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Vulvar carcinoma in Fanconi Anaemia: A case report with review of literature

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ABSTRACT

Fanconi anaemia is a rare autosomal recessive disorder associated with bone marrow failure and congenital malformations. The impaired DNA repair pathways in Fanconi anaemia predispose patients to a high risk of cancers of squamous cell origin, particularly in the head and neck region. Cancers of the vagina and vulva are rare in Fanconi anaemia. Here, we report a case of a 44-year-old female with Fanconi anaemia who developed an ulcerated lesion on the clitoris that extended into the labia majora. A biopsy of the lesion showed well-differentiated squamous cell carcinoma. The patient was treated with wide local excision of the vulval lesion. The patient developed neutropenia post-procedure but recovered in one week time. We have followed up the patient regularly since the procedure. No further issues have been detected to date.

1. Introduction

Fanconi anaemia is a rare autosomal recessive disorder characterised by severe bone marrow failure and congenital abnormalities (Green and Kupfer, 2009; Tischkowitz and Hodgson., 2003). First described by Guido Fanconi in 1927, this disease has a global incidence of 1 in 360,000 live births (Mamrak et al., 2017; Rosenberg et al., 2011). Haematological abnormalities manifest as severe pancytopenia during the first decade of life (Tischkowitz and Hodgson, 2003). The most frequent congenital malformations are short stature, absent or hypoplastic thumbs, radial ray anomaly (hypoplasia or complete absence of radius), altered skin pigmentation (café au lait spots), microphthalmia, renal disorders, and genitourinary tract abnormalities (Green and Kupfer, 2009; Tischkowitz and Hodgson., 2003). Currently, 23 genes involved in DNA repair are identified in Fanconi anaemia pathogenesis. The impaired DNA repair pathways predispose Fanconi anaemia patients to a high risk of cancer. Fanconi anaemia patients are 50 times more likely than the general population to develop squamous cell carcinomas of the head and neck, genitourinary and gastrointestinal tract and 700 times more likely to develop acute myelogenous leukaemia later in life (Nepal et al., 2017). Here, we report a 44-year-old lady with Fanconi anaemia who developed vulvar carcinoma of squamous cell origin.

2. Case presentation

This case describes a 44-year-old nulligravida with Fanconi anaemia and type 2 diabetes mellitus who presented with complaints of itching in the vagina and swelling in the vulvar region. The patient attained menarche at the age of 10, followed by amenorrhoea. She was diagnosed with Fanconi anaemia at the age of 10 years. An initial hemogram showed the following. Haemoglobin: 11.4 g/dL, total white blood cell count: 1630 cells/mm^3, absolute neutrophil count: 467 cells/mm^3, platelets: 45,900 cells/mm^3).

The patient was on frequent blood transfusions. An ultrasound of her abdomen showed bilateral small kidneys. Bone marrow studies showed hypocellular marrow with trilineage maturation. Bone marrow karyotyping was normal. Increased chromosome breakage after exposure to mitomycin C was also observed. She was started on stanozolol (10 mg twice daily) and folic acid. Her complete blood counts improved and became transfusion-independent. She was followed up regularly thereafter.

Physical examination revealed that the patient had a short stature (125 cm), café au lait spots, and short 4 metatarsals on both limbs. Patient had a performance status of ECOG 1. As per sexual maturity rating (SMR), patient's breasts were Tanner stage 2. No supraclavicular lymph nodes were palpable. One sub centimetric lymph node was present in the

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left groin. Clitoromegaly was observed. A 1.5 × 1.5 cm erythematous lesion was detected on top of the labia majora. The lesion had a speckled white and velvety pattern with a 2-mm induration into the underlying mucosa. The lesion also extended onto the clitoral hood and base. A similar 5 × 5 mm lesion was observed near the posterior fourchette, on the lower third of the right labia majora.

Punch biopsy from lesion over vulva showed well-differentiated squamous cell carcinoma keratinising type (Fig. 1). A whole-body PET CT showed abnormal focal FDG uptake in the enhancing lesion in the labial fold on the left side (SUV max 3.6, delayed 3.5) (Fig. 2). There was no evidence of metastasis. Laboratory workup showed a normal blood picture.

