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# Early presentation of squamous cell carcinoma after bone marrow transplantation in a boy with Fanconi anemia

*Apresentação precoce de carcinoma de células escamosas em um menino de 11 anos com anemia de Fanconi submetido a transplante de medula óssea*

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key words	abstract
Fanconi anemia	The authors report a case of an 11-year-old boy with Fanconi anemia presenting with squamous cell carcinoma of the tongue 763 days after bone marrow transplantation. Few cases have been reported in the literature, usually involving mucosal membranes in adult patients. The factors related to the development of malignancies after bone marrow transplantation are discussed and the early presentation is highlighted, once a high index of suspicion is required for the early identification of this kind of lesion in children.
Squamous cell carcinoma	
Bone marrow transplantation	

resumo	unitermos
Os autores relatam o caso de um menino de 11 anos de idade com anemia de Fanconi que foi submetido a transplante de medula óssea. Com 763 dias de evolução, foi detectada uma lesão ulcerada na língua, compatível com carcinoma de células escamosas. Poucos casos semelhantes foram reportados na literatura, geralmente envolvendo as membranas mucosas em pacientes adultos. Os fatores relacionados ao desenvolvimento de neoplasias secundárias em transplante de medula óssea são discutidos e a idade precoce de apresentação do paciente enfatiza a necessidade de um alto índice de suspeição, mesmo em pacientes muito jovens, para que se faça o diagnóstico da lesão em fase inicial.	Anemia de Fanconi Carcinoma de células escamosas Transplante de medula óssea

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## Introduction

Fanconi Anemia (FA) is a rare autosomal recessive disease characterized by a series of congenital abnormalities, bone marrow failure and increased predisposition to hematologic as well as solid tissue malignancies<sup>(4)</sup>.

With the improving modalities of treatment of FA, the formerly reported ten-year life expectancy now reaches 30 years<sup>(1)</sup>. This progress has led to the development of less commonly noted malignancies as the patients move into adulthood, especially liver cancer and squamous cell carcinomas (SCC). Besides, bone marrow transplantation (BMT), considered the treatment of choice for this disorder<sup>(5)</sup>, corrects only the hematologic abnormalities of FA and not its general failure to repair DNA damage.

Few cases of SCC in patients with FA post BMT have been reported<sup>(6,7,9)</sup>. There appears to be a predilection for mucosal tissue in the head and neck with a mean age of presentation of 23 years<sup>(1,9)</sup>. The authors report a case of SCC of the tongue in an 11-year-old child with FA post BMT. Clinicopathologic and ultra-structural features as well as a review of literature are presented.

## Case report

A 6-year-old male, blood group B and born from unrelated parents, presented with left hemiparesia in 1996. Computerized tomography suggested a hemorrhagic cerebrovascular episode and blood count revealed severe platelet depletion. FA was first suspected and the patient was referred to our institution. The diepoxibutane sensitivity (DEB) test provided the accurate diagnosis of FA and bone marrow transplantation was planned.

The patient underwent ABO-incompatible allogeneic bone marrow transplantation in February, 1997. The marrow donor was his HLA-identical AB+ blood group sister who did not have FA. The pre-transplant conditioning regimen consisted of cyclophosphamide (CY) 25mg/kg daily IV during four consecutive days (total dose of 100mg/kg) associated with MESNA 25mg/kg IV daily, for hemorrhagic cystitis prophylaxis. Irradiation was not included in the pre-transplant regimen. Prophylaxis for herpes virus with acyclovir, for *Pneumocystis carinii* with trimethoprim-sulfametoxazole, and for other variants of fungus with fluconazole were introduced. Prophylaxis for graft-versus-host disease (GVHD) consisted of cyclosporin A (CsA) and methotrexate (MTX) according to the Seattle protocol<sup>(10)</sup>. Sustained engraftment was achieved but

the patient developed acute GVHD followed by chronic GVHD in the oral mucosa and in the liver. For the initial management the patient received CY and corticosteroids. Since there was no complete regression of the disease, treatment with azathioprine was instituted and the doses of CY progressively reduced.

On day 763, still under treatment for chronic GVHD with azathioprine, he presented an ulcerated lesion of the tongue. Neither clinical lymphadenopathy nor signs suggesting systemic dissemination were observed. The blood count was Hb 8g/dl; white blood cells, 3,000/dl and platelets, 89,000/dl. The first suspicion was squamous cell carcinoma and due to its localization and extension, the lesion proved to be locally resectable. The patient underwent partial glossectomy after a frozen section diagnosis of squamous cell carcinoma. Chemotherapy and radiotherapy were avoided because of the primary disease (FA).

