CASE REPORT
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SQUAMOUS CELL CARCINOMA OF BASE OF TONGUE IN A PATIENT WITH FANCONI’S ANEMIA TREATED WITH RADIATION THERAPY: CASE REPORT AND REVIEW OF LITERATURE

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Abstract: Background. Fanconi’s anemia (FA) is a rare autosomal recessive genetic disorder characterized by congenital anomalies, progressive aplastic anemia, and a predisposition for malignancies. Solid tumors in the head and neck region, especially in the tongue, are rarely observed. Management of these patients is a challenge because of hematological complications and increased toxicities.

Methods. We report a case of Fanconi’s anemia in a 27-year-old man with carcinoma of the base of tongue (T2N0M0) who was treated with radical radiation therapy to a dose of 70 Gy/35 fractions/51 days. We have also done in vitro radiosensitivity tests.

Results. The patient tolerated the radiation treatment well and completed it without any interruptions. In vitro studies did not show any increased radiosensitivity in this patient.

Conclusion. Head and neck cancer in a patient with FA requires individualized treatment. The decision about opting for different modalities should be based on a balanced approach with respect to locoregional control and toxicities of the treatment. © 2009 Wiley Periodicals, Inc. Head Neck 32: 1422–1427, 2010

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Fanconi’s anemia (FA) is a rare autosomal recessive genetic disorder characterized by congenital anomalies, progressive aplastic anemia leading to pancytopenia, and a predisposition for malignancies.1 Congenital anomalies in FA clinically manifest as skeletal, renal, ophthalmological malformations, and chromosomal aberrations. The disease involves multiple organs that include skin, genitourinary, musculoskeletal, renal, and neurological systems. The clinical findings in FA patients are abnormal skin pigmentation like café au lait spots, abnormal male gonads (absent, atrophic, or abnormal...
testis, hypospadias, undescended testis), microcephaly, short stature, hypoplastic thumb with or without radial anomalies, renal defects, and developmental delay, mental retardation, and learning disability.\textsuperscript{2,3} FA is associated with increased risk of malignancies, and the risk further increases with bone marrow transplantation, which is done for treatment of hemopoietic failure associated with the disease.\textsuperscript{4,5}

The cause of development of cancer in FA is thought to be attributable to a defect in maintaining the genome integrity, leading to increased chromosomal instability with defective DNA repair mechanism.\textsuperscript{6–8} Although hematological malignancies are 1 of the most common cancers, solid tumors in the head and neck region, especially in the tongue, are also observed.\textsuperscript{9–11} Management of cancers in the head and neck region in patients with FA is challenging. Surgery, although considered as an optimal treatment, has its limitations as a result of low counts, risk of infection, and wound-healing issues.\textsuperscript{9,12}

Radiation therapy or chemotherapy is associated with increased risk of toxicity in these patients because of defective DNA repair mechanism.\textsuperscript{9,13,14} There have been instances of variable clinical radiosensitivity and fulminant radiation toxicities even with low doses of radiation.\textsuperscript{13–15} Therefore, in vitro sensitivity studies, although not common, have been performed on fibroblast cells or peripheral blood mononuclear cells to predict the in vivo radiation sensitivity.\textsuperscript{15,16} We report a case of a young man with FA who was diagnosed with carcinoma of the base of tongue and was treated with radical radiation therapy. We also report the results of an in vitro test for radiosensitivity in our patient and review the literature for FA patients with head and neck cancer.

**CASE REPORT**

A 27-year-old man was referred to our hospital for evaluation of a base-of-tongue lesion that had appeared 3 months earlier. Oral examination revealed a well-circumscribed, ulceroproliferative lesion on the left side of the base of tongue measuring 2.5 cm in diameter. Neck examination showed no cervical lymphadenopathy. On general physical examination, he was physically retarded (short stature, microcephaly, and microophthalmia) with atrophic testis and a few café au lait spots on skin, particularly of the lower extremities.

