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Feasibility of breast radiation therapy in a Fanconi Anemia patient diagnosed with breast cancer: A case report and review of literature

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ABSTRACT

Fanconi Anemia (FA) is a rare inherited autosomal recessive disease that results in impaired double stranded DNA repair. This leads to both increased susceptibility to various cancers, as well as hypersensitivity to radiotherapy and systemic therapy; thus, increasing the complexity of oncological treatment paradigm.

Here, we present an FA patient who initially developed invasive breast cancer for which she received breast conserving treatment with no significant treatment related toxicity. This was followed by a diagnosis of high-grade ductal carcinoma-in-situ in the contralateral breast, which was managed successfully by surgery and meticulously planned adjuvant radiotherapy, with no treatment interruptions.

1. Introduction

Fanconi Anemia (FA) is a rare autosomal recessive disease characterized by congenital anomalies, high frequency of bone marrow failure, and malignancies [1,2]. These patients have approximately 30- to 50-fold higher risk of developing acute myeloid leukemia (AML) and solid tumors due to increased chromosomal instability [3,4]. In addition, impaired DNA-damage response that makes them susceptible to malignancies also increases their sensitivity to DNA crosslinking agents [5] as well as ionizing radiation [6,7]. This "double trouble" makes oncological management of FA patients extremely challenging.

To our knowledge, feasibility of breast radiotherapy (RT) in FA patients has not been reported very well in the literature. Herein, we described the clinical course of a FA patient diagnosed with metachronous bilateral breast cancer and reviewed pertinent RT literature in the setting of FA.

2. Case report

A 34-year-old female with a history of intermittent thrombocytopenia and leukopenia underwent investigations for a palpable right breast mass. Diagnostic mammogram showed a 3 cm lesion in the upper inner quadrant of right breast; ultrasound-guided core needle biopsy revealed a poorly differentiated, triple-negative infiltrating ductal carcinoma (IDC). During her work up for neoadjuvant chemotherapy, she was noted to have history of recurrent pancytopenia and hypocellular bone marrow with macrocytosis. She therefore underwent extensive investigations for a possible diagnosis of Fanconi Anemia, including a trial of filgrastim. Following this, she was referred for cytogenetics which revealed that the patient's peripheral blood lymphocytes are highly sensitive to DNA crosslinking agents mitomycin C (MMC) and diepoxybutane (DEB), which was consistent with the diagnosis of Fanconi Anemia. Additional findings on physical examination included several café-au-lait spots, macular holes, scoliosis, and hyperextension of thumbs. Comprehensive genetic testing revealed absence of BRCA1/2 mutations, but Fanconi Anemia complementation group A mutation was identified. Her family history was remarkable for multiple myeloma in several family members and breast cancer in her paternal grandmother but was negative for Fanconi Anemia.

She underwent right segmental mastectomy and sentinel lymph node biopsy, with pathology revealing pT2N0, 3.5 cm, poorly differentiated invasive ductal carcinoma (IDC), triple negative, without lymphovascular space invasion, with negative margins, and negative sentinel lymph nodes. Following 12 weeks of adjuvant paclitaxel chemotherapy, she exhibited significant peripheral neuropathy resulting in inability to walk. Thus,

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paclitaxel was discontinued early, and her neuropathy improved soon thereafter.

Adjuvant breast radiotherapy was planned with intent to adjust her total radiotherapy dose according to the severity of acute toxicity developed during therapy. As improvement in radiotherapy dose homogeneity was shown to be associated with reduction in acute skin toxicity [8], tangential beam forward-planned static field-in-field intensity modulated radiation therapy (IMRT) [9] with 6MV and 23MV photons was used to minimize the volume of breast receiving high dose of radiation (Fig. 1A). With meticulous RT beam arrangement and planning, dose to contralateral breast was minimized to achieve lowest dose possible. Initial radiotherapy plan was designed to deliver 45 Gy in 25 fractions with an option to extend the course up to 50.4 Gy in 28 fractions, depending on her tolerability. When she was assessed for toxicity during RT, she was noted to have clinically significant breast erythema and axillary fold tenderness following 45 Gy of radiotherapy (CTCAE v5.0, Grade II RT dermatitis). As a result, a decision was made not to proceed with additional treatment. This acute RT toxicity has resolved rapidly over a span of four weeks. Following successful completion of breast conserving therapy, she was enrolled into an intensive FA surveillance program to closely monitor for any subsequent malignancies, including yearly breast mammogram/MRI surveillance.

