Fanconi anaemia and oral squamous cell carcinoma: management considerations

Thasvir Singh, Kavin Andi

ABSTRACT

Fanconi anaemia (FA) is a rare multi-system genetic disorder where patients are susceptible to the development of oral malignancies. Clinicians involved in their management should be vigilant in detecting lesions early, and an individualised treatment plan should then be formulated. Although surgery forms the mainstay of oncological treatment, adjuvant therapy can be instituted with care. Unfortunately, prognosis is poor, and close long-term follow-up is required. This short report describes pertinent management considerations in relation to a case of oral squamous cell carcinoma.

Fanconi anaemia (FA) is a rare hereditary genetic disorder with an incidence of approximately 1–5 per million births, although it is more common among Ashkenazi Jews and black South Africans.[1] It has an autosomal recessive inheritance pattern, and multiple genes (*FANC*) are involved in its pathogenesis.[2] FA is characterised by a range of clinical, haematological and endocrinological abnormalities, with a higher rate of malignancy compared to the general population. We present a case of a patient with FA who developed a squamous cell carcinoma (SCC) of the tongue, along with a discussion of pertinent management considerations relevant to the head and neck clinician.

Case

A 39 year-old female was referred in 2014 regarding a non-healing tongue ulcer (Figure 1). The patient had been diagnosed with FA at the age of six and had undergone a bone marrow transplant at the age of 17, and in 2012 she was treated for a pT2 (13mm) invasive ductal carcinoma of the left breast. At the time of presentation to the head and neck clinic, the left sided tongue lesion had been present for approximately 3–4 months and caused pain with eating, but was otherwise asymptomatic. She experienced no weight loss, otalgia or dysphagia, and upon examination no neck masses were palpable. The 1.5cm ulcer was centred on

Figure 1: Clinical photo of left sided tongue squamous cell carcinoma prior to surgical resection.

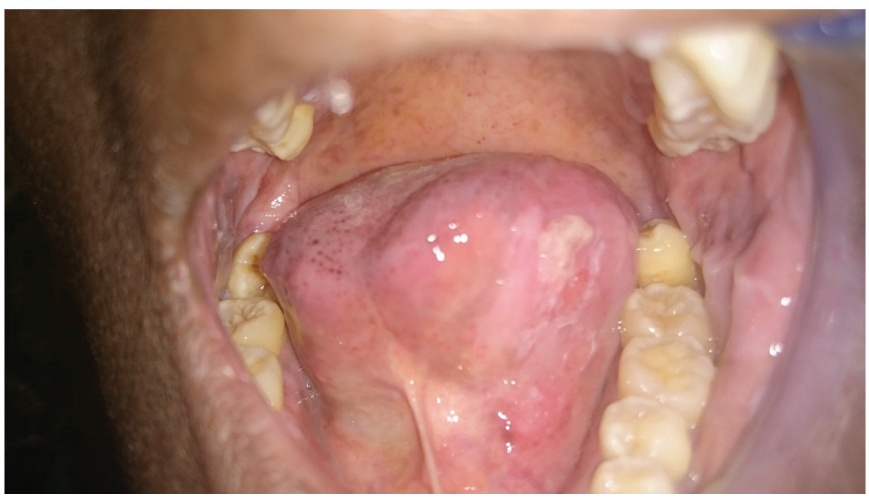
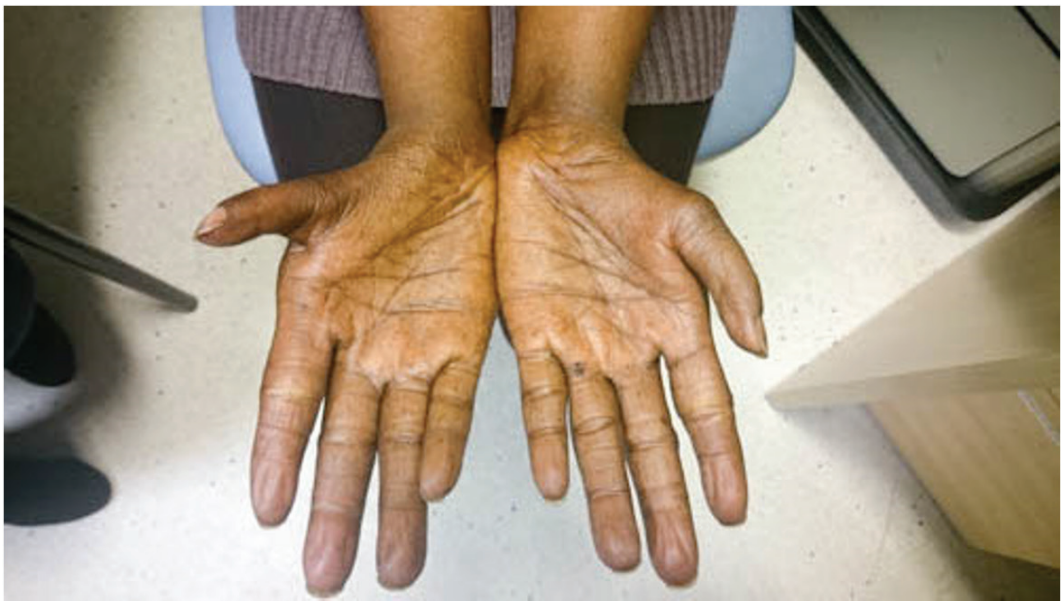


Figure 2: Clinical photo of bilateral thenar-hypoplasia, a feature often found with FA.



the ventral aspect of the tongue's lateral border with underlying induration and pain on palpation. She was short in stature and had bilateral thenar-hypoplasia (Figure 2), however no other physical features of FA were found on clinical examination. An incisional biopsy of the oral lesion revealed a well differentiated, keratinising SCC arising from dysplastic surface epithelium, with invasion into the underlying stroma.

