Fanconi anemia and vaginal squamous cell carcinoma

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Abstract

Fanconi Anemia (FA) is an autosomal recessive disease characterized by chromosome instability, cellular hypersensitivity to DNA cross-linking agents, and increased predisposition to malignancies. We describe here a 28 year-old female with FA and vaginal squamous cell carcinoma treated by radiation therapy alone. The patient developed arm phlebitis, pulmonary fungal infection, and severe rectal bleeding, followed by hypocalcaemia, hypokalemia, vaginal bacterial and fungal infection, with subsequent leg and arm phlebitis, perineal abscess, and sepsis. The patient died 12 weeks later.

Introduction

Fanconi anemia (FA) is a rare cancer susceptibility syndrome with an incidence of only 1-5 per million live births in the general population. FA is an autosomal recessive disease characterized by chromosome instability, cellular hypersensitivity to DNA cross-linking agents such as diepoxybutane, and increased predisposition to malignancies. Other clinical abnormalities associated with FA include bone marrow failure, congenital anomalies, short stature, hypo- or hyperpigmentation of the skin, radial ray bone abnormalities, thumb deformities, cardiac and renal anomalies and microcephaly.[1]

Cytopenias in FA patients usually occur during the first decade of life. Although the most common malignancies in FA patients are hematologic, they are at increased risk of certain solid tumors, in particular squamous cell carcinomas of the head and neck and gynecologic system. This susceptibility is due to mutations in the FA complementation group genes, which encode proteins that are part of a nuclear multiprotein core complex involved in activating mono-ubiquitination of the FANCD2 protein during the S phase of the cell cycle and after exposure to DNA cross-linking agents. The gold standard for the diagnosis of FA is the induction of chromosome fragility by DNA interstrand crosslink inducing agents such as diepoxybutane (DEB test).[2] This test allows FA to be diagnosed in patients without detectable congenital anomalies.

Case Report

A 28 year-old woman presented at our institution with vaginal bleeding and pelvic pain of 6 months duration. She was in generally good health, with no symptoms such as fatigue, other kinds of bleeding and recent episodes of fever. Physical examination showed several condilomatous like lesions in the cervix, the right side vaginal wall and the vulva, with a 3 cm ulcerative lesion on the left vaginal wall. She did not present with signs of bruising or petechiae, or significant cardiopulmonary impairment. Cervical and vaginal biopsies were performed resulting in pathological diagnoses of cervical intraepithelial neoplasia grade III (CIN III) and vaginal squamous cell carcinoma (SCC) grade II. Molecular assays showed the presence of p53 and high-risk HPV DNA. Laboratory workup revealed pancytopenia (hemoglobin=8.6 g/dL, hematocrit=26.8%, leucocytes=2.03×10^6/mm^3, platelets=57×10^6/mm^3). Magnetic resonance imaging (MRI) of the abdomen and pelvis showed a $4.1\times0.6\times2.5$ cm solid lesion on the distal posterior and inferior vaginal walls, with extension to the left side (Figure 1A). The tumor was classified as a stage II (FIGO) vaginal SCC.[3] Computerized tomography of the thorax was negative. The patient was referred to the Hematology Department for further examination. High dose-rate brachytherapy alone was indicated with curative intent without chemotherapy. Ten daily fractions were prescribed in two phases. The first, consisted of 6 fractions of 5 Gy administered to the vaginal mucosa surface and at 5 mm depth to the tumor bed. After a 15 days interval, two more fractions of 5 Gy each, followed by two fractions at 4 Gy each, calculated at a 5 mm depth were further administered as a boost to the tumor bed. As a result, the total dose of brachytherapy administered to the vaginal mucosa was 30 Gy, and to the tumor, 48 Gy, over a 32 day period. Moreover, biological equivalent doses to 2 Gy fractions (EQD2) were, respectively, 37.5 Gy to the vaginal mucosa surface, 59,3 Gy to the tumor (5 mm depth) ($\alpha/\beta=10$), and 75.2 Gy *maximum* dose at the anterior rectal wall ($\alpha/\beta=3$). During irradiation, the patient experienced mild to moderate rectal pain and moderate vaginal bleeding. A single blood transfusion was also required due to a reduction in blood cell counts that was observed. Following treatment, only a residual lesion remained. Afterwards, the patient presented with phlebitis in the arm and a pulmonary fungal infection associated with pancytopenia and required multiple blood transfusions (red blood cells and platelets).

