CASE REPORT

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Germline *ATM* Variation in a Young Patient Diagnosed with Breast Cancer Presenting with Vaginal Neuroendocrine Carcinoma

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ABSTRACT

ATM plays a crucial role in repairing DNA damage and maintaining genomic stability. Mutations in *ATM* are associated with increased breast cancer risk and the development of various neuroendocrine carcinomas, including small-cell lung carcinoma and neuroendocrine tumors of the gastrointestinal tract. Here, we present a case with a heterozygous *ATM* variant [NM_000051.4.7174C>T(p.Arg2392Trp)], which is classified as a variant of uncertain significance (VUS) in the ClinVar database. This patient, who was initially treated for breast cancer, was later diagnosed with a rare vaginal neuroendocrine carcinoma at month 31 post-breast cancer diagnosis. In contrast to most cases, the patient tested negative for human papillomavirus (HPV)-DNA. Based on the rare presentation of neuroendocrine carcinoma and the negative HPV-DNA status, we proposed that VUS of *ATM* may be associated with cancer development and has pathogenic roles.

Keywords: *ATM* protein; human; carcinoma; neuroendocrine; breast neoplasms

INTRODUCTION

ATM, a crucial component of the DNA damage response pathway, preserves genomic integrity by facilitating the repair of double-strand DNA breaks. Mutations in *ATM* are reported to contribute to breast cancer development.[1] Individuals with heterozygous or homozygous *ATM* mutations are at an increased risk of developing breast cancer. In particular, the prevalence of these mutations is high in some breast cancer subtypes. Additionally, *ATM* mutations are associated with various neuroendocrine carcinomas, including small-cell lung carcinoma, large-cell neuroendocrine carcinoma, and neuroendocrine tumors of the gastrointestinal tract.[2]

Here, we present a patient with a heterozygous *ATM* variant [NM_000051.4.7174C>T(p.Arg2392Trp)] that is classified as a variant of uncertain significance (VUS) in the ClinVar database. The patient was diagnosed with vaginal neuroendocrine carcinoma, which manifested as vaginal mass and vaginal bleeding, at month 13 post-breast cancer diagnosis. Previous studies and case reports have reported that vaginal neuroendocrine carcinoma, a highly rare condition, is typically associated with human papillomavirus (HPV) infection. However, the study patient tested negative for HPV. We hypothesized that this heterozygous *ATM* variant that is classified as a VUS may have a pathogenic role, potentially contributing to the development of cancer.

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CASE REPORT

A 30-year-old female patient presented with a palpable mass in the right breast. The patient had no known comorbidities and no family history of cancer. Magnetic resonance imaging, which was performed after the physical examination, revealed an axillary mass (16 mm×9 mm) with a malignant appearance. Pathological lymph node involvement was not observed in the axilla. Positron emission tomography/computed tomography (PET/CT) did not reveal distant metastasis. The patient, who was diagnosed with invasive ductal carcinoma via tru-cut biopsy, underwent breast-conserving surgery and a sentinel lymph node biopsy (Figure 1). After the surgery, a mass (13 mm×10 mm×10 mm) with clean surgical margins was excised. Perineural invasion and lymphovascular invasion were not observed in this mass. The molecular characteristics of the mass were as follows: estrogen receptor level, 20%; progesterone receptor level, 5%; ERBB2 status, negative; MKI67 expression level, 80%; tumor grade, grade 3 (Figures 2, 3). Sentinel lymph node biopsy did not reveal metastasis (0/3). The patient was referred to the oncology clinic with the diagnosis of pT1cN0M0 (stage 1A) luminal B invasive ductal carcinoma. Breast risk scoring tests were not performed owing to the lack of health system reimbursement. The histopathological findings were consistent with high-grade tumors (grade-3, MKI67-high). The patient received four cycles of dose-dense anthracycline-cyclophosphamide (doxorubicin=60 mg/m^2 and cyclophosphamide=600 mg/m^2) chemotherapy after genetic consultation. Next, the patient underwent adjuvant radiotherapy without adverse effects. The patient was then initiated on goserelin and tamoxifen treatment as adjuvant hormone therapy. The *ATM* variant [c.7174C>T(p.Arg2392Trp)] was detected in the heterozygous form (Figure 4). This variant was classified as VUS in the ClinVar database (ClinVarID: 186868).

