Ataxia Telangiectasia in a Patient with Breast Cancer: A Case Report

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Ataxia telangiectasia (AT) is a rare autosomal recessive disorder caused by the pathological variants of the *ATM* gene. Owing to its rarity and nature, complications of AT, such as malignant tumors, are often difficult to manage with standard imaging studies and treatments, and there are no established management strategies. We report the case of a woman who had AT in childhood and developed breast cancer in her 20s; the disease was successfully managed by the decision-making of multidisciplinary physicians professionals with ethics support. She was immunocompromised, ataxic, and mentally impaired. The patient's mother noticed a tumor in her right breast and subsequently brought her to our department. Although preoperative testing and surgical procedures were limited as AT is extremely radiosensitive, the patient was diagnosed with cT2N0M0 breast cancer and underwent right mastectomy and axillary lymph node sampling. The final diagnosis was pT2N0M0 pStage IIA mucinous carcinoma, and immunohistochemistry of the tumor specimen was estrogen receptor-positive, progesterone receptor-positive, and HER2-negative. Tamoxifen was administered as postoperative adjuvant therapy, and the patient has survived to date without recurrence.
Here, we report our experience with breast cancer treatment for AT, along with a review of the literature.

Key words: Ataxia telangiectasia, *ATM* gene, breast cancer

INTRODUCTION

Ataxia telangiectasia (AT) is a hereditary disease characterized by the triad of cerebellar ataxia, telangiectasia of the eyelid and conjunctiva, and susceptibility to infection [1–4]. Patients with AT are prone to recurrent sinus and lung infections, diabetes, stunted growth, and bone fractures [1, 4]. Though the clinical manifestations vary from patient to patient, cases are described as "classical" when the disease is severe and "variant" when mild [1, 2, 4]. The prevalence of AT is reported to be 1 in 40,000–300,000 people worldwide [1, 4] and approximately 1 in 100,000 people in Japan [10]. AT is caused by mutations in the *ATM* gene on chromosome 11, which is involved in DNA damage repair and exhibits an autosomal recessive pattern of inheritance [1, 2, 5, 6]. The *ATM* gene is located on chromosome 11q22–q23 and consists of 66 exons spanning 150 kb of genomic DNA [1, 6]. The *ATM* gene is activated in response to DNA damage and phosphorylates downstream targets such as *p53, CHEK2,* and *BRCA1,* causing cell cycle arrest, DNA repair, and apoptosis [5]. Thus, the presence of pathological variants in any of these genes leads to inadequate cell repair, and ultimately to a higher incidence of cancer and intolerability to radiation, in addition to the clinical symptoms described below [1, 6, 11]. *ATM* is a susceptibility gene for breast cancer [1]. AT is diagnosed by the absence or defective ATM protein or its kinase activity in cultured cells, or by the identification of pathological variants of the *ATM* gene [1], differentiated from other ataxias, such as Friedreich's ataxia.

AT develops mostly during childhood and adolescence [1, 2]. Malignancy and recurrent respiratory infections due to immunodeficiency are the primary causes of death. The incidence of nearly all cancer types is high, with lymphoma and leukemia being the most common [1–4, 7]. As patients with AT have extremely weak resistance to radiation, such exposure should be avoided as much as possible for them [1, 4, 6, 8, 9]. There is no established standard treatment; most patients die by their teens or early 20s. However, life expectancy for such patients is increasing annually with recent advances in medical care [1, 2]. Due to its rarity and the nature of the disease, complications of AT, such as malignancy, are difficult to manage by standard imaging modalities or treatments. Therefore, it is necessary to establish appropriate management strategies based on an accumulation of cases.

In this report, we describe the case of a 27-year-old female patient with breast cancer patient and underlying AT; the disease was successfully managed by the decision-making of multidisciplinary physicians. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CASE REPORT

The patient was a 27-year-old woman, diagnosed with ataxia telangiectasia (AT) after genetic testing at