MRI showed a well-localized soft tissue mass on the base of tongue (left > right), with no significant cervical lymphadenopathy (Figures 1A and 1B). The histopathology review showed squamous cell carcinoma. Therefore, a diagnosis of carcinoma of the base of tongue, T2N0M0 (stage II), was made. The complete blood count, showed features of generalized pancytopenia (total leukocyte count, $1.8 \times 10^9$/L; hemoglobin, 7.1 gm/dL; and platelets, $17 \times 10^9$). Complete blood count was repeated but pancytopenia persisted. The patient underwent a bone marrow aspiration and biopsy, which revealed hypocellular marrow. In view of his abnormal morphological features and unexplained hypocellular marrow, the patient was advised for chromosomal studies. Subsequently, chromosomal breakage analysis was done in peripheral blood lymphocytes in the presence of DNA crosslinking agents, diepoxybutane (DEB) and mitomycin C (MMC), which revealed a high frequency of chromosomal breakage (6.2

![Figure 1](image_url)
chromosome breaks per metaphase) compared with control (1.3 breaks per metaphase). Increased frequency of radial formation was also observed in this patient compared with controls (Figure 2). Bone marrow chromosomal analysis further revealed chromosomal aberrations. Finally, diagnosis of FA was made on the basis of clinical features, hematological picture, and chromosomal breakage analysis.

Hematological parameters precluded surgical interventions and chemotherapy. It was therefore decided to treat him with radical external beam radiation therapy. Radiation to the face and regional lymph nodes was started with conventional fractionation of 200 cGy/day once daily and 5 days/week schedule using bilateral parallel opposed portals. In week 4 of radiation, a nasogastric tube was inserted to improve the nutritional support. The patient was admitted after completion of 54 Gy, given that his total leukocyte count was $2.1 \times 10^9$/L and he developed fever. Broad-spectrum injectable antibiotics were started, along with granulocyte colony stimulating factor. He successfully completed the treatment to a total dose of 70 Gy/35 fractions over 51 days with reducing portals respecting the tolerances of critical structures. The treatment was completed without any interruptions. At the conclusion of treatment, he had Radiation Therapy Oncology Group (RTOG) grade 3 toxicity of skin and mucosa. His count was consistently low, for which he was kept on intensive supportive care. Admission was required because of systemic effects, and not because of radiation reaction. He was eventually discharged from the hospital after 4 weeks, when his fever had subsided but pancytopenia persisted.

In vitro study was done to determine the radiosensitivity by radiating peripheral blood mononuclear cells (PBMCs) isolated from blood to increasing doses of radiation. The rate of apoptosis in this patient was compared with a matched control. At each radiation dose as well as in the unirradiated sample, FA had more live cells than that of control. Spontaneous rate of apoptosis (ie, apoptosis at 0 Gy) was found to be less in this case of FA. The percentage of early apoptotic cells increased from 9% to 30% in the case of an FA patient with an increase in radiation dose from 0 Gy to 25 Gy compared with control, in which it increased from 14% to 48%. The percentage of late apoptotic cells was also found to be low in the case of the FA patient, which increased from 2% to only 5%, which in the case of control reached 14%. This experiment suggested that radiation-induced apoptosis was less in our patient. We also studied the
percentage of necrotic cells and observed that the percentage of necrotic cells was greater in the case of the FA patient compared with control. Necrotic cells increased from 1.5% to 12% in the case of the FA patient, compared with control, in which they remained <2% at each radiation dose, suggestive of cell death attributed to the necrotic inflammatory pathway in the FA patient, making them more radiosensitive.

The patient was followed up at 6 weeks post-radiation therapy, when he was evaluated for local control and toxicities. The radiation reactions of skin and mucosa had settled and there was no clinical evidence of disease. A follow-up evaluation at 3 months postradiation therapy revealed similar findings. An MRI scan showed evidence of level IV lymph node. This lymph node was not present in the preradiation therapy scan. Fine-needle aspiration cytology from this node showed the presence of squamous carcinoma. Opinion was taken for surgical salvage but was not considered because of fixation to surrounding structures, low counts, and the risk associated with surgery because of his FA. He was therefore considered for palliative reirradiation with electrons, which he completed with good symptom relief. He was alive with disease at his last follow-up, which was 14 months after his initial diagnosis.

**DISCUSSION**

FA is an autosomal recessive disorder associated with bone marrow suppression, congenital anomalies, and high risk of malignancies. It has been hypothesized that the malignancies occur either because of chromosomal instability or because of immunodeficiencies. Although the association of FA with malignancies was described in 1927, cancer of the head and neck region was reported in 1966 by Eparza and Thompson. Hematological malignancies are the most common malignancies seen in patients with FA, followed by solid tumors, especially head and neck cancers. In a large study of 1300 patients with FA, the incidence of solid tumors was around 5%. In a review of 754 patients from the International Fanconi’s Anemia Registry, 3% patients had head and neck cancer. This incidence was significantly higher compared with that of the normal population. Although the data on ethnic origin of these patients are not very clear, there is a scarcity of data from Asian countries. This is thus 1 of the important case reports in an Indian male patient.

