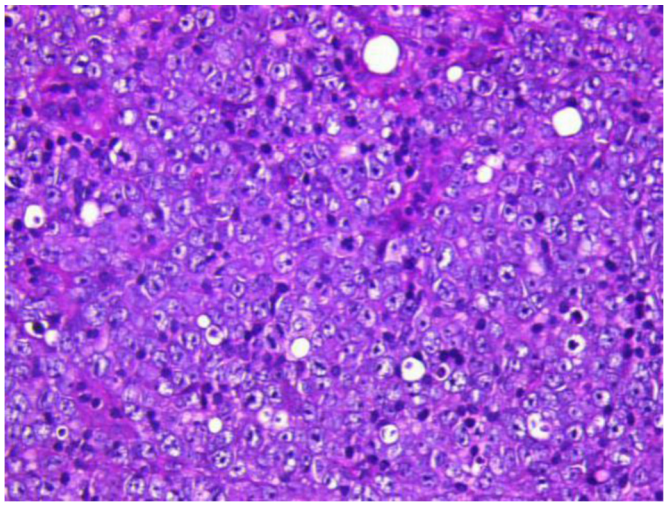

Fig. 3. Proliferation of large lymphoid cells (HES, X400).

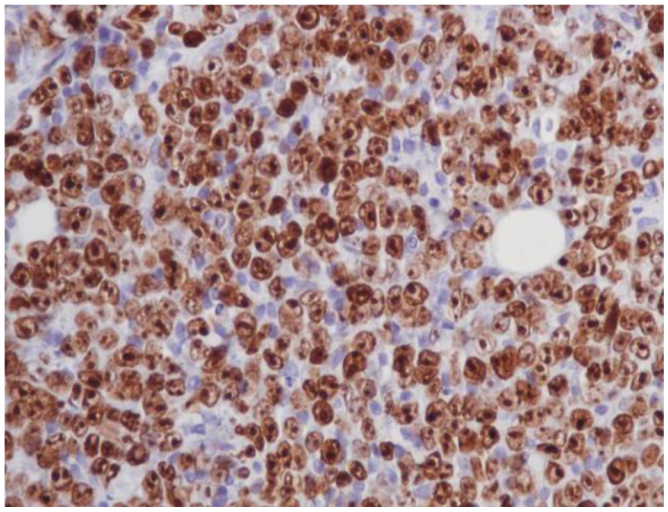

Fig. 4. The Ki-67 cell proliferation index was approximately 95% (X ;400).

Approximately 50 to 70% of PTLD are EBV related [11]. Once EBV infects B-lymphocytes, it achieves latent infection. This virus is a well-known oncogenic virus, with protein like latent membrane protein-1 (LMP-1) mimics CD40, activates the nuclear factor-kappa B and induces BCL-2 to escape from apoptosis and provide a proliferation [12]. Most cases of PTLD have been linked to unrestrained proliferation of EBV infected B cells caused by suppression of normal immune system mechanisms on account of immunosuppressive therapy [13].

In the study of Opelz *et al.* [14], among 18 682 kidney transplant recipients, the risk of lymphoma post transplantation was significantly increased for patients with a seronegative EBV status in all age groups in comparison with patients with seropositive EBV status. This is due to the primary EBV infection caused by transplanted infected organs [15]. These explain the higher risk of PTLD for transplanted children, naive of this infection and the association between early-onset disease and seronegative EBV recipient status [16]. These findings provide the need for an EBV serology before a graft [14] as well as a screen for EBV DNA in blood in high-risk recipients for 1 year after transplantation like recommended actual guidelines [17].

PTLD treatment has to guaranteee the complete remission as well as the preservation of the transplantation. The universal initial step is the reduction of immunosuppression [9,18]. Then, current treatment strategies used antiviral therapy, monoclonal antibodies, chemotherapy and local therapy (surgery and radiation) [19]. The most common is Rituximab (chimeric monoclonal antibody directed against the B cell antigen CD20) associated with chemotherapy CHOP (Cyclophosphamide, Hydroxy Adriamycine, Oncovin, Prednisone) [20]. Overall patient survival at 1, 5, and 10 years was 66%, 50%, and 37% respectively [15] and mean survival is 5.6 years [20].

Survival rate lowers, as well as graft survival rate for transplanted patients with PTLD compared to patients without.

Conclusion

PTLD is a complication following transplantation that can seriously threaten long-term outcomes, overall survival patient and graft survival. Screening for malignant lesions should continue to be a major focus in all transplanted patients. Dentists, oral surgeons and oral pathologists need to be vigilant about all oral lesions, realizing a biopsy for histopathologic examination and starting early treatments.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

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