ABSTRACT

Fanconi Anemia patients are a high risk group for solid and hematologic malignancies. The risk seems to be influenced by age, chronic graft versus host disease and immunosuppressive drug regimens. Reports of oral malignant transformation in Fanconi Anemia after hematopoietic stem cell transplantation (HSCT) are increasing probably because of longer survival rates. This is the report of an 18- and her 28-year old sister who developed a post-HSCT oral squamous cell carcinoma. There were significant differences regarding time to malignant transformation, marrow donor characteristics and graft versus host disease evolution and treatment. The report reinforce the need for a routine head and neck screening for cancer in this particular syndrome and suggest that familial history should also be considered in Fanconi anemia patients at risk for oral malignancy after HSCT.

KEY WORDS: bone marrow transplantation, oral cancer, Fanconi anemia

Oral squamous cell carcinoma in two siblings with Fanconi anemia after allogeneic bone marrow transplantation

Cassius Carvalho Torres-Pereira, DDS, PhD;[1]* Roberta Targa Stramandinoli-Zanicotti, DDS, PhD;[2] José Miguel Amenábar, DDS, PhD;[1] Laurindo Moacir Sassi, DDS, PhD;[3] Paola Andrea Galbiatti Pedruzzi, MD, MSc;[4] Cleto M. Piazzetta, DDS, MSc;[1] Carmem Bonfim, MD, MSc[5]

[1]Stomatology Department Professor, Universidade Federal do Paraná, Curitiba, Paraná, Brazil; [2]Oral and Maxillofacial Surgery Service of the Erasto Gaertner Hospital, Curitiba, Paraná, Brazil; [3]Chief of Oral and Maxillofacial Surgery Service of the Erasto Gaertner Hospital, Curitiba, Paraná, Brazil; [4]Head and Neck Surgery Department of Erasto Gaertner Hospital, Curitiba, Paraná, Brazil; [5]Bone Marrow Transplant Unit, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Paraná, Brazil.
*Corresponding author e-mail: cassius@ufpr.br

Spec Care Dentist 34(4): 212-215, 2014

Introduction

Fanconi anemia (FA) is an inherited disorder characterized by a progressive bone marrow failure and a predisposition to develop malignancies. The phenotype can also include skeletal, cardiac and renal malformations, skin pigmentation and delayed growth. The allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for this condition but it can increase the risk of hematologic and solid malignancies.[1]

The disease is usually identified in children, with a median age of 9 years. Treatment is mainly directed to the maintenance of a minimum level of platelets, red and white blood cell count to maintain physiologic stability until the identification of a matched related or unrelated hematopoietic stem cell donor. A suspected phenotype is confirmed through the diepoxibutane test, which allows the identification of the specific FA DNA repair deficiency.[1]

As FA patients grow older there is an increased risk for the development of hematologic malignancies, specially leukemia, and head and neck cancers. Oral cancer is the most frequent described solid malignancy in FA and the risk is augmented by the conditioning regimen, the HSCT and the onset of chronic graft versus host disease (GVHD).[2–5]

To the best of our knowledge this paper describes a nonprevious reported condition of oral malignant transformation in FA siblings after HSCT. It also highlights FA high susceptibility to malignancy and the known risk factors that support performing a routine oral mucosa screening.

Case report

An 18-year-old female with a FA was referred to oral consultation because of a progressive painful ulceration on the left side of the tongue. The patient had no history of smoking or alcohol intake and had undergone allogeneic (HSCT) procedure 10 years before (1997).
The donor was a 15-year old sister. The patient was conditioned with 100 mg/kg of cyclophosphamide and received cyclosporine and methotrexate for GVHD immunoprophylaxis. She did not

DOI: 10.1111/scd.12058

developed acute GVHD and chronic GVHD involving oral mucosa was mild requiring no treatment. The patient was previously evaluated for a white lesion in the same area 3 years earlier (2004). She reported the lesion was biopsied at her hometown and the pathology report was signed out with a diagnosis of "leukoplakia" with no mention of cellular dysplasia. The ulceration on the left side of the tongue measured 1.5 cm in diameter and showed diffuse white spots and indurate borders, with palpable lymph nodes (Figure 1). An incisional biopsy was performed and the histological analysis confirmed an invasive and moderately differentiated squamous cell carcinoma (SCC). The patient was referred to a head and neck surgeon who performed a glossectomy and neck dissection. On final pathological analysis, all tumor margins and the excised sentinel lymph node were free of disease and there was no evidence of distant metastasis. Radical excision of the tumor was possible because of early diagnosis. Adjuvant treatment by chemotherapy or radiation was not indicated. The function of the tongue was not compromised (Figure 2) and no further evidence of malignancy was detected as of last consultation in September 2012.

