A woman with a pleural mesothelioma and an inherited *ATM* mutation—a case report

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Background: Pleural mesothelioma (PM) is a rare and aggressive malignancy primarily linked to asbestos exposure. Up to 80% of patients have a history of such exposure. Several studies have investigated the possibility of a genetic predisposition for a subgroup of PM patients, but the data remains inconsistent. The ataxia-telangiectasia mutated (*ATM*) gene, crucial for DNA repair, is implicated in cancer susceptibility, with heterozygous mutations increasing risks, notably in breast and pancreatic cancers.

Case Description: We present a case of a 42-year-old woman, with no asbestos exposure history, diagnosed with metastatic PM. Initial treatment with immunotherapy showed limited efficacy. Given the rarity in young females, she opted for genetic testing via "The Screen Project", revealing a pathogenic *ATM* mutation. Due to enhanced radiosensitivity in *ATM* mutation carriers, to reduce adverse events conventional palliative radiotherapy (RT) was chosen over stereotactic hypofractionated RT. A follow-up computed tomography (CT) scan after 4 weeks indicated disease burden reduction.

Conclusions: This case highlights the importance of genetic testing in atypical PM cases, guiding treatment decisions tailored to individual genetic profiles. Awareness of *ATM* mutations can optimize therapeutic strategies, particularly regarding RT choices, in managing this challenging malignancy. Integrating genetic insights into clinical practice holds promise for enhancing treatment outcomes and refining management strategies in PM and related conditions.

Keywords: Ataxia-telangiectasia mutated mutation (*ATM* mutation); radiotherapy (RT); pleural mesothelioma (PM); case report

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Introduction

Mesothelioma of the pleura is a rare and aggressive malignancy. Pleural mesothelioma (PM) is often diagnosed at an advanced stage, with a 5-year overall survival of approximately 12%. Treatment options include surgery, radiotherapy (RT), and chemotherapy but the data regarding the therapeutic benefits of each are unclear (1). Despite decades of effort, there is still no curative treatment for mesothelioma. Patients with metastatic disease at diagnosis are not considered candidates for surgery.

The association between environmental exposure to asbestos and PM is well established. Asbestos is the primary risk factor for PM (1,2) and up to 80% of patients will have some previous exposure identified on careful occupational history. It is estimated that up to 5–17% of individuals with

chronic exposure to high levels of asbestos will develop PM (3).

Several studies have investigated the possibility that there is a genetic predisposition for a subgroup of PM patients. There is little evidence for familial clustering of PM, but studies have been conducted that examine the presence of germline mutations in several candidate genes (4,5). The ataxia-telangiectasia mutated (*ATM*) gene has a crucial role in the repair of double-strand DNA breaks (6). Homozygous mutations result in an autosomal recessive condition known as ataxia-telangiectasia. This condition is characterized by cerebellar degeneration, oculocutaneous telangiectasia, and immunodeficiency. Homozygotes are also at risk for a range of cancers, in particular leukemia and lymphomas. Although homozygous germ-line *ATM* carriers are rare, heterozygous mutations can be found in up to 1% of the population and these individuals (heterozygotes) have an increased risk of several types of cancer, most notably of the breast and pancreas (7). In two recent breast cancer surveys, an *ATM* mutation was found in 0.8% of breast cancer patients and 0.4% of healthy controls (CARRIERS study) (8) and in 0.6% of breast cancer patients and 0.3% of controls [Breast Cancer Association Consortium (BCAC) study] (9). It is estimated that *ATM* carriers have a two-fold higher risk of breast cancer than the general population (7,10). In the general population, *ATM* mutations are more numerous than *BRCA1* mutations and *BRCA2* mutations, and as genetic testing becomes more widespread, increasing numbers of *ATM* heterozygotes are being identified.

Here we report the identification of an *ATM* gene mutation in a young woman with PM and review the literature with regards to this association. We present this case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-24-138/rc).

Highlight box

Key findings

- Ataxia-telangiectasia mutated (*ATM*) mutation in pleural mesothelioma (PM): identification of *ATM* mutation can guide clinicians towards using palliative radiotherapy at appropriate doses, minimizing side effects.

What is known and what is new?

- PM is an aggressive cancer typically associated with asbestos exposure.
- Rare mutations in the *ATM* gene are known to increase susceptibility to various cancers. Limited studies have explored their implications in PM.
- Our case report is the first to show the presence of *ATM* gene mutation in a young woman with PM, and also correlated with clinical outcomes.

What is the implication, and what should change now?

- Genetic testing should be considered in cases of PM, especially when no asbestos exposure history is present. This case underscores its potential to identify target therapies tailored to genetic profiles, improving treatment outcomes.