After the evaluation, it was decided to proceed with wide local excision of the vulval lesion with bilateral lymphoscintigraphy and bilateral sentinel lymph node biopsy. Peroperatively, there was a 2 × 1.5 cm ulcerated lesion on the clitoris that extended into the left labia majora. There were no enlarged inguinal lymph nodes. A histopathology evaluation of the lymph nodes showed no evidence of lymph node involvement. As per AJCC 8th Edition, the cancer was staged as pT1bN0. The patient's surgery was completed uneventfully on 15th December 2020. After the procedure, the patient developed neutropenia and was managed with filgrastim and antibiotics. The patient's neutropenia resolved and she was discharged. Tests for human papillomavirus (HPV) by real time polymerase chain reaction (RTPCR) in the tumour tissue was negative. An ultrasound of bilateral inguinal lymph nodes 4 months after surgery (27th April 2021) showed no lymph node enlargement. 5 months post-surgery a vulval scrape smear was done (19th May 2021) which was negative for intraepithelial malignancy. Her last follow-up visit was on 12th June 2021 (6 months after surgery) and she was doing well.

3. Discussion

At the time of Fanconi anaemia's discovery, patients succumbed to haematological complications at a young age, well before the onset of any malignancies. Prior to 1960, the average life expectancy of a Fanconi anaemia patient was 10 years. However, advances in modern medicine have improved the life expectancy of these patients to well over 40 years.

The association between Fanconi anaemia and malignancies was reported in an epidemiological study conducted by Rosenberg et al. They observed a statistically significant increase in cancer risk among

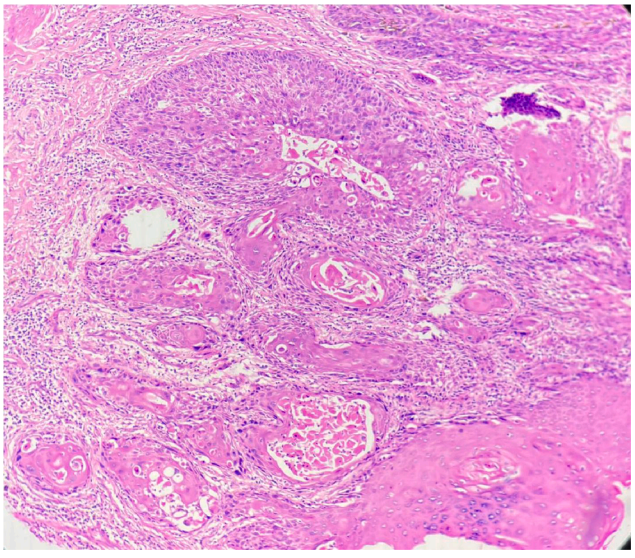

Fig. 1. Figure showing stratified squamous epithelium with a neoplasm arising from it composed of nests of cells with keratin pearl formation (H and E x40).

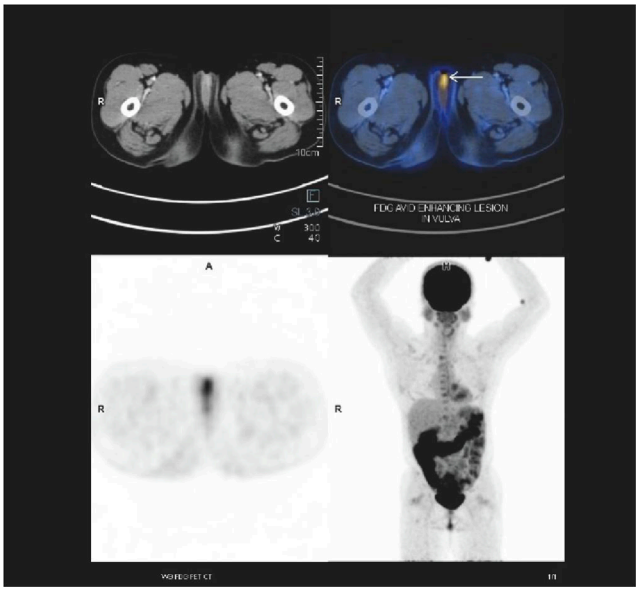

Fig. 2. Whole-body PET CT showing abnormal focal FDG uptake in the enhancing lesion in the labial fold on the left side (SUV max 3.6, delayed 3.5).