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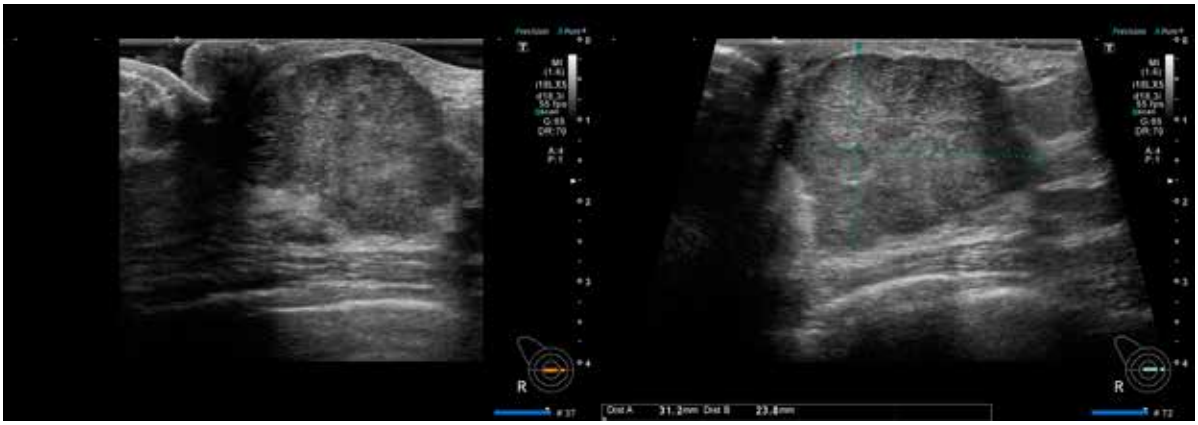

Fig. 1 Breast ultrasonography revealed a hypoechoic mass, 31 mm in diameter, in the EAB region of the right breast.

Table Laboratory data before operation.

WBC	4900 /μl	Na	139 mEq/L
Hb	9.3 g/dl	K	4.1 mEq/L
PLT	40.2 10^4/μl	Cl	105 mEq/L
Alb	3.9 g/dl	CRP	0.01 mg/dl
AST	49 IU/L	TSH	3.1 μIU/ml
ALT	49 IU/L	FreeT3	2.89 pg/ml
LDH	200 IU/L	FreeT4	1.21 ng/dl
Cr	0.42 mg/dl	IgG	939 mg/dl
Glu	84 mg/dl	CEA	2.3 ng/ml
T-bil	0.4 mg/dl	CA15-3	13.2 U/ml

the age of 4 years for ataxia, who had been on gammaglobulin replacement therapy for hypogammaglobulinemia and prophylactic oral antimicrobial therapy since the age of 5 years. Her family history included a mother who developed colorectal cancer in her 40s, but no other history of malignancies or consanguineous marriages. In addition to ataxic gait, hypostatic facial features, mental impairment, and hypogammaglobulinemia were also noted. Regarding the degree of mental impairment, she had delayed language development and difficulty communicating her intentions to others.

At the age of 27 years, her mother noticed a tumor in her right breast, which led to the suspicion of breast cancer and referral to our hospital. Breast ultrasonography showed a 31 mm hypoechoic mass in the inside region of the right breast, with no findings suggestive of metastasis to the axillary lymph nodes (Fig. 1). Needle biopsy revealed mucinous carcinoma, and immunohistochemistry was estrogen receptor-positive, progesterone receptor-positive, and human epidermal receptor 2 (HER2)-negative, with 20% Ki-67. Since patients with AT are very sensitive to the effects of radiation exposure, including medical radiography, the search for distant metastases was minimized. Chest radiography and abdominal ultrasonography showed no evidence of distant metastasis, and the preoperative diagnosis was right breast cancer, cT2N0M0, cStage IIA. Blood tests showed no abnormal findings other than a mild elevation in transaminase levels. Immunoglobulin G levels were maintained after gamma globulin replacement therapy (Table). Cardiac function was normal. Spirometry was performed to evaluate respiratory function but could not be measured accurately due to the patient's mental impairment. After consultation with the anesthesiologist, it was determined that general anesthesia was possible because the patient had no history of chronic lung disease or respiratory infection, although there was a risk of postoperative decline in respiratory function and pneumonia. Her SpO2 was maintained, and no lung disease was suspected on chest radiography.

Considering the patient's intellectual disability, we consulted our ethics team regarding the treatment plan. The ethics team decided that it was in the best interest of the patient to undergo surgery while taking all measures to minimize risks. Informed consent was obtained from the patient's mother who requested surgery. AT is accompanied by various complications; therefore, multidisciplinary cooperation is required for breast cancer treatment. During her hospital stay, a pediatrician was on call when her general condition deteriorated, and an oncological nurse provided the patient with a comfortable environment. Since the patient was prone to infection and postoperative pneumonia can be severe, early rehabilitation intervention was provided to prevent the deterioration of swallowing function. In addition, oral surgeons provided oral health screenings and perioperative oral care to prevent postoperative pneumonia of oral bacterial origin. At her mother's request, counseling was provided by a genetic counselor who shared information about AT and provided psychological and social support.