Sixteen months following initial breast cancer treatment, she underwent partial vulvectomy for vulvar intraepithelial neoplasia (VIN) 3. Five years following completion of right breast RT, she was diagnosed with high grade ductal carcinoma in situ (DCIS) in the lower inner quadrant of left breast (contralateral breast). She underwent left breast segmental mastectomy, with pathology revealing a 2.4 cm DCIS, ER negative, PR negative, nuclear grade III DCIS with comedo necrosis, with adequate margins.

She was referred to radiation oncology for adjuvant breast RT recommendations given high risk of in breast tumor relapse. After appropriate counselling, RT was planned to deliver 45 Gy in 25 fractions to whole breast followed by tumor breast boost of 16 Gy in 8 fractions, resulting in a total dose of 61 Gy to area of operative site (Fig. 1B). Radiotherapy boost was contemplated given the emerging evidence of its efficacy in young patients with high grade DCIS [10]. The added benefit of radiotherapy boost for DCIS patients was also shown in the more recently presented BIG 3-07/TROG 07.01 study at the 2020 San Antonio Breast Cancer Symposium. Field-in-field tangential IMRT [9] using a mixture of 6MV/18MV photon beams was used for RT planning to minimize dose heterogeneity and thereby resultant acute and late toxicity [11]. Maximum point dose to breast was limited to 105.2%. Deep inspiratory breath hold (DIBH) technique was used for RT planning and treatment to reduce the dose to heart and lungs [12]. En-face 12 MeV electrons were used to plan and deliver the boost component of radiotherapy in lateral decubitus position (Fig. 1C). This technique has been shown to minimize breast toxicity by enabling selection of lower energy electrons due to differential position of breast boost site when compared to supine position [13,14].

During RT, she was seen regularly to assess toxicity, mainly RT dermatitis. Four weeks into treatment, she developed CTCAE v5.0 grade II patchy moist desquamation in her left axilla and left breast, with moderate pain. Overall, she tolerated radiation well and acute RT dermatitis has improved rapidly following treatment completion. At forty-five month follow-up visit, examination has