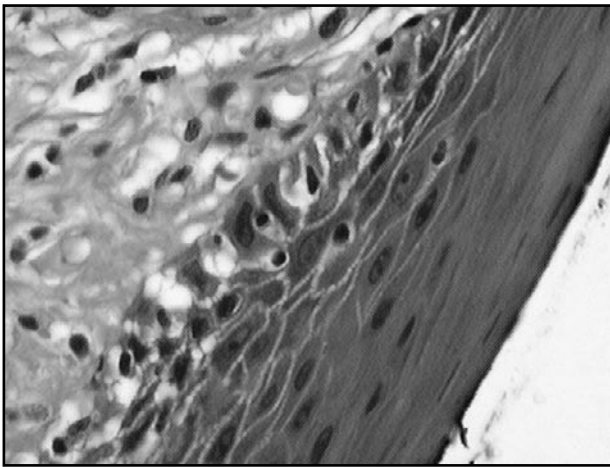
The resected specimen showed an invasive squamous cell carcinoma without evidence of vascular or perineural spread (**Figure 1**). The margins were free of tumor involvement. Foci of chronic GVHD, with hydropic degeneration of the basal layer and lymphocytic infiltrate, were present in the surgical specimen (**Figure 2**). Assessment for human papillomavirus infection was performed by *in situ* hybridization coupled with streptavidin-peroxidase and catalyzed signal amplification (DAKO). Probes for types 6/11, 16/18, 31/33 and a wide spectrum probe (DAKO) were employed, however, no signal was obtained.

## Discussion

FA is an inherited disease characterized by chromosomal instability and a series of congenital morphologic



**Figure 1** – Tongue invasive squamous cell carcinoma (hematoxylin-eosin, 100x)



**Figure 2** – Graft-versus-host disease in the tongue, displaying hyperkeratosis, hydropic degeneration and infiltration of lymphocytes in the basal layer (hematoxylin-eosin, 400x)

abnormalities. It has been claimed that it is caused primarily by a defect in DNA crosslink repair<sup>(4)</sup>.

The predisposition of FA patients to hematologic abnormalities and cancer, and the chronology of the events has been well-documented<sup>(1)</sup>. Aplastic anemia has a high penetrance, developing in approximately 80% of patients, usually in the first decade of life<sup>(1, 4)</sup>. The most common hematologic malignancy is acute myelogenous leukemia, differing from the usual pediatric and adolescent population pattern. It develops in approximately 9% of patients, at a mean age of 14 years. Some patients who develop leukemia have pre-existing myelodysplasia and typical cytogenetic abnormalities<sup>(1, 4)</sup>.

FA patients also present an increased incidence of solid tumors, particularly liver and mucosal membrane cancer. With new approaches to hematologic abnormalities, FA patients are achieving longer survival rates and being prone to develop solid organ malignancies. Liver tumors occur in 9% of patients with FA, at a mean age of 16 years. Adenomas and metastatic tumors have been reported, but the most common histological type is hepatocellular carcinoma<sup>(1)</sup>.

Other solid tumors occur later, at a mean age of 23 years<sup>(1, 9)</sup>. The vast majority is squamous cell carcinoma of mucous membranes, including oral, anal, esophageal

mucosa and the tongue<sup>(1, 4, 7-9)</sup>. It is worth noting that FA patients present with solid organ tumors at an age younger than the general population. Our report describes a boy presenting with tongue SCC at the age of 11 years, much younger not only than the general population but also younger than average FA.

The treatment of FA involves transfusion support, androgens, when aplastic anemia develops, and BMT, when feasible. The latter represents an effective curative procedure for FA<sup>(4)</sup>. However, all the process involving BMT is also known for its increased predisposition to secondary malignancies, especially lymphomas and solid organ carcinomas. The development of secondary tumors after BMT is multifactorial and involves the tendency of the primary disease (as in FA); exposure to radiation, cytotoxic effects of chemotherapy and immunosuppression rendered by the conditioning regimen; the effect of free oxygen radicals; the disruption of normal regulatory mechanisms by GVHD and viral infections, particularly with Epstein-Barr virus, HPV and Human Herpes virus<sup>(2, 3)</sup>.

Along with the increasing number of reports of solid tumors after BMT, risk factors have been established. FA, *per se*, is associated with an increased incidence of solid tumors after BMT<sup>(2)</sup>. Irradiation (either thoracoabdominal or total body) as part of the conditioning regimen, GVHD, treatment of chronic GVHD with azathioprine and treatment of acute GVHD with anti-thymocyte globulin have also been related to increased risk of developing solid organ neoplasms<sup>(2, 3)</sup>. Among these risk factors, our patient developed acute and chronic GVHD, the latter having been treated with azathioprine and the former with CY and corticosteroids.

In summary, FA patients receiving BMT should have a close follow-up. Careful examination should be directed to mucosal membranes, since these patients present increased risk for squamous cell carcinomas. Risk factors must be considered and avoided whenever feasible. Furthermore, patients with FA develop solid organ tumors younger (mean 23 years old) than the population average. This report reinforces these data and highlights the need to consider an even earlier presentation.

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