Case Report

# *STRN-ALK* rearranged malignant peritoneal mesothelioma—Presenting with bilateral extensive pelvic masses in a young woman: Mimicking low-grade serous ovarian carcinoma

**Pinar Bulutay, Dogan Vatansever [2], Cagatay Taskiran[2], Cisel A. Mericoz, Fatma Tokat[1], Nilgun Kapucuoglu, Ibrahim Kulac**

Department of Pathology, School of Medicine, Koc University, Istanbul, [1]Department of Pathology, School of Medicine, Acıbadem University, Istanbul, [2]Department of Gynecology and Obstetrics, School of Medicine, Koc University, Istanbul, Turkey

**Address for correspondence:**
*Dr. Pinar Bulutay, Department of Pathology, Koc University School of Medicine, Zeytinburnu, Istanbul 34010, Turkey.*
*E-mail: pbulutay@kuh.ku.edu.tr*

## ABSTRACT

Malignant peritoneal mesothelioma (MPM) is an exceptionally rare tumor type. Although some somatic/germline genetic alterations including BAP1 loss have been identified in some cases, the molecular properties of MPMs are remained poorly understood. In recent years, anaplastic lymphoma kinase (ALK) gene rearrangement was revealed in a subset of (3.4%) MPMs. Low-grade serous carcinomas (LGSCs) are a rare subtype of ovarian carcinoma and have some morphologic and immunophenotypic overlapping features with MPMs and this may cause misdiagnosis in daily practice. Here, we report a case of 18-year-old women with *STRN-ALK*-rearranged MPM and no previous exposure to asbestos. This case was presented with bilateral pelvic masses and histologically was displaying pure papillary morphology with mild-to-moderate nuclear atypia, psammoma bodies, and diffuse PAX8 expression as LGSCs. With the detection of *ALK* alteration in some of the MPMs, a targeted treatment option has emerged for these unusual tumor types.

**KEY WORDS:** ALK, PAX8, peritoneal malignant mesothelioma, *STRN-ALK* fusion

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## INTRODUCTION

Malignant peritoneal mesothelioma (MPM) accounts for 10–30% of all malignant mesothelioma cases and is rarely seen in children and adolescents.[1] The prior asbestos exposure history is found only in 33–50% of MPMs.[2] The pathogenesis remains unclear. In the context of recurrent somatic and/or germline "breast cancer-associated protein 1" (BAP1), mutations have been noted in 50–70% of MPMs.[3] Additionally, anaplastic lymphoma kinase (*ALK*) gene rearrangement has been recently shown in a small subset of the MPM cases (3.4%).[4] Low-grade serous carcinoma (LGSC) represents approximately 6–8% of all ovarian cancers.[5] Since both are rare at a young age and they have some morphological and immunohistochemical overlapping features, the clinical and morphological distinction of MPMs from serous ovarian neoplasms can be difficult. Here, we present an *ALK*-rearranged MPM case that clinically, morphologically, and immunohistochemically mimics LGSC.

## CASE PRESENTATION

An 18-year-old female with no family history of cancer and no previous exposure to asbestos was presented with abdominal pain and swelling. Magnetic resonance imaging revealed bilateral-multiloculated cystic adnexal masses, which consisted of 4-cm solid and 13-cm cystic component in the right ovary and 3-cm solid and 11-cm cystic

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component left ovary [Figure 1a]. Serum Cancer antigen-125 (CA-125) level was elevated (232 U/ml). In the frozen section, the tumor was exhibiting small papillae, nests, and micropapillary formations, and some psammoma bodies were seen. The intraoperative diagnosis was given as "low-grade serous ovarian carcinoma." She underwent debulking surgery, consisting of a total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, splenectomy, cholecystectomy, sigmoid colon resection, total peritonectomy, bladder peritoneum stripping, and paraaortic lymph node dissection. A histopathological examination of the resected specimens revealed that the tumor was forming from the numerous papillary, micropapillary structures, and some solid sheets. The tumor cells were round, oval, and polygonal in shape with small nucleoli, and there was a mild-to-moderate nuclear pleomorphism [Figure 1b–c]. There was extensive bilateral ovarian surface involvement. The posterior face of the uterus was almost completely covered by tumoral implants as well. Dispersedly settled psammoma bodies were also easily seen [Figure 1d]. Three of the 20 dissected paraaortic lymph nodes were also metastatic.

