

CASE REPORT

Successful radiotherapy of de novo hypopharyngeal cancer in a Fanconi anemia patient with previous esophageal cancer

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Abstract

Definitive radiotherapy was effectively used for treatment of de novo hypopharyngeal SCC in a previous esophageal cancer patient with a history of Fanconi anemia, resulting in a complete clinical response.

KEYWORDS

esophageal SCC, Fanconi anemia, hypopharyngeal SCC, radiotherapy

1 | INTRODUCTION

Fanconi anemia (FA) is a genetic disorder characterized by a range of phenotypic presentations and susceptibility to malignancies. We report an FA patient with previously treated esophageal cancer, vulvar, and cervical intraepithelial premalignant lesions, who was diagnosed with hypopharyngeal squamous cell carcinoma and was treated successfully with definitive radiotherapy.

Fanconi anemia is an autosomal recessive genetic disorder caused by mutations in any of the 22 FA pathway genes currently identified.¹ Initially described by Guido Fanconi in 1927,² this disorder is characterized by a wide range of phenotypic presentations in musculoskeletal, skin, endocrine, genitourinary, and other body systems, as well as hematologic manifestations and a very high predisposition to cancer.³

According to the International Fanconi Anemia Registry (IFAR), the cumulative incidence of bone marrow failure in FA patients by age 40 is about 90%, usually manifested by thrombocytopenia, anemia, and neutropenia.⁴

2 | CASE PRESENTATION

A 39-year-old woman, known case of FA and previous esophageal cancer, was referred to our clinic due to a recent new onset dysphagia. She did not manifest any major detectable congenital malformations related to FA except for a short stature. The FA diagnosis was confirmed previously by diepoxybutane DNA cross-linking study. The patient had a sophisticated past medical and surgical history since 7 years ago. When she was 32, after experiencing a long period of

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dysphagia and odynophagia for at least 6 months that did not improve with medical treatment, she underwent a diagnostic upper GI endoscopy. Suspicious scattered white plaques were discovered along the middle esophagus, 25 cm far from the incisor teeth. The endoscopic view resembled leukoplakia or eosinophilic esophagitis and with a less probability, recovering herpetic esophagitis. However, the biopsy result indicated invasive well-differentiated squamous cell carcinoma. She underwent total esophagectomy with colon interposition. The surgical pathology report indicated a 2 cm long, circumferential lesion of large cell keratinizing type squamous cell carcinoma with focal submucosal invasion without any metastatic involvement of lymph nodes. All surgical margins were free, and the tumor did not show any features of angiolymphatic or perineural invasion. The morbidity of this surgery had been very devastating for the patient due to the massive hematochezia that she experienced a few days after surgery because of anastomosis ulceration and leak. She was kept in the intensive care unit for 3 weeks in order to control the surgery consequences before being discharged. She also had to receive multiple transfusions of platelet units as well as packed red blood cell units, due to her Fanconi-associated thrombocytopenia at that time.

Four years after esophagectomy, she noted multiple unusual skin lesions in her labia majora. She underwent multiple biopsies of the lesions which showed vulvar intraepithelial lesions grade 1-3 (VIN-1-3). Immunohistochemistry results showed positivity for P-16 and human papilloma virus (HPV). Subsequently, she underwent surgery (simple excision) to remove the lesions; however, due to the recurrence of her vulvar lesions, the surgery was repeated three more times. Due to abnormal vaginal spotting, she also had pap smears which showed high-grade squamous intraepithelial lesion, therefore, she underwent colposcopy. Biopsies through colposcopy also indicated cervical intraepithelial neoplasia 1 (CIN-1) with koilocytosis. She underwent follow-up clinical and colposcopic examinations and cervicovaginal smear testing which showed no further lesions.

