

Radiation Therapy-Induced Toxicity in a Breast Cancer Patient With Variance of Unknown Significance in the Ataxia Telangiectasia Gene

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Abstract

Breast conservation has been an effective part of the multimodality treatment of localized breast cancer. Appropriate candidates for breast conservation include patients with early stage disease. However, there are certain absolute contraindications for breast cancer, including radiation during pregnancy, multiple positive margins, and homozygosity mutations in the ataxia telangiectasia mutated (*ATM*) gene. *ATM*, an autosomal-recessive disorder, is associated with the childhood onset of neurologic impairment, immunodeficiency, and ocular and cutaneous telangiectasias. Typically, patients with heterozygous *ATM* mutations remain candidates for breast conservation. However, *ATM* mutations have been linked to increased sensitivity to radiation therapy and, in some cases, to severe toxicity. We present a case of a 51-year-old woman with variance of unknown significance (VUS) in her *ATM* gene, who was treated with adjuvant radiation and subsequently developed fibrosis, reduced shoulder movement, and telangiectasias. Thus, our case highlights the need for patients with VUS to be appropriately counseled on radiotoxicity.

Keywords: ataxia telangiectasia, telangiectasias, fibrosis, breast radiation, radiation pneumonitis, dermatitis, toxicity, side effects

Case Summary

A 51-year-old woman presented in 2018 after a screening mammogram discovered asymmetry in the right subareolar region with a 15 × 13 × 14 mm mass on ultrasonography. Breast biopsies revealed triple-positive infiltrating ductal carcinoma. She had no history of collagen vascular diseases or prior radiation. Genetic testing

revealed a heterozygous variance of unknown significance (VUS) in the ataxia telangiectasia (*ATM*) gene (c.3158A>T(p.Asp1053Val)) and negative BReast CAncer gene (*BRCA*) testing. She underwent neoadjuvant chemotherapy with Adriamycin and cyclophosphamide, followed by Taxol, Herceptin, and pertuzumab. Subsequent right partial mastectomy showed grade 2 residual invasive ductal carcinoma. She received a

total dose of 5000 cGy of 3D radiation therapy to the right breast and the supraclavicular and axillary lymph nodes with a boost.

The patient developed cutaneous symptoms, which progressed to telangiectasias and significant fibrosis (**Figure 1**). In addition, she developed radiographically detected asymptomatic radiation pneumonitis (**Figure 2A-B**).

Platelet-rich infusions, used for fibrosis treatment, were ineffective. The patient subsequently underwent a mastectomy.

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Discussion

By facilitating DNA double-stranded breaks, ionizing radiation is known to cause damage to both

Figure 1. Significant fibrosis and poor cosmesis seen following radiation.



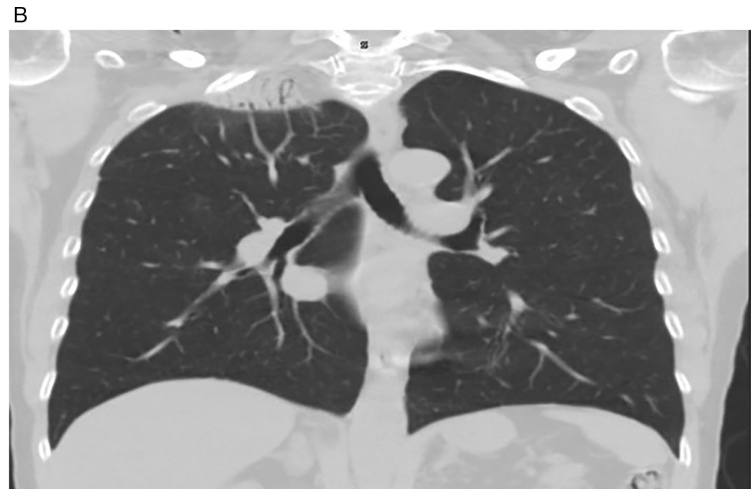
malignant and nonmalignant cells. In patients with mutant *ATM* genes, DNA repair via nonhomologous DNA end-joining is impaired, which raises concern for an increased sensitivity to radiation therapy^{1,2}. The data regarding increased toxicity from radiation therapy in heterozygous carriers of *ATM* mutations are unclear. Furthermore, it is also unclear whether there is a correlation between VUS mutations and an increased sensitivity to radiation. An extensive database regarding VUS mutations across several genes is available on the ClinVar website. Of the 8945 submitted variants of the *ATM* gene, more than 50% (4742) were deemed to be VUS mutations.³

Clinical investigations attempting to assess the link between VUS and increased radiation sensitivity have been unclear, with different studies yielding contradictory results. In a study assessing 91 evaluable carriers of *ATM* variants, of whom 23 harbored a pathogenic variant while 68 harbored VUS, researchers determined no evidence of increased radiation-associated toxicity among carriers of pathogenic *ATM* germline variants.⁴ Another study assessed 357 pan-cancer patients who received a cumulative total of 727 courses of radiation therapy, determining that genetic inactivation of *ATM* was associated with an improved radiotherapeutic efficacy.⁵

However, one case series demonstrated that patients with heterozygous germline *ATM* mutations can have widely varying clinical responses to radiation therapy, ranging from benign to severe,⁶ as was seen in our patient's case. Moreover, the landmark WECARE study discovered increased contralateral breast cancers in radiated patients possessing otherwise nonpathologic *ATM* variants.⁷

ATM heterozygotes make up approximately 1% of the general population, and it has been shown in epidemiologic studies that this mutation confers a 3- to 5-fold increase in the risk of developing breast cancer. However, understanding the clinical significance of VUS in the *ATM* gene is vital for patients undergoing radiation treatment. While it has been discussed that VUS should be considered normal and should not confer increased radiosensitivity to patients,⁸ our patient's severe cutaneous toxicity serves as a reminder that adverse radiation-induced effects can be seen in patients with VUS. Recent guidelines recommend that radiation therapy should be offered when clinically indicated for women with breast cancer who are carriers of an *ATM* mutation.⁹ Therefore, more investigation is needed into VUS mutations to determine the significance of single-nucleotide alterations. We present this case so that it can be added to the ClinVar website and future patients could be counseled and avoid the severe side effects seen in this patient.

Figure 2. Apical scarring of the right lung following radiation as seen on an axial view (A). Apical scarring of the right lung following radiation as seen on a coronal view (B).



Conclusions

The ATM gene is a critical regulator of DNA double-strand breaks and ensures appropriate mismatch repair. We present a case of a patient with triple-positive breast cancer and a VUS ATM gene, who developed significant fibrosis and cutaneous scarring following radiation therapy. Certainly, it is possible that there is a subset of VUS in which some patients may develop more deleterious side effects than others. Nevertheless, our case underscores the need for further analysis of VUS mutations and appropriate patient counseling, determining the risk of radiation toxicity in these patients.

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