Although there were no congenital anomalies, FA was suspected due to cytopenias associated with SCC at a young age. A bone marrow biopsy and smear were compatible with myelodysplastic syndrome (MDS) and karyotyping revealed clonal cytogenetic abnormalities involving chromosomes 11, 6 and 18. Chromosome fragility induced by diepoxybutane (DEB test) confirmed FA. Without compatible donors in her family, she was placed on a waiting list for bone marrow transplantation.

Pelvic MRI performed 1 month after treatment showed complete regression of disease (Figure 1B). Two months later, however, the patient developed rectal pain and bleeding. Rectoscopy showed ulceration of the anterior rectal wall, with biopsy negative for tumor, related to radiation. Subsequently, the patient presented hypocalcaemia, hypokalemia, vaginal bacterial and fungal infection, leg and arm phlebitis, perineal abscess and sepsis. She died 12 weeks after the initial diagnosis of vaginal carcinoma, remaining hospitalized for the last 3 weeks.

Discussion

FA patients are at 500- to 1000-fold increased risk of developing SCC, particularly of the mucosal linings of the head and neck region (HNSCC),

tumors that are a major cause of mortality in these patients.[4] FA patients are also highly susceptible to SCCs at other anatomic sites, including the cervix and vulva.[5] There have been only two previous reports on vaginal cancer in FA patients. In the first, two patients had vaginal SCC preceded by *Condyloma acuminatum*. In the second, involving 75 cancers in 64 FA patients, only one patient had vaginal cancer. That patient was treated with radiation but developed a skin reaction and died 3 months later. Most FA patients whose tumors were treated with radiation died shortly thereafter.[6] Although radiation therapy is the treatment of choice for patients with advanced vaginal SCC, it should be used cautiously in FA patients because adverse reactions to radiotherapy are common in these patients. Radiosensitivity is associated closely with the homozygous inheritance of defective proteins necessary for the recognition and/or repair of DNA double strand breaks.[7,8] At the time of radiotherapy, a diagnosis of FA had not been confirmed, and the patient presented with pelvic/vaginal pain and vaginal bleeding with persistent pancytopenia. Thererore, in an effort to preserve her bone marrow and underlying normal tissue, besides the indication of pelvic irradiation for stage II vaginal cancer, brachytherapy alone was indicated, until a definitive diagnoses was obtained. A total tumor dose (equivalent to 2 Gy fractions) of 59.3 Gy was prescribed to the patient, a dose that could be considered appropriate for tumor control.[9] A split-course was planned, during which tumor response and normal tissue reaction could be observed. The *maximum* rectal dose (75 Gy) was on the range that may increase the risk of complications, according to the GEC-ESTRO guidelines.[10] However, the tumor was located in the posterior and left lateral walls of the lower vagina, so rectal preservation was compromised in favor of achieving better tumor coverage, since external beam irradiation was not indicated. Nevertheless, the dose

prescription depth at 5 mm (not 6 mm according to the tumor thickness) was chosen as a rectal tolerance dose, which did not prevent the severe proctitis presented by the patient. It is possible that tridimensional image-guided brachytherapy could have provided better sparing of normal tissue, since image-guidance and dose-volume evaluations could have avoided the application of excessive doses of radiation to the rectum and other normal adjacent tissues. However, at the time of this case, this technique was not available at our institution. Despite the doses of brachytherapy applied in this case being in accordance with previous studies, this treatment regimen was certainly the cause of the rectal complications observed in the case, and did contribute to the outcome of the patient. Currently, the optimal management of hemorrhagic proctitis due to radiation remains unclear. However, the maintenance of rectal doses below tolerance limits remains the best approach to preventing this condition. Furthermore, it is possible to treat proctitis with topical corticosteroids, sulfasalazine, mesalazin, formalin, argon plasma coagulation, laser photocoagulation, or hyperbaric oxygen therapy.[11] In this case, the patient died due to complications of FA with radiation-induced proctitis. To our knowledge, there have been no specific guidelines, or similar reported experiences, to compare with the present case. Therefore, we can only speculate that radiation proctitis could have been avoided if a lower total dose, or dose/fraction, of brachytherapy had been used. Moreover, although local control was achieved after a short follow-up period, there was not enough time for an appropriate rectal treatment to be applied to better evaluate the outcome of radiation proctitis that developed in association with FA. In conclusion, vaginal squamous cell carcinoma in FA patients is a rare, and always fatal, disease. Currently, there is no conclusive evidence to guide the management of this disease in FA patients, although the results