Case presentation

In November 2023, a 42-year-old female with no history of smoking and an unremarkable medical background presented to the emergency department with progressive shortness of breath, coughing, fever, and chest pain. To her knowledge, she has never been exposed to asbestos, either environmentally or occupationally. She had one maternal and one paternal relative with a (postmenopausal) diagnosis of breast cancer. An X-ray revealed a pleural effusion suspicious for a lung tumor. Further investigation via computed tomography (CT) scan confirmed the presence of a nodule in the upper right pleura. Thoracentesis and pleural biopsy led to the diagnosis of a diffuse biphasic PM. A positron emission tomography (PET) scan revealed metastasis and invasion of surrounding structures.

Given the presence of metastatic disease, the patient was deemed ineligible for surgery, and she was started on first-line treatment with immunotherapy (nivolumab and ipilimumab every 3 weeks). The CT evaluation after 8 weeks of treatment indicated a partial response. The patient continued to experience severe fatigue and shortness of breath necessitating oxygen therapy.

Given the rarity of this condition in young women, the patient herself opted to undergo genetic testing through "The Screen Project" a program which offers online genetic testing to all Canadian adults on a pay-for-service basis, operating through Women's College Hospital. Next-generation sequencing (NGS) revealed a pathogenic mutation in the *ATM* gene (c.2377-2A>G). Consequently, she was seen at our clinic at Women's College Hospital for genetic counseling.

Several RT options were considered (including more hypofractionated courses like 30 Gy in 5 daily fractions) but, in light of the enhanced radiosensitivity of *ATM* mutation carriers with cancer, she was treated with conventional palliative RT consisting of 20 Gy in 5 daily fractions. Ten days post-treatment, she experienced G2 esophagitis

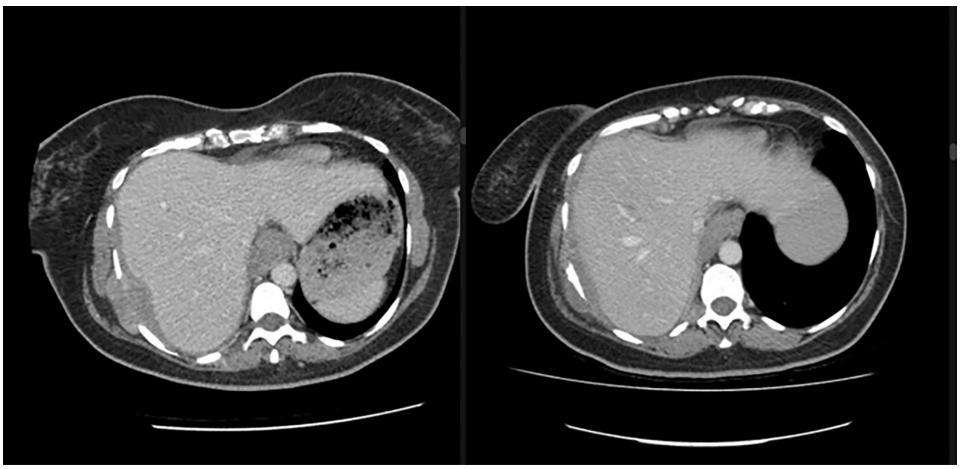

Figure 1 CT scan pre- and post-RT treatment. Left CT scan pre-RT treatment: moderate to enlarge right pleural effusion, extensive pleural right masses in the right middle lobe, and right lower lobe consolidation. Bony erosion of the right eighth lateral rib. Right CT scan post-RT treatment: interval decrease in the size of right pleural mass-like and nodular circumferential thickening with interval improvement of chest wall invasion and of mediastinal invasion. Decrease in the size of a small right pleural effusion. Regression of multiple lymph nodes. Interval increased periosteal reaction of ribs adjacent to chest wall invasion. CT, computed tomography; RT, radiotherapy.

and G1 fever, managed with a 7-day regimen of dexamethasone 4 mg with an excellent response. A CT scan conducted after 4 weeks indicated a reduction in disease burden (*Figure 1*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

PM is an uncommon tumor, with a global incidence of 0.46 per 100,000 persons (1,11). PM often goes undiagnosed until it reaches an advanced stage, primarily due to the absence of specific symptoms. Common clinical manifestations of PM are chest pain and shortness of breath (from the pleural effusion). For patients not candidates for surgery, a non-surgical approach involving systemic combination therapy with pemetrexed and platinum-based chemotherapy is often recommended. Advanced therapies now include targeted therapy drugs like nivolumab, a monoclonal antibody targeting the PD-1 protein on the T cell surface, and ipilimumab, a second monoclonal antibody that binds to the CTLA-4 protein on the surface of T cells (12). The combination of ipilimumab and nivolumab stands as a promising first-line therapy for patients with unresectable PM (12). Recent trials have shown the efficacy of nivolumab alone in second-line chemotherapy option (13).