In November 2009, her 28-year-old sister, also diagnosed with FA, presented with red atrophic and bleeding lesions in the oral mucosa (Figure 3). This patient was also submitted to an allogeneic HSCT in September 2006. She was conditioned with 60 mg/kg of cyclophosphamide and received cyclosporine and methotrexate for GVHD immunoprophylaxis. The graft was obtained from her 30-year old brother and her posttransplant history was remarkable for mucositis grade III (WHO scale) and acute GVHD involving liver and skin. The acute manifestation was treated with systemic steroids. This patient also developed extensive and progressive chronic GVHD involving liver, skin, oral mucosa, and eyes. Chronic GVHD was treated with a protocol of immunosuppressive drugs such as tacrolimus, mycophenolate mofetil and steroids. Dexametasone and eventually clobetasol plus nistatine mouthwashes were also prescribed. Three years after transplant (August 2009) the patient was submitted to a basocellular carcinoma resection on the nose.

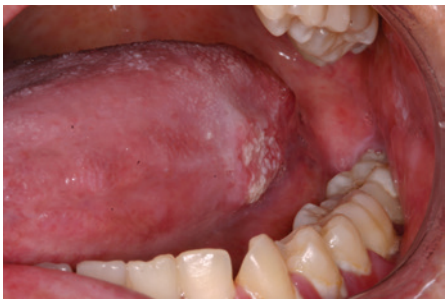

Figure 1. Initial presentation of OSCC in the lateral border of the tongue (Case 1).

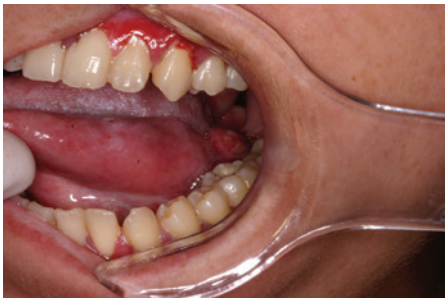

Figure 2. Clinical post-surgical aspect after a partial glossectomy (Case 1).

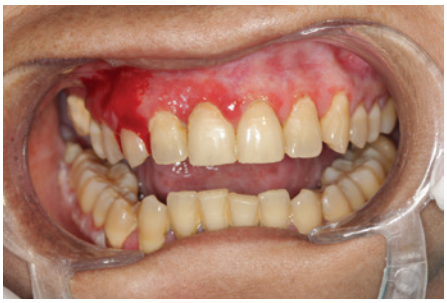

Figure 3. Maxillary OSCC mimicking a bacterial periodontal disease (Case 2).

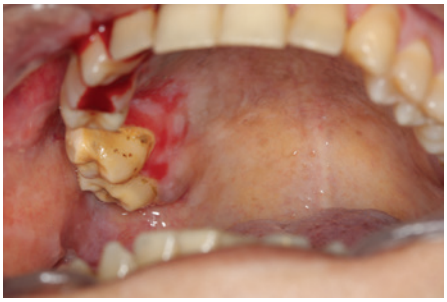

Figure 4. Palatal aspect clinically characterized as an erythroleukoplakia (Case 2).

This patient presented oral lesions extending in right gingival vestibular and palatal papilla (Figure 4) and erosions in the left mandibular retromolar area. The incisional biopsy of three distinct areas showed moderately differentiated invasive SCC. A CT scan showed an infiltrative lesion in the gingival mucosa with erosion of the upper right alveolar ridge. No evidence of infiltration in the maxillary sinus or other adjacent structures was noted. A partial maxillectomy was carried out without major complications. A resection of the erythroplasia located at the retromolar site revealed SCC with specimen margins free of the disease. Six months after transplant there was no evidence of local recurrence and she remained free of the disease as of November 2012.

The patients were from a poor socioeconomic and educational background with sporadic access to dental services. Oral health was not a priority to the family and most of the efforts and financial resources were directed to the HSCT therapy. Moreover, the Brazilian FA reference center is located in the city of Curitiba, south Brazil, approximately 1.300 km distant from Brasília, the sisters hometown.

Discussion

In most cases, head and neck SCC are closely related to tobacco and alcohol exposure, mainly affecting males above 50 years of age.[7,8] Cumulative evidence, however, shows an increasing number of case reports and case series of head and neck SCC as a complication of allogeneic HSCT particularly in patients diagnosed with FA.[2–6] A number of risk factors have been identified and suggested as potential causes for oral malignant transformation after HSCT such as chronic GVHD, prolonged immunosuppressive therapies, greater spontaneous and induced chromosomal instability,

abnormal cell cycles, defects in DNA repair, and alterations in the immune system as the most important.[4,9–11] An interesting finding of this report is the oral malignant transformation in two sisters, both of them after an allogeneic HSCT. However, although the siblings have developed oral cancers, their post-HSCT evolution was quite distinct, particularly concerning the chronic GVHD history. Some researchers have shown evidence of donor-derived oral cancers after HSCT.[12] Although in the cases presented no effort could be made to analyze specimens for donor or recipient origin of the tumors, the cases indicate that familial history should be more carefully investigated in head and neck malignancies after HSCT, especially oral malignant neoplasia in recipients of a bone marrow allogeneic graft. Interestingly, the patients received grafts from distinct donors. Reports of oral cancer have been already described in twins and in siblings.[13,14] Malignant transformation in FA siblings has also been described.[15] However, to our knowledge, this is the first report of oral malignant transformation in two FA siblings after allogeneic HSCT.