With these features, we included LGSC as well as MPM in our differential diagnosis and performed a wide immunohistochemical (IHC) panel using primary monoclonal antibodies against Wilms' Tumor protein-1 (WT1) (Cell Marque, 6F-H2), Paired box gene 8 (PAX 8) (Cell Marque, MRQ50, 1:100), Estrogen Receptor (ER) (Ventana, SP1), Progesterone Receptor (PR) (Ventana, 1E2), p53 (ScyTek, DO7, 1:200), Calretinin (Ventana, SP65), Cytokeratin 5/6 (CK 5/6) (Biocare, CK 5/6), CK 7 (Cell Marque, OV-TL 12/30, prediluted), Claudin4 (Invitrogen, 3E2C1, 1/200), BerEp4 (Biocare, BerEp4), and BRCA1 Associated Protein 1 (BAP1) (Santa Cruz, C-4, 1:50) with a Benchmark XT Automating Staining System (Ventana).

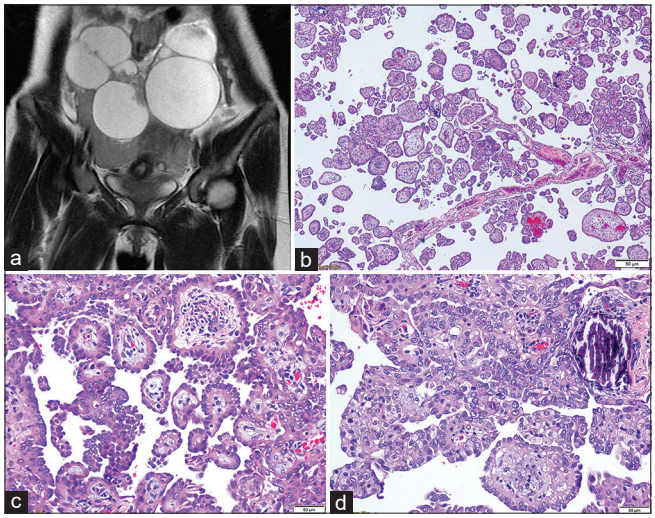



**Figure 1: (a) Malignant peritoneal mesothelioma radiological and histopathological features: magnetic resonance image (MRI) of bilateral cystic masses with some papillary projections through the cyst wall. (b) Tumor cells sharing multiple papillary projections radiating from a central fibrovascular core (H and E; ×40). (c) Higher magnification of papillary projections with mild-to-moderate nuclear atypia (H and E; ×200). (d) Psammoma body formations on the right (H and E; ×200)**

The IHC revealed that the tumor cells were positive for the mesothelial markers as WT1, calretinin, CK 5/6 as well as CK 7, whereas negative for antimesothelial markers as claudin4 and BerEp4. The tumor cells were also diffusely positive with PAX8 and focally positive with ER and PR [Figure 2]. There was wild-type p53 expression in tumor cells. Both these morphologic and IHC features led us to define a diagnosis of "epithelioid type peritoneal malignant mesothelioma." IHC BAP1 loss was not observed. She received three cycles of adjuvant paclitaxel and carboplatin therapy after cytoreductive surgery. It has been eight months since the operation had and no recurrence has been observed; the patient is still clinically and radiologically disease-free. Since *ALK* rearrangement has been shown in some rare MPM cases in recent studies, we also evaluated the *ALK* rearrangements by using different methods together.