The OncoRisk next-generation sequencing (NGS) panel (comprising 31 genes associated with several hereditary cancer syndromes) was used for the analysis. The panel did not detect any variants, except for the *ATM* variant. Next, *BRCA1* and *BRCA2* were subjected to multiplex ligation-dependent probe amplification analysis, which revealed no deletions or duplications.

The patient underwent follow-up mammography, breast ultrasound, and abdominal ultrasound and received hormone therapy without adverse effects. However, the patient developed a vaginal mass and vaginal bleeding at month 31 post-breast cancer diagnosis. An excisional biopsy of the vaginal mass was performed. The MKI67 score in the vaginal mass was 60%. Additionally, the mass tested negative for mammaglobin, p63, p40, estrogen receptor, progesterone receptor, ERRB2, CK 5/6, GATA-3, and PAX-8 (Figure 5). The nuclei were mostly large and hyperchromatic. The mass tested positive for chromogranin A (Figures 6, 7). The results of the excisional vaginal mass biopsy revealed neuroendocrine carcinoma. PET/CT scanning was performed for staging. Increased ^{18}F-fluorodeoxyglucose (FDG) uptake consistent with primary malignancy was observed in the vagina. Meanwhile, increased ^{18}F-FDG uptake consistent with metastasis was observed in the inguinal, femoral, and pelvic lymph nodes. Additionally, increased FDG uptake consistent with metastasis was observed in the left sixth rib, L1 vertebra, and right pubic bone (Figures 8-11). The patient tested negative for HPV-DNA. The patient was diagnosed with stage 4 metastatic neuroendocrine carcinoma and treated with etoposide, cisplatin, and zoledronic acid. The patient is currently under treatment.

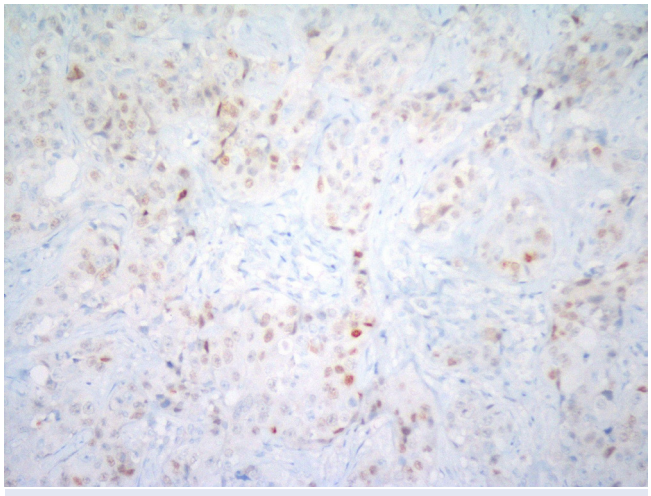

FIGURE 1: Breast cancer-pleomorphic invasive tumor cells adjacent to normal breast ducts (H&E, x10).

H&E: Hematoxylin&eosin

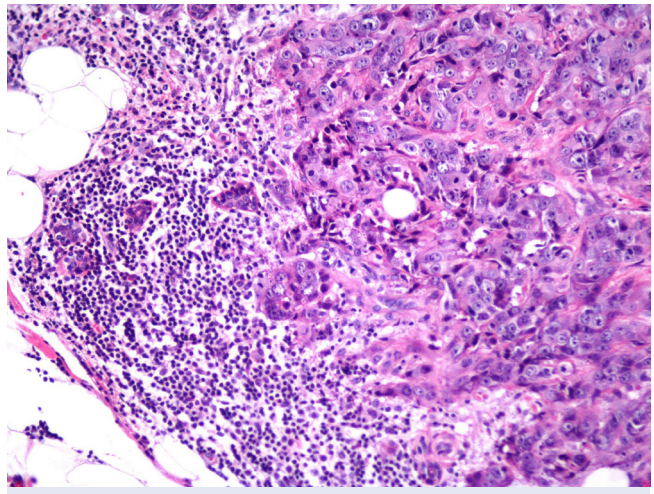

FIGURE 2: Breast cancer-weak ER positivity in tumor cells (DAB, x10).

ER: Estrogen receptor

Informed consent forms were obtained from the patient and the physicians who participated in the study.