Here we present a unique case of PM in a young woman with an *ATM* mutation. The *ATM* gene encodes for a serine-threonine kinase crucial for repairing double-strand breaks (DSBs) in DNA by mediating the repair of DNA damage while activating cell-cycle checkpoints via TP53, thereby controlling genome stability and cell survival. DSBs can occur when cells are exposed to oxidative stress, ionizing radiation, or chemotherapy. Mutations in the *ATM* gene can impair its function, leading to an inability to repair DNA damage effectively. This deficiency increases the susceptibility to genomic instability, a hallmark of cancer development (14,15).

The association between *ATM* mutation and mesothelioma has been reported before and we believe that there is now sufficient evidence to consider mesothelioma to be part of the cancer spectrum for *ATM*. Panou *et al.* sequenced 85 cancer susceptibility genes on the germline DNA from 198 patients with pleural, peritoneal, and tunica vaginalis malignant mesothelioma (16). They identified 24 germline mutations in 13 genes (12% of all study subjects). Two patients carried a germline *ATM* mutation. Mutations

in *BAP1* were the most prevalent (n=6 cases) (16). Betti *et al.* assessed the presence of germline mutations in 93 individuals affected by PM exposed to asbestos (17). They identified a pathogenic variant in nine subjects (17), one of whom carried an *ATM* mutation (*c.8436delT p.Ser2812fs*) (17). They noted that the anti-*ATM* antibody displayed normal nuclear staining, indicating the presence of a wild-type allele (17). van Kooten *et al.* completed an NGS analysis on 19 patients with peritoneal mesothelioma in Rotterdam (18); 2 patients (11%) carried an *ATM* mutation (18). To our knowledge, ours is the sixth reported case.

Somatic mutations are common in PM tissues and are present in the majority of cases. Hiltbrunner *et al.* conducted NGS sequencing on tumor tissue samples of 1,113 PM and 355 peritoneal mesothelioma patients in the United States (19). They were able to identify 19 genes with a prevalence exceeding 2%. Among the most commonly mutated genes were *CDKN2A* (48.2%), *BAP1* (45.0%), *CDKN2B* (42.2%), *NF2* (32.8%), and *MTAP* (32.3%) They found that 2% of peritoneal mesotheliomas contained *ATM* mutations, whereas fewer than 1% of PM tumor carried an *ATM* mutation (19). This observation aligns with the literature, which indicates that while *ATM* mutations are relatively rare in PM, they are more prevalent in peritoneal mesothelioma. Additionally, these mutations appear to be more frequently observed in women (20). *ATM* inactivation in the tumor cells is associated with radiosensitivity (6,21,22). Pitter *et al.* investigated the role of somatic *ATM* inactivation as a predictive marker of improved tumor response to RT in 357 patients affected by various types of cancer (lung, colon, prostate, breast, thyroid) who received radiation therapy (23). Notably, loss of function of *ATM* through somatic mutation was associated with a clear clinical benefit from RT. It will be important to extend these findings to carriers of inherited mutations as well.

In a phase II study, Bang *et al.* compared olaparib plus paclitaxel *vs.* paclitaxel alone in patients with recurrent metastatic gastric cancer with low *ATM* expression (24). The study showed a statistically significant benefit in overall survival in subjects who received olaparib in combination with paclitaxel; the difference was greater in patients with low *ATM* expression.

We describe a case of a young woman affected by metastatic PM with a heterozygous *ATM* mutation, where the immunotherapy was not very effective. In this case, the genetic finding led her clinicians to avoid stereotactic hypofractionated RT and recommend conventional palliative RT due to increased radiosensitivity and higher risk of both acute and late radiation toxicities such as radiation pneumonitis, esophagitis, pulmonary fibrosis, and esophageal stricture. We recommend that all patients with PM be tested for a wide panel of genetic mutations, including *ATM*, and that their clinical course be documented. Other genes which have been shown to predispose to mesothelioma include *CDKN2A*, *NF2*, *BAP1*, *TP53*, and *SETD2* (25). It is of interest to determine if heterozygotes with PM respond well to standard RT schedules or if they experience untoward side effects. It is also of interest to determine how well they respond to novel chemotherapies such as PARP inhibitors and immunotherapy.

Conclusions

In conclusion, identifying genetic mutations in patients with PM is crucial for personalizing treatment and improving outcomes, as it may affect their response to both conventional and novel therapies.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-24-138/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised

in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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