After the viable tumor sample was deparaffinized for RNA isolation, DNA and RNA were obtained using the Qiagen AllPrep Kit isolation kit. The concentration measurement of the obtained RNA was done with the Qubit HS RNA Assay kit (178.7 ng/µl). The library was prepared for sequencing with the ArcherDx Fusion Plex CTL for Illumina kit. The library was then sequenced with the Illumina NextSeq 500 instrument using the Illumina flow cell. Sequence data were analyzed with Archer Analysis V6.2.7 and evaluated by I. Kulac and C. Mericoz. The genes targeted by the Archerr FusionPLex CTL are as follows: *AKT1*, *ALK*, *BRAF*, *CCND1*, *CTNNB1*, *DDR2*, *EGFR*, *ERBB2*, *FGFR1*, *FGFR2*, *FGFR3*, *GNAS*, *HRAS*, *IDH1*, *IDH2*, *KRAS*, *MAP2K1*, *MET*, *NRAS*, *NRG1*, *NTRK1*, *NTRK2*, *NTRK3*, *PIK3CA*, *PPARG*, *RAF1*, *RET*, *ROS1*, *THADA*. After the analysis of sequencing data, a fusion between exon 20 of the *ALK* gene and exon 3 of the *STRN* gene was detected.

Fluorescence in-situ hybridization (ZytoLight SPEC ALK Dual Color Break Apart Probe Kit; Zytovision, Bremerhaven, Germany) and IHC (D5F3 antibody; Ventana, AZ, USA) assays were applied. The tumor cells showed strong and diffuse, granular cytoplasmic staining with ALK antibody [Figure 3a]; ALK break-apart was detected in 30% of tumor cells by the Fluorescence in situ hybridization (FISH) technique [Figure 3b].

## DISCUSSION

Both MPM and LGSC are rare tumors, and no standard treatment strategy is available owing to their rarity. *ALK* translocation can be observed in various cancer types, primarily non-small cell lung cancers.[6] Discovery of *ALK* rearrangements in MPMs raises the possibility of treatment with ALK inhibitors.[7] There is a total of 16 *ALK*-rearranged MPM cases shown in the literature by molecular methods. Among these, *ALK* translocated most frequently with *STRN* (54.8%) and *TPM1 (*27.2%), *ATG16L1 (*9%), *FN1 (*9%), respectively.[4] *BAP1* alteration was detected in almost 69% of the MPM cases and also 31% of them have concomitant alterations in *PRBRM1 (*46%) and *SETD2 (*35%) with *BAP1*. However, any of them are associated with *ALK* translocation so far. The fact that the *ALK* translocation