Fanconi anaemia patients (Observed to expected ratio 50 for all cancers, 48 for solid tumours and 785 for leukemia) (Rosenberg et al., 2003). Ageing increases the risk of malignancies in patients with Fanconi anaemia. These patients are at high risk of developing cancers of squamous cell origin due to defective DNA repair pathways. The risk of solid tumours increases from 1%/year by age 17 years to 4%/year by age 30 and approximately 8%/year by age 40 (Rosenberg et al., 2003). One in three Fanconi anaemia patients could develop a solid tumour by the age of 40 years (Rosenberg et al., 2003). Alter et al. found that there was a higher risk of solid tumours developing in female Fanconi anaemia patients compared to males at a ratio of 3:1, even after excluding gynaecological malignancies, but the same was not observed by Rosenberg et al. (Alter, 1996; Rosenberg et al., 2003). In both of these reviews, the majority of cancers were squamous cell carcinomas of the head and neck, gastrointestinal tract, and the female reproductive system. Hepatic malignancies are also seen, which could be attributed to androgen use (Alter, 1996; Rosenberg et al., 2003).

Observed gynaecological malignancies were cancers of the breast, cervix and vulva. The cancers of the lower reproductive tract are rare. The literature regarding cancers of the vagina and lower reproductive tract in Fanconi anaemia is limited to case reports (Arnold et al., 1980; Carvalho et al., 2002; Dinh et al., 1988; Han et al., 2009; Harper et al., 2004; Kennedy and Hart, 1982; Mousavi et al., 2010; Ortonne et al., 1981; Quiñonero et al., 2020; Roginsky et al., 2004; Swift et al., 1971; Wilkinson et al., 1984).

In our literature search, we were able to identify 13 case reports pertaining to the occurrence of vulvar cancer in Fanconi anaemia patients (Table 1). The majority of these cases describe the onset of cancer in the second and third decades of life. Impaired DNA damage responses make Fanconi anaemia patients highly sensitive to the toxic effects of both radiation and chemotherapy.

This is evident from previous reports on vaginal cancer in Fanconi anaemia patients. In a case described by Dias et al. (2012), a patient with FIGO stage II vaginal squamous cell carcinoma was treated with high dose brachytherapy (Dias Jr et al., 2012). The patient developed haemorrhagic proctitis, a bacterial/fungal infection and sepsis, which lead to death (Dias Jr et al., 2012). Mousavi et al. (2010) treated their patient with external beam radiotherapy. The patient developed moderate skin reactions in the vaginal folds and vulvar area, with no fatality (Mousavi et al., 2010).

In the case reported by Wilkinson et al. (1984), the patient developed

Table 1
Comparison of case reports on vulvar carcinoma in Fanconi anaemia based on age at diagnosis of vulval malignancy, histology of treatment, HPV status and outcome of treatment.

SL NO	Author	Age at diagonsis of vulval malignancy	Histology	HPV Status	Treatment	Outcome
1	Quiñonero et. al. (2020)	20 years	moderate-well differentiated invasive squamous cell carcinoma	HPV 16 +	surgery adjuvant radiotherapy	dead
2	Dias et al. (2012)	28 years	squamous cell carcinoma grade 2	HPV +	radiotherapy	dead
3	Mousavi et al. (2010)	23 years	squamous cell carcinoma-high grade vulvar intraepithelial neoplasia (vin3)	nil	surgery adjuvant radiotherapy	alive
4	Han et al. (2009)	32 years	invasive squamous cell carcinoma-keratinizing type	HPV16+	surgery adjuvant radiotherapy	dead
5	Harper et al. (2004)	25 years	invasive squamous cell carcinoma	nil	surgery 3D CRT	dead
6	Roginsky et. al. (2004)	25 years	invasive squamous cell carcinoma	nil	surgery	dead
7	Carvalho et al. (2002)	14 years	well differentiated squamous cell carcinoma	HPV16 +	neoadjuvant chemotherapy (cisplatin) + radiotherapy	dead
8	Dinh et al. (1988)	26 year old	squamous cell carcinoma	HPV16+	unknown	unknown
9	Wilkinson et. Al (1984)	Unknown	squamous cell carcinoma	HPV+	radiotherapy	dead
10	Kennedy and Hart (1982)	20 years	microinvasive differentiated squamous cell carcinoma	nil	surgery	alive
11	Ortonne et al. (1981)	24 years	squamous cell carcinoma	nil	surgery	alive
12	Arnold et al. (1980)	26 years	moderately invasive well differentiated squamous cell carcinoma	nil	surgery	alive
13	Swift et al. (1971)	38 years	squamous cell carcinoma	nil	nil	alive
14.	Present case (2021)	40 years	squamous cell carcinoma	HPV-ve	surgery	alive

