

Oral squamous cell carcinoma in patients with Fanconi anemia: A case series

S. Goncalves, Montgomery-Cranny J., Hunter K.D., A. Yousefpour, L. Durham, A.M. Hegarty

ABSTRACT

Introduction: Fanconi anemia (FA) is a rare inherited disorder characterized by progressive bone marrow failure, congenital malformations and increased susceptibility to malignancies particularly acute myeloid leukemia and solid tumors such as head and neck, gastrointestinal and genitourinary tract carcinomas. The squamous cell carcinoma of the head and neck (HNSCC), known for its aggressive growth capacity, multifocal origin and propensity to metastasize is the most frequent solid tumor in these patients and is frequently associated with poor prognosis. An increased understanding of Fanconi anemia associated with malignancies is important in the clinical management of these patients and can elucidate the role of the disease in the development of malignant tumors namely head and neck squamous cell carcinoma. Case

Series: We describe three unrelated cases of patients with FA and multifocal head and neck squamous cell carcinomas. **Conclusion:** This study highlights the susceptibility of patients with Fanconi anemia to malignant tumor development and reinforces the need for a routine head and neck cancer screening. The reader should understand the clinical features, implications of this association and the appropriate management of patients with Fanconi anemia.

Keywords: Anaemia, Carcinoma, Fanconi, Squamous

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INTRODUCTION

First described by Guido Fanconi in 1927, Fanconi anemia is a rare disease with an incidence of approximately 1 in 360,000 individuals and prevalence estimated at 10 cases per 1 million individuals [1, 2]. The disease occurs at a higher rate in populations of Ashkenazi Jews and South Africa [3, 4].

Fanconi anemia (FA) is an autosomal recessive bone marrow failure syndrome (IBMFS) characterized by high cancer-predisposition [5]. The disease is caused by mutations to one of 17 FANC genes (FANCA to FANCS) whose protein products play key roles in the DNA repair pathway. The increased susceptibility to cancer is a consequence of the genomic instability due to defective DNA repair mechanisms and the severity of the disease is determined by the type of genetic mutation [6].

Clinically, Fanconi anemia is characterized by congenital malformations, progressive bone marrow failure and development of malignancies [7]. Congenital abnormalities include skin pigmentation like café au lait spots, skeletal, genitourinary and gastrointestinal abnormalities. The disease can also be recognized based on the presence of hematological changes such as aplastic anemia, pancytopenia, single lineage cytopenias and acute myeloid leukemia [8]. The diagnosis is made commonly towards the end of their first decade of life, or established earlier in presence of family history or characteristic congenital and developmental abnormalities [9]. In the diagnostic evaluation, there are several useful investigations which include peripheral blood tests, genetic subtype analysis, skin biopsy, bone marrow examination and imaging. The median life expectancy of patients with FA is around 20 years [1].

Patients with Fanconi anemia are at increased risk of developing malignancies including acute myeloid leukemia and solid tumors such as head and neck, esophageal, gastrointestinal and genitourinary cancers [7]. The oral cavity is the most frequent site of HNSCC in patients with Fanconi anemia. The disease affects particularly the tongue and gingivae [10].

Patients with FA and HNSCC tend to have a poor prognosis as a consequence of the aggressive disease presentation as well as the limitations of multimodality therapy due to the underlying bone marrow failure [1]. The long-term survival is also limited by the high risk of developing multiple malignancies during their lifetime [2].

CASE SERIES

Case 1

A 32-year-old male with a history of type II diabetes and chronic graft versus host disease subsequent to sibling allogeneic stem cell transplant for Fanconi anemia presented at the ENT service at the Hallamshire Hospital in Sheffield at the age of 18 with a static lymph node on the right side of the neck (Figure 1). An ultrasound guided core biopsy proved to be squamous cell carcinoma (SCC).