DISCUSSION

Pathological *ATM* variants are rare in breast cancer. The pooled prevalence rate of *ATM* variants in patients with breast cancer is reported to be 7%.[3] However, these variants are commonly detected in certain subtypes of breast cancer, such as triple-negative breast cancer.[4] The clinical characteristics of patients with breast cancer exhibiting pathological *ATM* variation are distinct. Previous studies have reported that *ATM* mutation-associated breast cancers are likely to be high-grade tumors, have an increased frequency of *TP53* mutations, and exhibit genomic instability.[4] Based on the clinical implications of pathological *ATM* variation, genetic testing may be recommended for patients with breast cancer, especially for those with a family history of breast or other related cancers.

Neuroendocrine carcinoma of the vagina, a rare malignancy, typically affects postmenopausal women, although it has also been reported in younger individuals.[5-8] This aggressive and high-grade cancer is often diagnosed at an advanced stage.[9] Vaginal cancers account for less than 1-2% of all gynecological cancers, and neuroendocrine carcinoma represents a small percentage of vaginal cancers.[5,6] Previous studies have reported that patients with gyneco-oncological neuroendocrine cancers test positive for HPV-DNA.[9] In addition to the case reported in this study, 28 cases of primary vaginal neuroendocrine carcinoma have been previously reported.[9] The data on *ATM* mutations in neuroendocrine carcinoma are limited as it is a rare cancer.

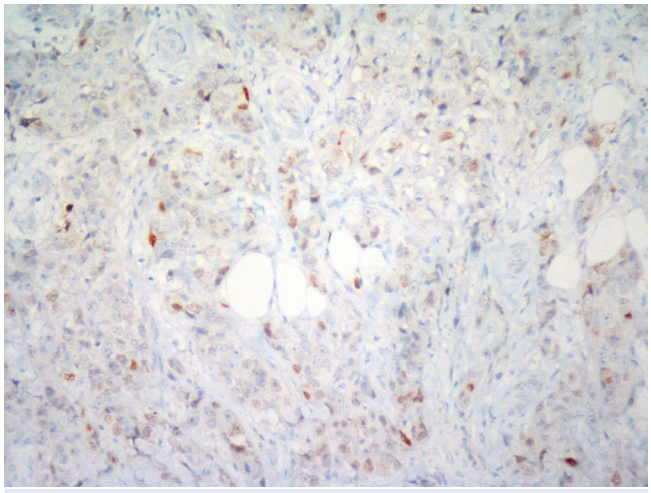

FIGURE 3: Breast cancer-weak PR positivity in tumor cells (DAB, x10).

PR: Progesterone receptor

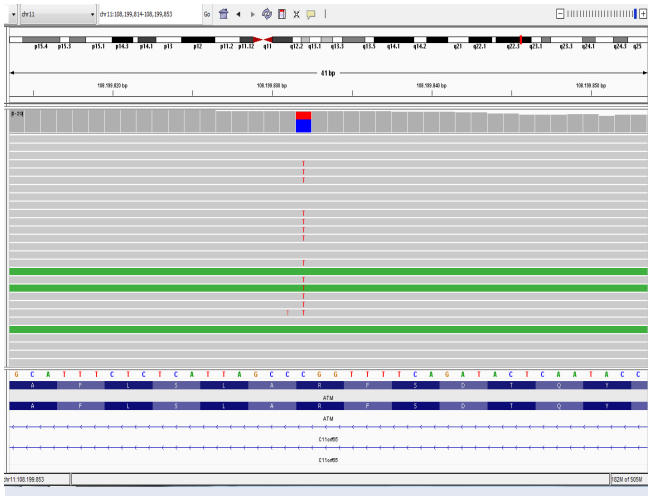

FIGURE 4: Genetical analysis for ATM variation.

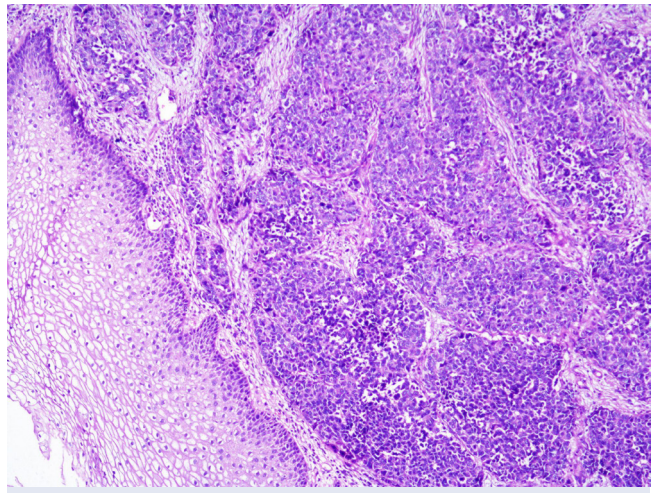

FIGURE 5: Vagen-solid tumor islands under vagen squamous epithelium (H&E, x100).