After 7 years since her first major surgery (esophagectomy) when she was 39 years old, she experienced dysphagia, odynophagia, and hemoptysis. She declined any past

or present cigarette smoking or alcohol consumption. Due to her symptoms, she underwent upper re-endoscopy. It showed a vegetative ulcerative mass in hypopharynx with right pyriformis involvement (Figure 1). Cervical esophagus, esophago-colonic anastomosis, and the rest of the interpositioned colonic mucosa were normal. Biopsy results indicated well-differentiated squamous cell carcinoma of the hypopharynx. On magnetic resonance imaging (MRI), there was a 20 × 16 mm mass lesion in right pyriformis sinus with suspicious involvement of right aryepiglottic fold which extended inferiorly down to the cricoid level. There was no infiltration of perivertebral fascia or penetration of hypopharyngeal wall (T2N0M0). The patient was discussed in a multi-disciplinary treatment planning session in the presence of radiation oncologists, medical oncologists, pathologists, radiologists, and onco-surgeons. She was offered either surgery including laryngopharyngectomy or definitive radiation therapy. Because of the previous extensive surgery and significant bleeding risk due to her Fanconi anemia-associated thrombocytopenia, and her reluctance for another major surgery, radiation therapy was chosen for her. She was treated with 3D-conformal external beam radiation therapy delivered by 6 MV photons for a total dose of 70 Gy in 35 fractions over 6 weeks. The treatment planning was delivered through two lateral fields with cord sparing after 46 Gy, and delivering 60 Gy to the planning treatment volume consisting of the associated high-risk lymph node levels as well as the primary tumor, and a final boost until 70 Gy to the primary tumor site. She experienced grade 2 mucositis and nausea/vomiting during and for 3 weeks after treatment which resolved afterward.

Before radiotherapy, her WBC counts were around 3000 per microliter (65% neutrophil), hemoglobin was about 9 g/dL (MCV of 97 fL), and platelet levels were below 70 thousand per microliter; therefore, the following medication was prescribed for her: Capsule Danazole 200 mg PO daily, Amp Romiplostim 250 µg SC weekly, Amp Filgrastim 300 µg SC weekly, and Amp Erythropoietin 10 000 IU SC weekly. She received her radiotherapy treatment without delay and with stable WBC, hemoglobin, and platelet counts.

She has been undergoing close follow-up every 3 months after radiotherapy with upper endoscopy, and 1 year after

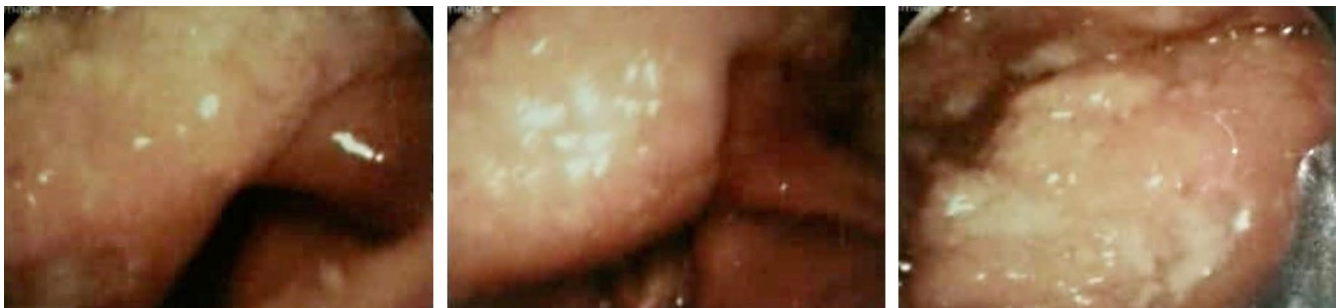
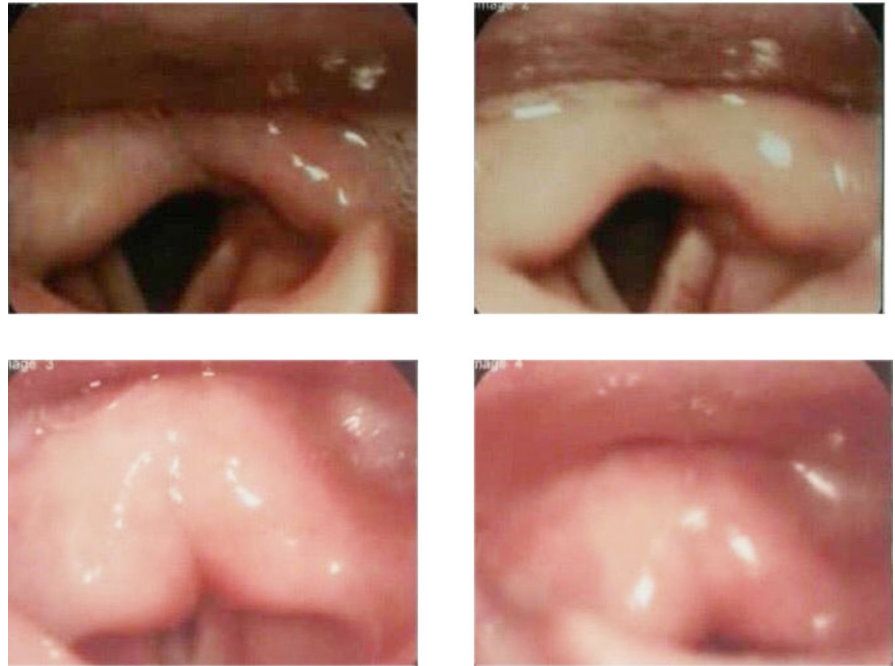