The median age of onset of tumors in patients with FA is as early as 16 to 31 years in different series. In our patient, the age of onset was at 27 years, which was much earlier compared with the median age of 56 years in our population for head and neck cancer. In our patient, the diagnosis of malignancy was made before that of FA. His routine investigations showed pancytopenia, which led to further investigations, such as bone marrow biopsy and chromosomal studies, which eventually confirmed the diagnosis of FA. Surgery has been considered as the primary modality of treatment in many patients with FA. Of the 19 patients with head and neck cancer in the International FA Registry, 17 have undergone primary surgery. Surgery in these patients was well tolerated. It has been suggested that surgery should be encouraged in these patients, to prevent the issues associated with chemotherapy and irradiation.

Chemotherapy—associated with very high morbidity attributed to DNA damage and impaired repair mechanism—was thus not considered in our patient. In addition, this patient had stage II low-volume disease; therefore single-modality treatment in the form of radiation therapy was considered. Use of alkylating agents that crosslink DNA can have serious adverse effects in these patients. Furthermore, chemotherapy is also known to cause a deleterious effect of myelosuppression in patients with baseline bone marrow suppression.

There have been varying reports of tolerance to radiation therapy in cancer patients with FA and there appears to be increased radiosensitivity in these patients. This could possibly be ascribed to an increase in chromosomal breakage and impaired cell repair mechanisms. In 1 of the reported cases, the radiation mucositis was observed as early as 3.2 Gy, whereas in another patient radiation was delivered without much toxicity. Marcou et al reported a patient with tonsillar cancer who developed unusually brisk reactions after 24 Gy. Varying doses of radiation have been documented in the literature, ranging from 3.2 Gy to 80 Gy. Overall, radiation has been associated with increased normal tissue toxicity, delayed healing, and increased supportive care.
FA along with ataxia telangiectasia, Bloom's syndrome, and xeroderma pigmentosum are called cancer breakage syndromes because they are associated with chromosomal instability and defective repair, thereby predisposing to development of cancers.15 Cells from FA show variable levels of cellular radiosensitivity, and results of an in vitro experimental study done for predicting the hypersensitive response may not coincide with in vivo radiosensitivity results.8,9 Various experimental techniques including alkaline single-cell gel electrophoresis (Comet assay), colony-forming test, Western blot, and foci immunofluorescence analysis of the expression of DNA repair proteins, and also the cytochalasin-blocked micronuclei (MN) test using FA fibroblasts have been adopted to correlate the in vitro radiation sensitivity with the outcome of therapy.10,11 However, the limitation of these techniques is the 4-week delay required for colony growth.12–14 Comet assay is widely regarded as a robust and informative method for radiosensitivity measurements immediately after DNA damage,15,16 but it is only a qualitative assessment of the response. Western blot and foci immunofluorescence analysis give qualitative results, but are labor intensive and also lack correlation between in vitro results and in vivo radiation response.17 In view of the conflicting data on radiosensitivity of FA cells, and particularly FA fibroblasts, there is a pressing need for the development of new rapid and predictive assays of radiation responses. We have performed our study on PBMCs isolated from blood. Compared with most of the previous studies using fibroblasts, collecting blood has an advantage over invasive procedures of obtaining fibroblasts from patients' skin biopsies, avoids time-consuming methods of generating monolayer cultures, and is also less labor intensive.

Clinical radiosensitivity in unpredictable in patients of FA with cancer, especially of the head and neck region, and outcome varies.18 Of the 19 patients in the International FA Registry who had head and neck cancer, 14 died because of disease. The median time to recurrence in their patients was 16 months and the median follow-up of surviving patients was 19 months.9 Kennedy and Hart10 noted multiple primary malignancies either synchronous or metachronous in patients with FA to the extent of 36% (5 of 14 patients). Our patient developed a lymph node at level IV at 3 months follow-up and was alive with disease at 14 months.

There are no standard guidelines for management of FA patients with malignancies. This is primarily a result of the scarcity of data and heterogeneous population.13 It has therefore been recommended that more data in the form of case reports should be encouraged.15 Until then, the treatment of patients with malignancies with FA should be individualized. Any decision about opting for different modalities should be based on a balanced approach with respect to locoregional control and toxicities of the treatment.

REFERENCES