H&E: Hematoxylin&eosin

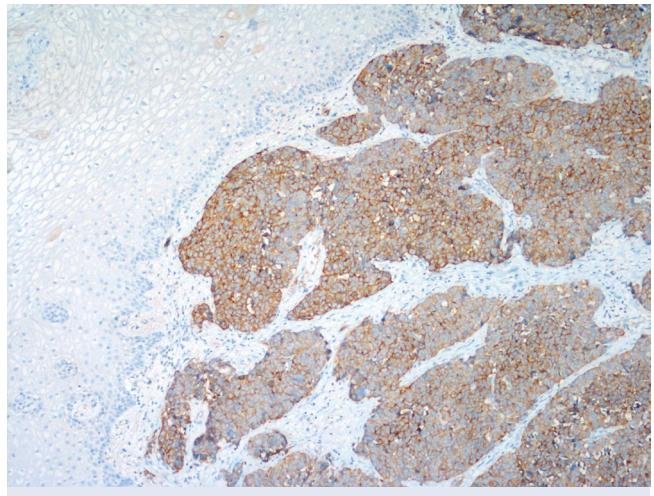

FIGURE 6: Vagen-diffuse synaptophysin positivity in tumor cells (DAB, x100).

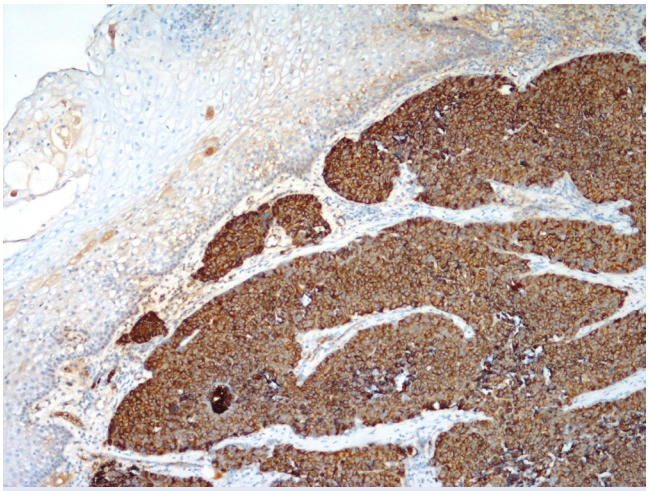

FIGURE 7: Vagen-diffuse chromogranin positivity in tumor cells (DAB, x100).

The *ATM* variant [c.7174C>T(p.Arg2392Trp)] detected in the study patient was classified as VUS in the ClinVar database and as a "possible pathogenic variant" according to the American College of Medical Genetics criteria.

This is the first study to report this variant in neuroendocrine carcinoma. This variant is potentially associated with both breast cancer and neuroendocrine carcinoma.

The study patient tested negative for HPV-DNA, which was in contrast to the HPV-DNA-positive status previously reported in gyneco-oncological neuroendocrine cancers.[10,11] This indicates that this genetic variant is specifically associated with vaginal neuroendocrine carcinoma.

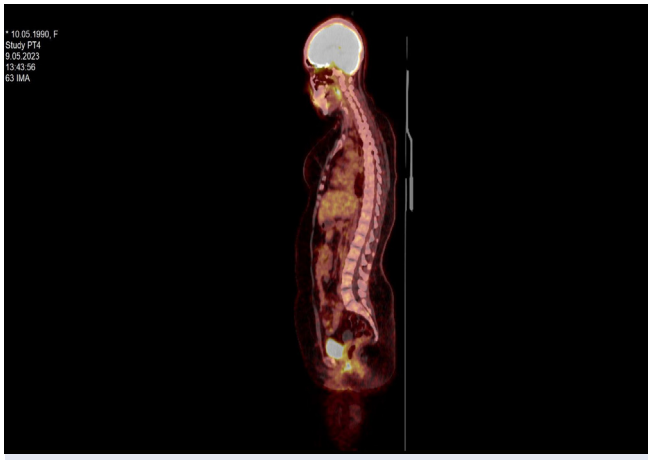

FIGURE 8: Positron emission tomography/computed tomography scan for neuroendocrine carcinoma-1.