FIGURE 1 Upper endoscopy images showing a vegetative mass in the right pyriform sinus of hypopharynx

FIGURE 2 Upper endoscopy images demonstrating disappearance of the initial mass. Note the mild radiation related edema and erythema



Date	2013.12	2014.2	2014.3	2018.2	2018.10	2018.11	2019.9	2019.10	2019.12	2020.11	2020.12
Event	Esophageal SCC Dx	Esophagectomy + colon interposition	Admission to hospital after massive hematochezia	Vulvar VIN-III resection	Colposcopy CIN-I	Vulvar VIN-III resection	Vulvar VIN-III resection	Hypopharyngeal SCC Dx	End of RT	Vulvar VIN-III resection	MRI and upper endoscopy disease-free

FIGURE 3 Timeline showing different procedures done for the patient regarding her malignancies

treatment, she remains symptom-free without evidence of recurrence or relapse on upper gastrointestinal tract according to the endoscopy and MRI results (Figures 2 and 3).

3 | DISCUSSION

According to the 20-year results of 754 FA patients from IFAR registry, apart from acute myeloid leukemia, and myelodysplastic syndrome, SCCs of the head and neck, vulvo-cervical SCCs, and liver tumors are the most common solid tumors in Fanconi anemia patients.^{5,6}

Cumulative incidence of solid tumors in FA patients has been diversely reported to be about 30%-76% by age 45 in the two largest published cohorts.^{5,6}

As FA patients are very susceptible to DNA cross-linking, alkylating chemotherapy agents are contraindicated in them. However, despite remaining concerns about increased risk of secondary malignancies, radiotherapy is inevitably used in relevant clinical situations. Our patient had previously undergone radical esophagectomy with colon interposition, and due to a persistent thrombocytopenia, a second extensive surgery with increased risk of bleeding was not an appropriate option for her.

There are only a few published cases in the literature that were treated successfully with radiotherapy as a part of their treatment or definitively.⁷⁻¹¹

Some studies indicate a severely excessive clinical radiosensitivity mandating radiotherapy cessation in patients with AT (ataxia-telangiectasia) or FA, not correlated with cellular radiosensitivity in the cell line cultures of these patients.^{12,13}

There are very few published cases in the literature with more than one solid malignant tumor associated with Fanconi anemia.^{5,7,14-17} The patient presented in this article, experienced two malignancies (esophageal and hypopharyngeal SCC), and two loci for recurrent premalignant lesions (vulvar and cervical intraepithelial neoplasia). Fifty-four percent of FA patients with cervical, vulvar, and anal SCCs had a history of HPV-associated condylomas in IFAR;⁵ however, the association of HPV with head and neck SCCs in FA patients is less well established.¹⁸⁻²⁰ As previously stated, our patient was tested positive for HPV in a biopsy of her vulvar lesions. Whether the genetic mutations in the FA pathway genes make these patients more susceptible to HPV infection is not clearly understood yet; however, these patients are asked to get vaccinated against HPV virus.

Although our patient is currently disease-free 1 year after multiple treatment modalities for her primary cancers and

pre-malignant lesions, we will have to observe her life-long for any signs of recurrence or new malignant disease, especially that we are concerned about possibility of secondary malignancies following receipt of high dose of radiation.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

MB, KR and MS: were the physicians in charge of patient treatment, and contributed in data gathering, drafting and scientific revision of the manuscript. MG and KK: contributed in writing, editing, and final revision of the manuscript.

ETHICS APPROVAL

The presented manuscript is concordant with ethical guidelines and all information was included after patient's written informed consent while maintaining anonymity.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, K.K, upon request.

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