Authors describe that oral cancers after BMT have a very aggressive course. In a study in which 754 HSCT and non-HSCT FA patients were assessed, the authors noticed an increase of approximately 500-fold in the incidence of head and neck tumors, mainly in females (2:1), and average age at diagnosis of 31 years, when compared to the general population.[6]

In post-HSCT FA anemia patients, radio or chemotherapy for SCC treatment have limited indications because these patients shows a high frequency of immediate and postimmediate complications because of FA syndrome high susceptibility for toxicities. Both patients had oral lesions diagnosed as chronic GVHD. The younger had also manifested an oral leukoplakia previous to the tongue SCC. Biopsy revealed no sign of dysplasia. It is not possible however to establish a correlation of the evolution of the leukoplakia to SCC because the oral patch was not observed on a regular basis and in a single institution. The older sister had an extensive and severe chronic GVHD requiring long-term systemic and local immunossupression. This may explain the earlier oral cancer transformation after the HSCT for the older sister.

Both siblings have been screened for oral lesions before and after HSCT. Screening post-HSCT patients for cancers has been recommended with special attention to oral sites.[16] Special concerns are the chronic oral GVHD lesions, a history of prolonged immunosuppressant therapy and a diagnosis of FA.[16] A consensus on screening guidelines and long-term follow-up of HSCT complications recommends that oral mucosa and dental status should be examined annually.[17] In FA patients, the consensus suggests this interval to be every six months throughout their lives.[17] Clinical judgment and a rigorous chart or image registry should be established for routine care. In the patients described herein, a regular screening interval was compromised by distance to reference health services and a deprived socioeconomic and educational status.

This report reinforce that FA patients should be thoroughly and frequently screened for the occurrence of oral malignancies, and suggests that a familial history of cancer should be carefully investigated.

Source of funding

None.

Conflict of interest

The authors declare no conflict of interest.

References

1. Smith AR, Wagner JE. Current clinical management of Fanconi anemia. *Expert Rev Hematol* 2012;5(5):513-22.
2. Rosenberg PS, Socie G, Alter BP, *et al*. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood* 2005;105: 67-73.
3. Masserot C, Peffault de Latour R, Rocha V, *et al*. Head and neck squamous cell carcinoma in 13 patients with Fanconi anemia after hematopoietic stem cell transplantation. *Cancer* 2008;113(12): 3315-22.
4. Elad S, Zadik Y, Zeevi I, Miyazaki A, deFigueiredo MA, Or R. Oral cancer in patients after hematopoietic stem-cell transplantation: long-term follow-up suggests an increased risk for recurrence. *Transplantation* 2010;90(11):1243-4.
5. Salum FG, Martins GB, deFigueiredo MA, Cherubini K, Yurgel LS, Torres-Pereira C. Squamous cell carcinoma of the tongue after bone marrow transplantation in a patient with Fanconi anemia. *Braz Dent J* 2006; 17(2):161-5.
6. Kutler DI, Auerbach AD, Satagopan J, *et al*. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. *Arch Otolaryngol Head Neck Surg* 2003;129:106-12.
7. Torres-Pereira CC, Angelim-Dias A, Melo NS, Lemos CA Jr, Oliveira EM. Strategies for management of oral cancer in primary and secondary healthcare services. *Cad Saude Publica* 2012;28 Suppl:s30-9.
8. Torres-Pereira C. Oral cancer public policies: is there any evidence of impact? *Braz Oral Res* 2010;24 Suppl 1:37-42.
9. Curtis RE, Metayer C, Rizzo JD, *et al*. Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. *Blood* 2005; 105(10):3802-11.
10. Demarosi F, Lodi G, Carrassi A, Soligo D, Sardella A. Oral malignancies following HSCT: graft versus host disease and other risk factors. *Oral Oncol* 2005;41(9): 865-77.
11. Kruse AL, Grätz KW. Oral carcinoma after hematopoietic stem cell transplantation–a new classification based on a literature review over 30 years. *Head Neck Oncol* 2009; 1:29.
12. Janin A, Murata H, Leboeuf C, *et al*. Donor-derived oral squamous cell carcinoma after allogeneic bone marrow transplantation. *Blood* 2009;113(8):1834-40.
13. Bhaskar PB, Smith RG, Baughman RA. Oral squamous cell carcinoma in identical

twins: report of a case. *J Oral Maxillofac Surg* 1988;46(12):1096-8.
14. Ide F, Shimoyama T, Horie N. Carcinoma of the tongue in two siblings. *J Oral Maxillofac Surg* 1999;57(1):66-8.
15. Sarna G, Tomasulo P, Lotz MJ, Bubinak JF, Shulman NR. Multiple neoplasms in two siblings with a variant form of Fanconi's anemia. *Cancer* 1975;36(3): 1029-33.
16. Reddy NM, Sullivan MA, Hahn TE, Battiwalla M, Smiley SL, McCarthy PL. Association of squamous cell carcinoma of the oral cavity in allogeneic hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2007;40(9):907-9.
17. Majhail NS, Rizzo JD, Lee SJ, *et al*. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Rev Bras Hematol Hemoter* 2012;34(2):109-33.