Two months later, a suspicious lesion was noted in the buccal sulcus of the right maxilla whose histopathological examination revealed a poorly differentiated SCC which would be in keeping with the PET/CT findings suggestive of an area of activity on the right maxilla. The patient underwent a right modified radical neck dissection,



Figure 1: (A, B) Clinical appearance of the gingival lesions, (C, D) The later the tongue and lip lesions lesion, and (E) The clinical appearance after the right modified radical neck dissection, showing poor healing (Case 1).

partial maxillectomy and adjuvant radiotherapy post-operatively. Histological analysis showed a widely infiltrative moderate to poorly differentiated SCC with a non-cohesive invasive pattern. The tumor did not express p16, and thus was judged not to be infected with HPV. The defect was not surgically reconstructed due to the possibility of recurrence of disease. A nasogastric feeding tube was inserted and an obturator prosthesis constructed. The patient was under the care of the Speech & Language Team for the management of the dysphagia and speech difficulties. The patient was kept under close follow-up which allowed the detection of recurrence of SCC in a right level Ib lymph node. The management included right neck dissection.

Two years later a new well differentiated SCC was surgically removed from the lower lip. Further biopsy of the area revealed a new moderate to poorly differentiated SCC which motivated a second surgical intervention with wide local excision. A new lesion on the floor of the mouth was detected at that point whose histopathological result showed a moderately differentiated SCC. The patient underwent two marginal mandibulectomies due to positive margins. The patient died four months later of multifocal disease.

Case 2

A 25-year-old white British female, with history of asthma, primary biliary cirrhosis and Fanconi anemia diagnosed at the age of four was referred by her hematologist to the head and neck oncology clinic at the Royal Hallamshire Hospital, for ongoing oropharyngeal screening, on a semiannual basis, as per published United Kingdom Fanconi Standards of Care. A year later, incisional biopsies were performed from an erosive area on the left buccal mucosa and left lateral border of the tongue which revealed severe epithelial dysplasia. The management consisted of laser ablation.

Seven months later, the patient complained of soreness of the upper left quadrant where an erythematous area was present on the upper left gingivae with overlying irregular mucosa (Figure 2). The biopsy revealed moderate epithelial dysplasia.

Eight months later, generalized fragility of the gingivae with associated contact bleeding was reported and it was noted a variable pattern of ulceration and inflammatory changes on the lips and enlargement on the left lateral border of the tongue. Urgent incisional biopsies revealed moderate to poorly-differentiated squamous cell carcinoma of the tongue (T3 N2b) and upper lip (T1) and early invasive moderately-differentiated squamous cell carcinoma of the anterior maxillary gingivae (T1). None of the tumors expressed p16. The patient underwent left selective neck dissection, left partial glossectomy, resection of the left upper lip and anterior maxillary gingiva and reconstruction with radical free forearm flap. Since then undertook prosthetic rehabilitation and has remained under close clinical follow-up, with no recurrence to date.

Case 3

A 37-year-old Spanish female presented to the Oral Medicine Department at the Charles Clifford Dental Hospital having been urgently referred by her General Dental Practitioner regarding a fixed erythematous lesion with ulceration on the left lateral border of the tongue and associated difficulties eating (Figure 3). The patient had previously been under the care of the Maxillofacial surgery team for annual oral cancer screening given her diagnosis of Fanconi anaemia but she had defaulted from review for the previous two years.

Clinical examination revealed a palpable lymph node in the left submandibular region of 1 cm diameter clinically, which was mobile. Intraorally, there was a raised, thickened erythematous patch to the left ventrolateral tongue and some superficial ulceration.

An urgent incisional biopsy was performed and confirmed features of a poorly differentiated squamous cell carcinoma, extending through the full thickness of the biopsy. The tumor was p16 negative.

An MRI scan showed a 1.9 cm area of abnormal enhancement of the left side of the tongue extending up to the midline of the tongue tip. No invasion into the adjacent mandible and no enlarged lymph nodes in the neck were noted. The tumour was staged as T2a N0. The patient underwent a partial glossectomy with left neck dissection and a left radial forearm free flap for reconstruction. The histopathological analysis revealed down-graded the tumor to a moderately well differentiated squamous cell carcinoma with no evidence of metastasis to the neck nodes. A full body PET scan showed no convincing evidence of local recurrence nor metastatic disease three months later.