HPV: human papilloma virus.
3D-CRT: Three dimensional conformal radiotherapy.

a severe skin reaction after radiotherapy and died soon thereafter (Wilkinson et al., 1984). Carvalho et al. (2002) treated a 14-year-old girl with a high grade rapidly growing vaginal squamous cell tumour with cisplatin concurrent with radiotherapy (Carvalho et al., 2002). The patient developed an abdominal infection, pelvic abscess, neutropenia, and fungal sepsis, which led to death.

Hence, chemotherapy and radiotherapy are high-risk interventions and remain controversial in Fanconi anaemia patients. 3D conformal radiotherapy (3D CRT) may be a safer option in situations where surgery is not feasible. 3D CRT focuses the radiation on the tumour site and minimises the exposure of normal tissues. Harper et al. (2004) described a case where they used 3D CRT to treat recurring vaginal cancer post-surgery (Harper et al., 2004). No severe toxicities were observed, but benefits could not be seen, as the patient died due to brain metastasis while undergoing the treatment (Harper et al., 2004). Since our patient was in the early stage of the disease, she was treated with surgery alone. Our patient tolerated the procedure well and has been followed up with regularly since. There has been no evidence of recurrence to date.

HPV infection may increase the risk of squamous cell cancer in Fanconi anaemia patients (Liu et al., 2015). In the cases described by Carvalho et al. (2002) and Quiñonero et al. (2020), HPV positivity status might have contributed to the occurrence and rapid progression of cancer due to enhanced genetic instability (Carvalho et al., 2002; Quiñonero et al., 2020). In a study by Storey et al. (1998), a specific p53 gene polymorphism at codon 72 (Arg72) was found to increase the risk of HPV-related malignancy (Storey et al., 1998). However, in our patient, HPV by RT PCR was negative.

Kutler et al. conducted a case-control study to assess the HPV status, p53 mutations and polymorphisms of Fanconi anaemia patients. They observed that a high proportion of Fanconi anaemia with squamous cell carcinoma and HPV positivity harboured the p53 Arg72 polymorphism (Kutler et al., 2003; Liu et al., 2015). Also, in vitro models of HPV 16 infection in cells with defective Fanconi anaemia pathway showed increased proliferation and hyperplasia (Hoskins et al., 2009; Spardy et al., 2007). This indicates the need for an HPV vaccination and routine screening for Fanconi anaemia patients.

4. Conclusion

Even though bone marrow transplants may be able to correct haematological abnormalities, this does not obviate the need for lifelong screening for solid tumours. In females with Fanconi anaemia, yearly examinations of the head and neck area and lower reproductive tract are essential for the early detection of cancers. Any evidence of malignancies, especially on mucosal surfaces, must be biopsied. Genetic tests may also aid in predicting the type of malignancy that can occur. Advanced forms of cancer may require chemotherapy and radiotherapy along with surgery. However, these techniques must be administered with extreme caution and in low doses among Fanconi anaemia patients. New advances in gene therapy provide hope for correcting defects in the DNA repair pathway and reducing cancer risk in Fanconi anaemia patients.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images

CRediT authorship contribution statement

Vysakh Visweswaran: Conceptualization, Writing - original draft. **Hridya Jayamohanan:** Writing - review & editing, Resources. **Anupama Rajanbabu:** Supervision, Investigation. **Keechilat Pavithran:** Conceptualization, Investigation, Resources, Writing - review & editing, Supervision. **:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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