of this study and others, demonstrates that due to increased radiosensitivity of these patients, radiation should be used with caution, with doses kept below clinically recommended levels. In addition, surgery should be considered as an alternative treatment.

References

1. Vundinti BR, Korgaonkar S, Ghosh K. Incidence of malignancy and clonal chromosomal abnormalities in Fanconi anemia. Indian J Cancer 2010;47:397-9.
2. Alter BP, Greene MH, Velazquez I, Rosenberg PS. Cancer in Fanconi anemia. Blood 2003;101: 2072.
3. FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. Int J Gynaecol Obstet 2009;105:3-4.
4. Kutler DI, Auerbach AD, Satagopan J, et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. Arch Otolaryngol Head Neck Surg 2003;129:106-12.
5. Carvalho JP, Dias ML, Carvalho FM, et al. Squamous cell vulvar carcinoma associated with Fanconi's anemia: a case report. Int J Gynecol Cancer 2002;12:220-2.
6. Wilkinson EJ, Morgan LS, Friedrich EG Jr. Association of Fanconi's anemia and squamous-cell carcinoma of the lower female genital tract with condyloma acuminatum. A report of two cases. J Reprod Med 1984;29:447-53.
7. Alter BP. Radiosensitivity in Fanconi's anemia patients. Radiother Oncol. 2002; 62:345-7.
8. Pollard JM, Gatti RA. Clinical radiation sensitivity with DNA repair disorders: an overview. Int J Radiat Oncol Biol Phys 2009;74:1323-31.
9. Mock U, Kucera H, Fellner C, et al. High-dose-rate (HDR) brachytherapy with or without external beam radiotherapy in the treatment of primary vaginal carcinoma: long-term results and side effects. Int J Radiat Oncol Biol Phys 2003;56:950-7.
10. Pötter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 2006;78:67-77.
11. de Parades V, Bauer P, Marteau P et al. [Non surgical treatment of chronic hemorrhagic radiation rectitis]. Gastroenterol Clin Biol 2007;31:919-28
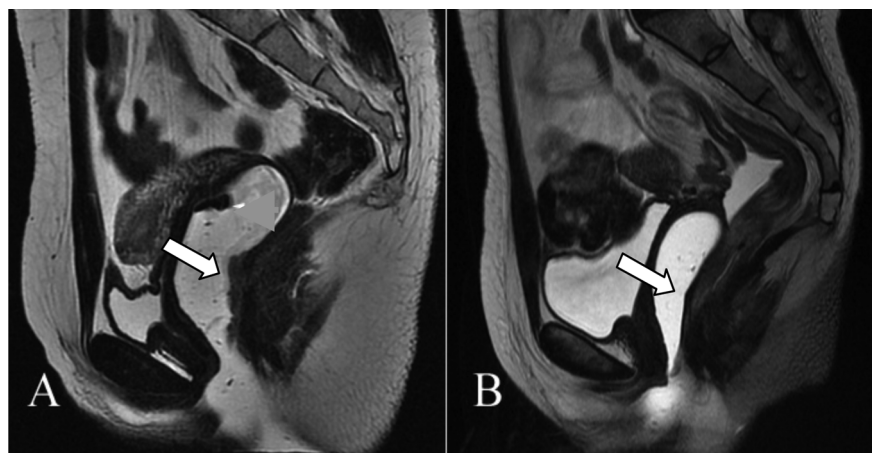

Figure 1. Magnetic resonance imaging sagittal view showing a vaginal squamous cell carcinoma (indicated with arrow) in a patient with FA, prior to (A), and one month after (B), receiving radiation therapy.