Approximately 2 months after her initial visit to our hospital, she underwent right mastectomy and axillary lymph node sampling. Because of the sensitivity of patients with AT to radiation, the use of radiation therapy and radiomimetics, as well as testing, should be avoided whenever possible [1, 2, 4]. To avoid radiation exposure, axillary lymph node sampling was performed instead of sentinel node biopsy, which uses radionuclides. Eight lymph nodes were sampled. Intraoperative frozen sections showed no lymph node metastases; therefore, an axillary dissection was not performed. The patient

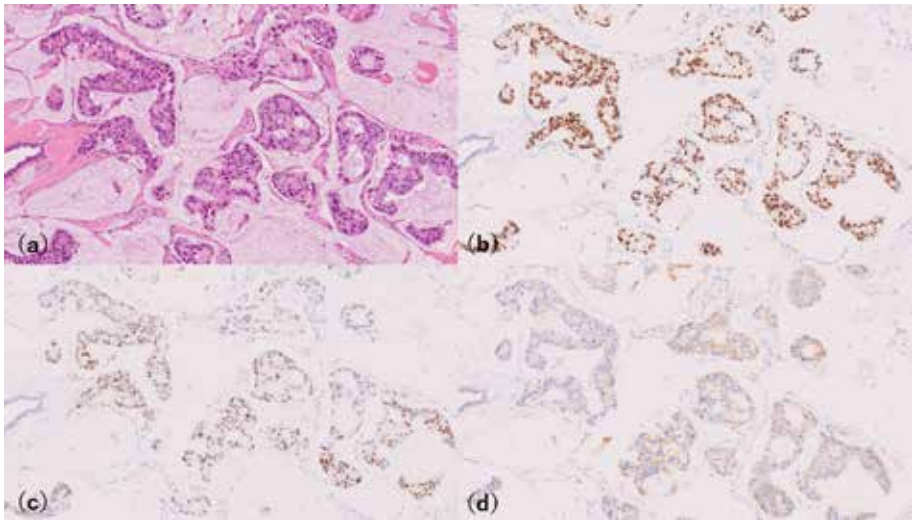

Fig. 2 (a) Histopathological findings show a large amount of mucus around the carcinoma, indicating mucous carcinoma. (a) HE staining. Immunostaining showed ER positive (b), PgR positive (c), and HER2 1+ (d).

was discharged 8 days after surgery without any perioperative complications. Histopathological examination of the surgical specimen revealed mucinous carcinoma with an invasive diameter of 23 mm, negative lymph nodes, positive estrogen receptor, positive progesterone receptor, negative HER2, and 15% Ki-67 (Fig. 2). She was administered tamoxifen 20 mg/day as a postoperative adjuvant therapy, which progressed without any apparent adverse events. The patient did not have any recurrences 1 year after surgery.

DISCUSSION

This was a rare case of a patient with AT surviving to adulthood and developing a solid tumor. As AT is accompanied by various complications, it is difficult to apply standard testing methods and strategies for cancer treatment. It is important to develop a plan based on sufficient preoperative evaluation and perioperative management by multiple specialists to ensure appropriate management while minimizing risk.

In this case, the patient was diagnosed with AT at the age of 4 years due to progressive ataxia, which is considered "classical." In addition to ataxia and failure to thrive, the patient received periodic immunoglobulin therapy for hypogammaglobulinemia. To date, she has not experienced any severe respiratory tract infections.