Staging investigations did not reveal any metastatic spread to the neck or chest (cT1N0M0 SCC), and following multi-disciplinary team discussion she was planned for a left partial glossectomy and selective neck dissection (I–IV). Pre-operative work-up and consultation with her haematologist did not reveal any signs of bone marrow dysfunction, and an anaesthetic team review cleared her for a general anaesthetic procedure. Surgery progressed uneventfully and the patient was discharged from hospital two weeks post-operatively. Her final staging was confirmed as pT1N1M0 with no adverse features seen on histopathological examination. She is currently being followed up on a regular basis, and there are no signs of loco-regional recurrence after three years of follow-up.

Discussion

FA is the result of a genetic defect in a cluster of proteins responsible for DNA repair, with 16 distinct *FANC* genes reported in the literature.[1,2] Genetic testing can be complicated due to the number of associated mutated genes, and large deletions, duplications or sequence variations are frequently found.[3] Genetic counselling should be carried out for those families affected by, or are carriers of, FA as the implications of these genetic changes are important. Despite many FA patients developing a malignancy, their pathogenesis is not well understood. Kaplan et al suggested that there are two major defects that play a role in the development of malignancies in patients with FA: defective chromosomal stability and immunodeficiencies.[4] This not only results in FA patients developing cancer at a relatively young age compared to the general population (median age of 31 vs 45 years old), but their risk compounds as they become older.[5,6,7] The human papilloma virus (HPV) is now a well-known aetiological factor in the pathogenesis of oropharyngeal squamous cell carcinoma, and there is a growing body of evidence to show that FA patients have a higher rate of oral HPV than control subjects,[8,9] thus further increasing their risk of developing head and neck SCC (HNSCC). Vaccinating all FA individuals against HPV has been suggested in the UK standards of care guidelines.[10]

In a literature review of 1,300 patients diagnosed with FA between 1927 and 2001, 9% developed leukaemia (primarily acute myeloid leukaemia), 5% developed solid

tumours and 3% had liver tumours.[11] Of the solid tumours, more than 40% occurred in the aerodigestive tract, including SCC of the oral, pharyngeal and oesophageal regions. Kutler et al showed that in 754 patients with FA, 3% developed HNSCC, resulting in an approximate 500 times higher risk compared to the general population.[6] Of these patients, 68% developed cancer of the oral cavity with the most common subsite being the tongue.

Pancytopenia and bone marrow impairment is a common feature in patients with FA, and initial management is supportive through transfusions, growth factors and hormonal replacement therapy. Bone marrow transplant is often required for those with features of severe bone marrow failure,[7] however there is an increased risk of developing HNSCC following haematopoietic stem cell transplantation.[10] Congenital defects are seen in 60–75% of FA patients, including short stature, abnormalities of the skin, arms, head, eyes, kidneys and ears, along with developmental disabilities. Furthermore, approximately 75% of FA patients also have endocrinological abnormalities with varying degrees of severity.[12]

Due to this wide and complex range of clinical features, individualised management plans will have to be formulated when a patient requires treatment for their head and neck malignancy. Congenital defects (especially in the upper limb) and short stature may alter anatomy during resective and reconstructive procedures, and additional pre-operative investigations (eg, skeletal imaging prior to osseocutaneous free-flap planning) and multi-disciplinary consultations (eg, endocrine and haematology units) may be required to ensure an appropriate treatment plan is formulated. In particular, bone marrow dysfunction can lead to an elevated risk of haemorrhage and infection with potentially life-threatening consequences.[2]

Like most oral cavity malignancies, surgical management is the mainstay of primary treatment. In a review of 19 patients with FA and head and neck cancer, the majority (89%) underwent primary surgical resection, with approximately one-third of these patients successfully undergoing reconstructive procedures.[6] A low threshold for elective neck dissection should be considered in those with early oral cavity SCC due to an overall higher risk of oncogenesis. Defective cellular processes (such as altered DNA repair mechanisms) may increase the sensitivity and complication rates associated with conventional cytotoxic chemotherapy and radiotherapy treatment regimes. Early treatment-related complications can be more frequent, and more severe, including cytopenias, skin ulceration, infections and mucositis.[2,6] Alternative treatments, including biological therapeutics, have been recently used in the literature, which may reduce the issues surrounding the use of non-surgical therapies in this patient cohort.[2]

Prognosis following the treatment of head and neck malignancy in FA is generally poor,[7] however definitive figures are not possible given the small patient numbers. Reasons are multi-factorial, including more advanced disease at presentation,[6] a reduced tolerance and effectiveness of radiotherapy and chemotherapy, and the possibility of further tumours development. In the largest published series, 63% of patients developed multiple malignancies with some developing more than two.[13] As suggested in a review by Schethenbach et al,[14] improved collaboration between international FA units and clinics is now needed to allow the exchange of medical and genetic information. This will help form a unified treatment approach for all FA patients, in particular for those affected by HNSCC.

In conclusion, FA is a rare genetic disorder that has a range of clinical features and potential management difficulties. Patients should be have regular screening for HNSCC with a low threshold for biopsing suspicious lesions. The treatment of oral SCC in FA should conducted in a multi-disciplinary setting to ensure a safe and effective treatment plan is completed. Surgery should be the primary method of management where possible, and adjuvant therapy should be approached cautiously. Close post-operative follow-up is required due to the life-long risk of recurrent disease and multiple malignancies.

Competing interests:
Nil.

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