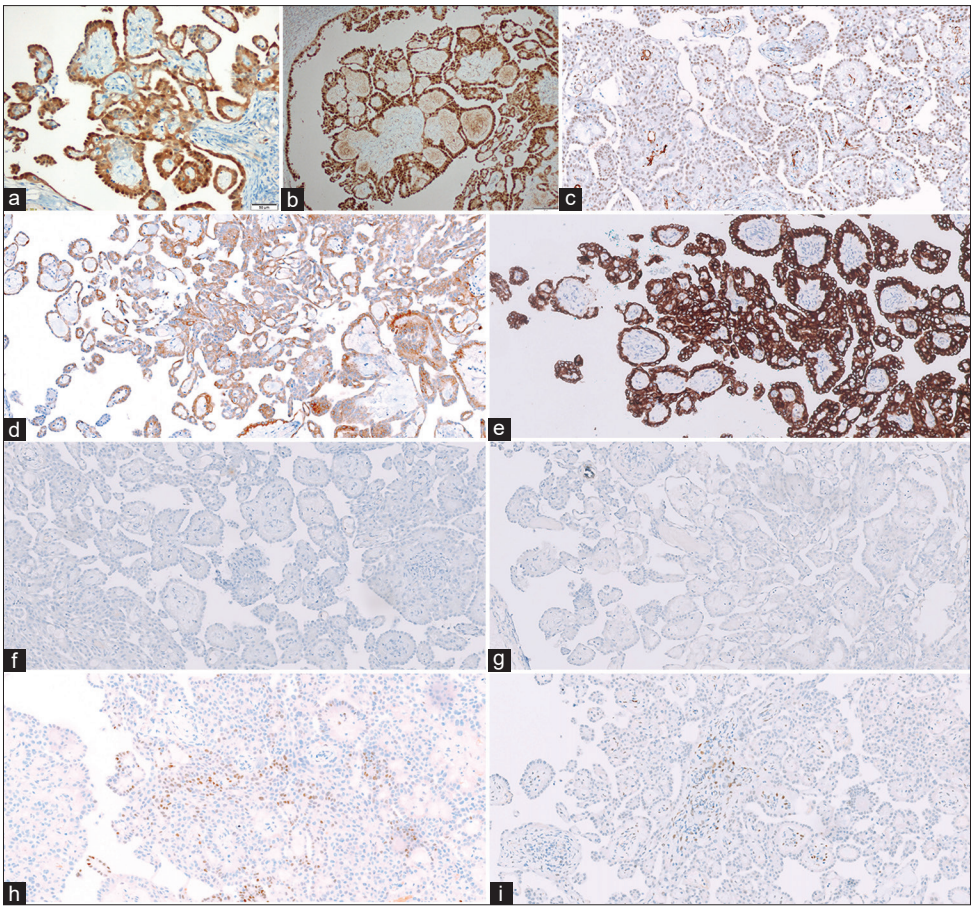



**Figure 2: Tumoral immunohistochemical staining profile (DAB; ×200). (a) Calretinin diffuse positive. (b) PAX8 diffuse nuclear positive. (c) WT1 diffuse nuclear positive. (d) CK5/6 diffuse positive. (e) CK7 diffuse positive. (f) Claudin 4 negative. (g) BerEb4 negative. (h) ER focal scattered nuclear positive. (i) PR focal scattered nuclear positive**

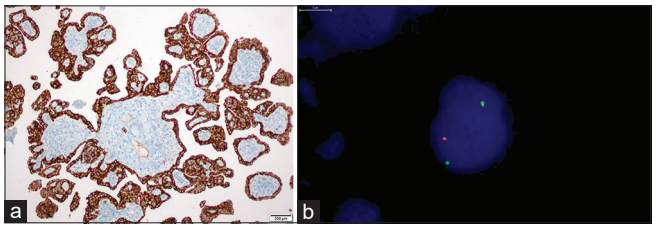



**Figure 3: (a) Diffuse strong cytoplasmic ALK immunohistochemistry positivity in tumor cells (×200). (b) ALK break-apart FISH utilizes DNA probes that hybridize to the 3′ (red signal) and 5′ (green signal) regions of the common fusion breakpoint in ALK. ALK rearrangement is identified by splitting of the red and green signals in both nuclei in this field**

accompanying *BAP1* alteration in MPMs has not been detected in the literature yet may strengthen the possibility of different pathogenetic pathways.

The main differential diagnosis of epithelioid MPM is LGSC because they present over a wide age range in women.[8] LGSC histologically exhibits a variety of patterns, including micropapillae, compact cell nests, elongated papillae, glandular, or macropapillae formations with mild-to-moderate nuclear atypia as MPMs and typically diffusely positive for cytokeratin 7 (CK7), PAX8, ER, and WT.[9] PAX8 staining in mesotheliomas is so low, however, a recent study has reported the PAX8 expression 22.5% in their MPM cohort.[10] In conclusion, here we present an unusual MPM case showing *STRN-ALK* translocation in a young female and mimicking LGSC along with diffuse PAX8 expression and overlapping histological features. Although it is rare, epithelioid malignant mesothelioma (MM) should be considered in the differential diagnosis of ovarian and peritoneal tumors of young females. To avoid misdiagnosis, extended IHC markers should be used to differentiate serous carcinomas and epithelioid MPM. Also, we would like to emphasize the importance of molecular testing for MPM, especially in young patients with no history of asbestos exposure situations, because ALK inhibitors could be a treatment option for this small subset of patients.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest
There are no conflicts of interest.

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