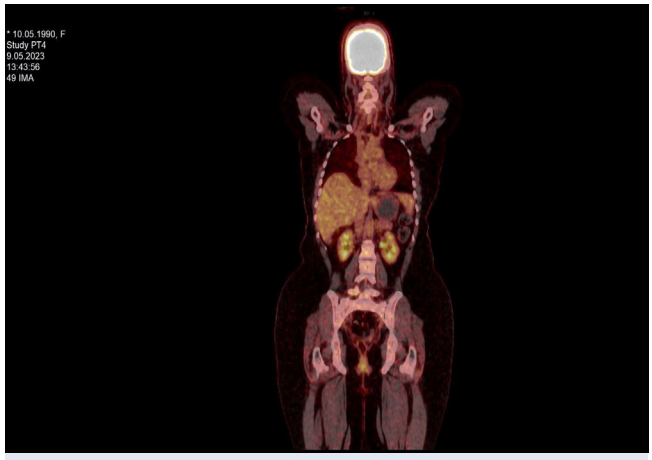

FIGURE 10: Positron emission tomography/computed tomography scan for neuroendocrine carcinoma-3.

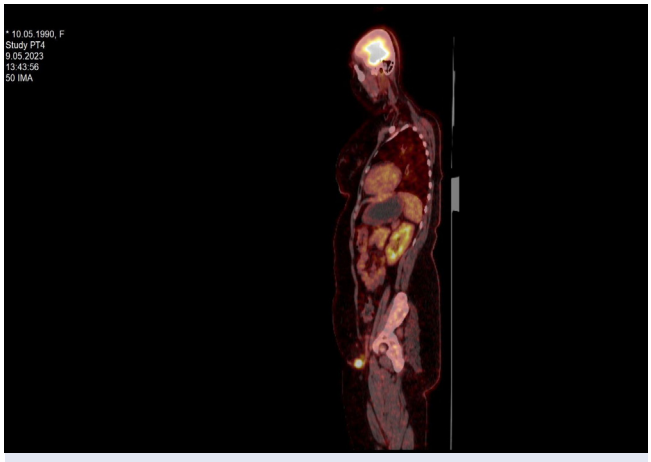

FIGURE 9: Positron emission tomography/computed tomography scan for neuroendocrine carcinoma-2.

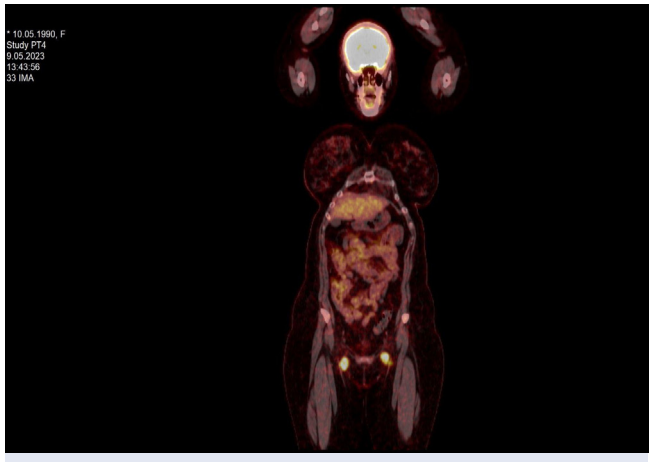

FIGURE 11: Positron emission tomography/computed tomography scan for neuroendocrine carcinoma-4.

CONCLUSION

Limited information is available on the genomic profile of vaginal neuroendocrine cancer based on the NGS panel owing to the rare occurrence of this cancer. Further genetic studies will improve our understanding of the genetic characteristics of vaginal neuroendocrine cancer.

Ethics

Informed Consent: Informed consent forms were obtained from the patient and the physicians who participated in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.Ü.Ü., S.A., Concept: E.G.K., Design: E.G.K., Data Collection or Processing: E.G.K., E.E.P., Analysis or Interpretation: E.G.K., Literature Search: E.G.K., Writing: E.G.K., Critical Review: T.R.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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