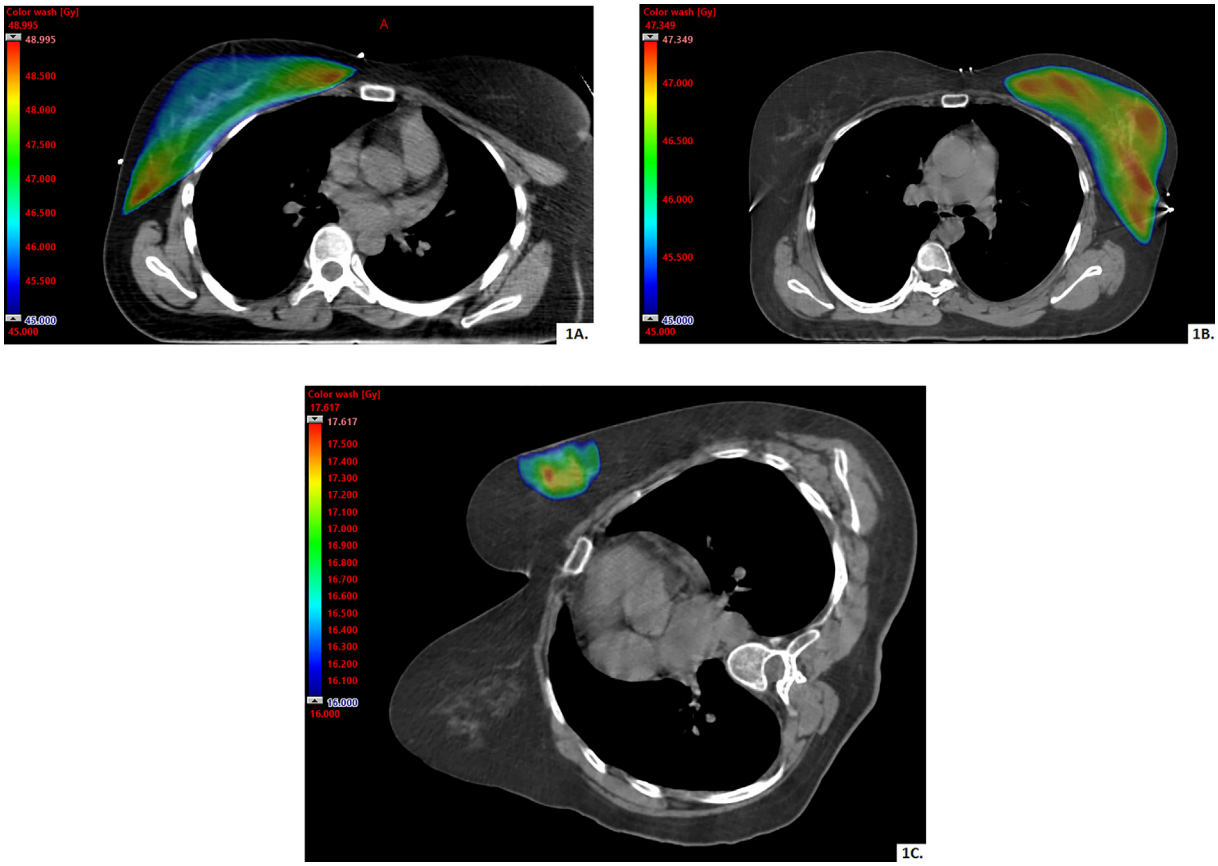

Fig 1. Radiotherapy Plans for right and left breast treatments. (A) Dose-color wash for right whole breast radiotherapy. (B) Dose-color wash for left whole breast radiotherapy; (C) Dose-color wash for left breast cavity boost using en-face electron field.

shown no identifiable residual toxicity related to bilateral breast radiotherapy.

More recently, she was diagnosed with thyroid carcinoma and underwent total thyroidectomy for a pT2N1a papillary carcinoma. Radioactive iodine was not pursued due to concerns with FA. She was rendered disease-free with respect to breast, vulvar, and thyroid malignancies on her most recent imaging that was performed ten years following her initial breast cancer diagnosis.

3. Discussion

Cumulative incidence of solid tumors in FA patients reaches approximately 20% by the age of 65 years [15], with head and neck SCC (HNSCC) being the most common solid malignancy [16]. FA patients are also known to have increased risk of breast cancer [15,17], though it is not pathognomonic of FA. Recently, several FA genes including BRCA1/FANCS, BRCA2/FANCD1, PALB2/FANCN, and RAD51C/FANCO have been identified as breast carcinoma susceptibility genes [18].

Added complexity in the management of FA patients includes enhanced RT sensitivity [6,7,19]. In FA HNSCC patients, significant RT toxicities including dose limiting pancytopenia, mucositis, and skin ulceration have been reported [7,19]. More recently, a successful therapeutic trial of sequential RT volume and dose escalation has been reported in a post-operative HNSCC patient [20]. To the best of our knowledge, such data about breast cancer RT in FA patients is limited.

Here, we described the journey of FA patient with multiple cancers, with a focus on metachronous bilateral breast cancer diagnoses and adjuvant breast radiation therapy that was delivered successfully.

Thoughtful RT planning with respect to RT dose homogeneity and technique are required to ensure that FA patients do not have excessive toxicities. Various breast RT techniques that have been described in literature to reduce dose homogeneity and resultant toxicity include IMRT [9,21,22] and prone positioning of patient [23]. We therefore planned both courses of RT using forward-planned IMRT to reduce the volume of breast tissue receiving high doses of RT. By using this technique, we were also able to reduce the volume of normal tissue receiving low doses of radiotherapy as this has been shown to be associated with increased risk of radiation induced second primary malignancies [24]. Deep inspiratory breath hold was also used for her left breast RT planning and treatment to reduce the dose to heart and lungs [12]. In addition, clear stopping rules were defined including daily review and skin check during RT to detect earliest signs of toxicity which would have then precluded subsequent treatments. As a result, our patient tolerated treatment well with no significant acute or late skin toxicity during either course of breast radiotherapy. Advances in the understanding of breast cancer radiobiology and RT techniques have paved the way for transition from conventional radiotherapy to hypofractionated RT schedules [25]. More recently, 5-fraction accelerated partial breast RT(APBI) [26] schedule was shown to result in favorable toxicity and equivalent efficacy when compared to whole breast radiotherapy. This modern APBI technique could have potential value in FA patients to further reduce RT related morbidity.

Breast RT is contraindicated in patients with genetic susceptibility syndromes that place them at higher risk of either RT toxicity or RT induced second primary cancers. A recent publication by Bergorm et al., provided a detailed framework for RT decision making following genetic testing in breast cancer patients [27]. Such data is not available for FA patients with a diagnosis of breast cancer.

Our experience with breast RT contrasts with head and neck radiation where FA patients were known to develop significant mucosal toxicity [28]. In addition, heterogeneity with respect to RT tolerance had been described in FA patients receiving RT to the same anatomical site, most likely due to different underlying FA mutations.

In this report, we outlined the journey of a FA patient who received radiation therapy for two different breast cancer diagnoses, thus demonstrating its feasibility and safety. Reporting outcome of oncological treatments in FA patients might help elucidate factors that contribute to varying RT tolerance in this highly heterogenous population.

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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