Figure 2: Clinical appearance of (A) Gingival, (B) Tongue, and (C) Labial mucosa lesions (Case 2).



Figure 3: Clinical appearance of the lesion on the ventral surface of the tongue (Case 3).

DISCUSSION

The pathogenesis of cancer risk in patients with bone marrow failure syndromes such as Fanconi anemia is still not fully understood. The disease is characterized by genomic instability and consequently increased risk of development of solid tumors in early ages.

The most frequent solid tumor is the squamous cell carcinoma of the head and neck which is known for its aggressive growth capacity, multifocal involvement and propensity to metastasize [1]. The probability of development of HNSCC in patients with FA is 14% in contrast to 0.038% in the general population [3]. Tobacco smoking and alcohol consumption, which are known carcinogens associated with head and neck cancer in the general population, do not seem to play a significant role in the pathogenesis of Fanconi anemia [11].

Some preclinical studies have suggested an association between Fanconi anemia and HPV-associated cancers. Studies of Fanconi anemia SCCs, mainly from United States studies, revealed the presence of high-risk human papillomavirus (HPV) DNA in 84% of tumors analyzed in contrast with other studies where HPV DNA was detected only in 10% of tumors, none of them HNSCCs [12]. The interaction between HPV infection and cancer risk in these patients is not yet fully understood [11].

Patients with Fanconi anemia have a 500 times greater incidence of developing head and neck cancer than the general population and younger age of onset [13]. Although these tumors are histopathologically similar to those without Fanconi anemia, the frequency, distribution and clinical course are different.

The management of HNSCC in patients with Fanconi anemia requires early aggressive treatment and a multidisciplinary approach. Although there are potentially increased perioperative risks, surgery is the primary therapeutic option for most patients considering the poor tolerance to standard therapies such as chemo- and radiotherapy. Chemotherapy, especially with DNA cross-linking agents such as cisplatin, can be poorly tolerated due to the defective DNA repair which increases the sensitivity and toxicity. There is also an increased risk of radiosensitivity and therefore, toxicity with radiotherapy [8].

For the treatment of hematological disorders, patients often require hematopoietic stem cell transplantation. The prolonged exposition to immunosuppressive treatment after transplantation also potentiates the risk of development of cancer [7].

These three cases highlight the susceptibility of young patients with FA background to head and neck malignant tumor development in the absence of the typical risk factors. The first case report demonstrated the increased incidence of malignancies in patients with chronic graft versus host disease after bone marrow transplantation. Compared to non-transplanted FA patients, history of GVHD increases the risk of HNSCC [1]. In transplanted patients, the onset of the disease also occurs approximately 10 years earlier [13]. Despite regular follow-up, it was not possible to stop the tumor progression which made any curative therapeutic intervention impossible.

Clinicians involved in the care of patients with FA must be aware of the malignant potential of this disease. A systematic follow-up of patients with FA is essential for early therapeutic intervention, which may improve the survival rate and reduce the need for more aggressive therapeutic approaches.

CONCLUSION

Fanconi anemia is a complex heterogenic and cancer prone disorder of genomic instability. The three cases reported enhance the higher incidence of aggressive HNSCC in these patients which occurs at young age in the absence of the common risk factors. The management of head and neck cancer in the setting of Fanconi anemia is complicated by the hematological changes, poor tolerance to chemotherapy and potentially increased radiosensitivity. The overall prognosis is poor with many patients dying from complications of treatment, early disease progression or second primaries. An increased understanding of Fanconi anemia associated malignancies is important in the clinical management of these patients but also to elucidate the role of chromosomal instability in the development of SCC in general. The high incidence of HNSCC in these patients emphasizes the importance of regular screenings and rigorous surveillance measures.

Author Contributions

S. Goncalves – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Montgomery-Cranny J. – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Hunter K.D. – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

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L. Durham – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

A.M. Hegarty – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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