The lifetime risk of developing a malignancy in patients with AT is approximately 25% [1, 7]. The median age at diagnosis is reported to be 12.5 years with differences among cancer types [7]. Younger patients (<20 years) have a 35% increased risk of lymphoma and leukemia (especially acute lymphoblastic leukemia and Hodgkin's and non-Hodgkin's lymphoma), whereas adults are susceptible to various solid tumors (breast, liver, stomach, esophagus, and thyroid) in addition to lymphoma [1, 3, 4, 7]. Approximately 0.8% of patients present with solid tumors by the age of 30 years and 6.6% by the age of 40 [7]. Both AT patients and heterozygous carriers of an *ATM* mutation have been shown to have an increased risk of cancer (especially of the breast and gastrointestinal tract) [2]. Pathological carriers of the *ATM* gene have an overall higher risk of cancer, especially female carriers who have a 16% risk of developing breast cancer [2]. The patient's mother had colorectal cancer, and we informed her of the importance of breast cancer screening during genetic counseling sessions. The overall prevalence of *ATM* mutations in patients with breast cancer is 7% [12]. A systematic review and meta-analysis about the association between *ATM* pathological variants and breast cancer risk showed the Asian population to have the highest association among racial groups (odds ratio 4.21; 95% confidence interval [CI]: 0.78–22.88; I square: 89.5%; PI square: 0.0001), and the European population to have the lowest (odds ratio 1.24; 95% CI: 0.94–1.64; I square: 18.5%; PI square: 0.297) [6]. It has been reported that most *ATM*-related breast cancers are hormone receptor positive [13]. A recent study examining the effects of the *ATM* gene in the mammary epithelium suggested that ATM kinase deficiency greatly increases the cell growth-stimulating effects of estrogen E2, and that this mechanism may be relevant to breast cancer subtypes [14]. The breast cancer was hormone receptor-positive in our patient.

In a study in which AT patients received general anesthesia, they were anesthetized at the same risk as other pediatric patients, with no major perioperative anesthetic complications or prolonged ICU stay; all patients survived to discharge and were not unexpectedly hospitalized after it [8]. However, patients with severe restrictive lung disease may require postoperative noninvasive positive pressure ventilation. Therefore, preoperative evaluation of respiratory function is necessary for patients scheduled for general anesthesia. Although spirometry could not be performed in this patient because of mental retardation, as there was no history of chronic lung disease or respiratory infection, SpO2 was maintained, and no lung disease was suspected on chest radiography, we determined that she had adequate respiratory function and proceeded with the surgery.

As mentioned above, radiation therapy and radiomimetics should be avoided because of their cytotoxic effects in patients with AT [1, 4, 9]. Diagnostic computed tomography (CT) scans and radiographs should be limited to the extent that they do not affect treatment [1]. Breast cancer patients with pathological *ATM* variants develop secondary tumors earlier than usual when

they receive radiation therapy [6]. Therefore, CT and radiation therapy were avoided. Similarly, radioisotopes for sentinel node biopsy were not used during surgery, and axillary lymph node metastasis was assessed by sampling the axilla. In addition, total mastectomy was performed to avoid radiation therapy after breast-conserving surgery. The use of cyclophosphamide can cause severe bleeding due to telangiectasia in the bladder and should be administered with caution [1, 4]. However, there is no consensus regarding the use of other anticancer agents. Although there is little information on hormone therapy for patients with AT, it has been used in this patient to date without any apparent adverse events.

The clinical utility of *ATM* genetic testing for screening *ATM* pathological variant carriers has not yet been established and there are currently no specific guidelines. The National Comprehensive Cancer Network recommends early screening with annual digital breast tomosynthesis with contrast-enhanced magnetic resonance imaging beginning at the age of 40 years for *ATM* pathological variant carriers [2, 4, 15]. Recently, some Canadian provinces have applied these guidelines only to women carrying *ATM* pathological variants, whereas Australia has applied them to women heterozygous for *ATM* c.7271T > G (p.Val2424Gly), which is known to increase breast cancer risk to the same extent as BRCA2 [4, 16]. There is insufficient evidence for risk-reducing mastectomy, and management based on family history is required [4, 15]. Thus, there are recommendations for breast surveillance of *ATM* pathological mutation carriers but not for patients with AT. We will explore how to conduct contralateral breast surveillance in the future and how to provide treatment when recurrence occurs as the patient has intellectual disabilities and is unable to fully understand testing and treatment. Accumulation of further evidence is necessary.

CONCLUSION

Here, we report a case of AT in a patient with breast cancer. AT is a rare disease with a high risk of concurrent malignancy, and standard testing or treatment strategies are difficult to apply. Sufficient preoperative evaluation and perioperative management by multiple specialists are important to minimize perioperative risk. Radiation intolerance should be considered when planning the evaluation and treatment of breast cancer. With appropriate medical care, life expectancy has increased over the past years, and with further developments in genetic analysis, it is expected that new therapeutic strategies, such as treatment and surveillance tailored to genetic pathological variants, may be considered in the future.

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