CASE REPORT

Malignant Peritoneal Mesothelioma With EWSR1-ATF1 Fusion: A Case Report

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ABSTRACT

Malignant mesothelioma with EWSR1-ATF1 fusion is a rare malignancy described in young adults without asbestos exposure. To the best of our knowledge, outcomes to local and systemic therapies for this subtype of malignant mesothelioma have not been described. This case report describes the clinical course of a 19-year-old man diagnosed with malignant peritoneal mesothelioma with EWSR1-ATF1 fusion localized to the abdomen. His disease followed an aggressive course and resulted in limited survival (18 mo). There was treatment resistance to several lines of conventional local and systemic treatments for peritoneal mesothelioma and biologically targeted MET inhibition with crizotinib. More research is required in this rare subtype of peritoneal mesothelioma.

Keywords: Case report; Peritoneal mesothelioma; EWSR1; ATF1

Introduction

Malignant mesothelioma is a rare and aggressive tumor of mesothelial linings including the pleura and

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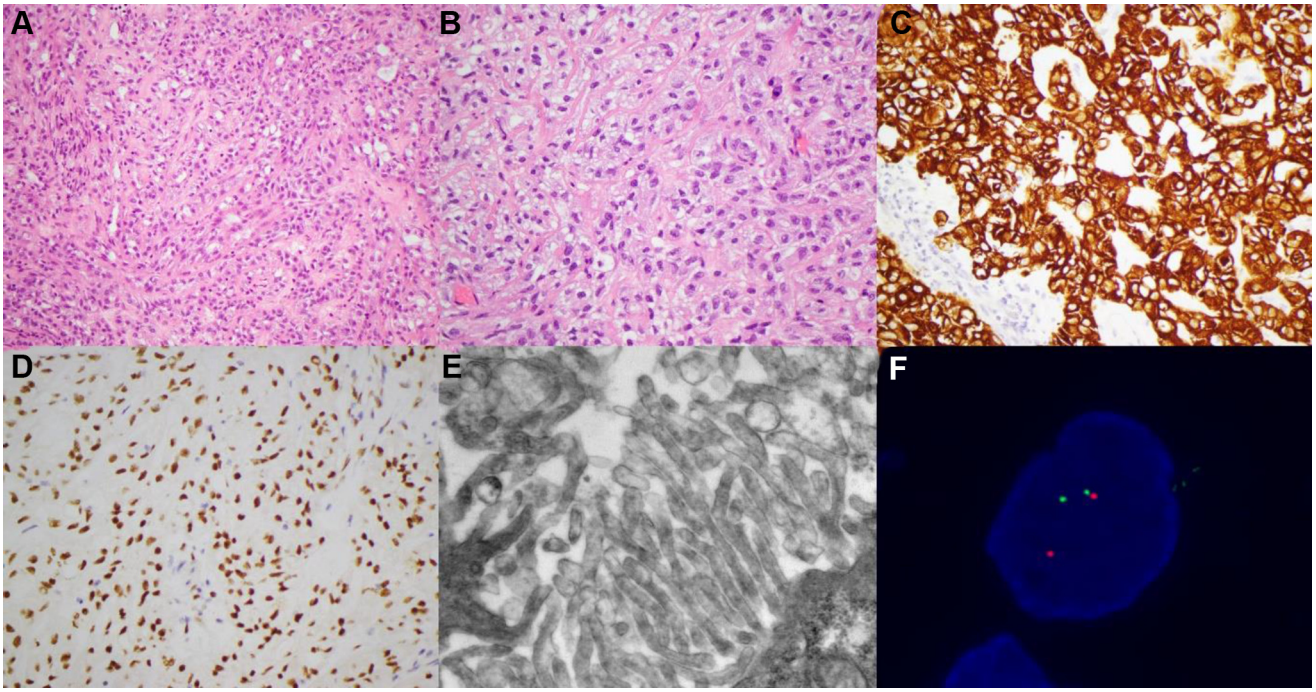

Figure 1. The tumor was characterized by a *(A)* diffuse infiltrate of malignant epithelioid cells *(B)* with a somewhat nested and glandular architecture. By immunohistochemistry, the tumor was positive *(C)* for cytokeratins, and *(D)* mesothelial markers including WT1. Electron microscopy revealed *(E)* the long slender microvilli that are typical of mesothelioma. FISH studies using an EWSR1 break-apart probe revealed a split signal indicating gene rearrangement. FISH, fluorescence in situ hybridization.

peritoneum, with a well-established causal relationship with asbestos exposure. Primary peritoneal mesothelioma accounts for 7% to 10% of all mesothelioma diagnoses. A rare subset of malignant mesothelioma associated with EWSR1 and FUS-ATF1 fusion has been identified in young adults with no known asbestos exposure.[1] Systemic treatment options available for malignant mesothelioma have been expanded by the recent inclusion of immune checkpoint inhibitors; however, the optimal treatment strategy for mesothelioma with *EWSR1* gene rearrangement has not been defined. We present a 19-year-old man with peritoneal mesothelioma exhibiting EWSR1-ATF fusion and no known asbestos exposure with substantial resistance to a range of treatment strategies. This case report details the clinical outcomes in this subset of mesothelioma.

Case Presentation

A 19-year-old male student with no known history of asbestos exposure was diagnosed with epithelioid primary peritoneal mesothelioma. Biopsies revealed a diffuse infiltrate of malignant epithelioid cells, in areas with a somewhat nested or pseudoglandular architecture (Fig. 1). By immunohistochemistry, the tumor was positive for cytokeratins (AE1/AE3, CK8/18) and mesothelial specific markers (calretinin, WT1, D2-40) but negative for epithelial markers (BerEP4, CEA). BAP1 staining was retained. Electron microscopy revealed long slender microvilli devoid of the surface glycocalyx and terminal webs, typical for mesothelioma. Fluorescence in situ hybridization studies using an EWSR1 break-apart probe revealed a split signal indicating gene rearrangement at the EWSR1 locus in keeping with a gene rearrangement.

Next-generation sequencing confirmed an EWSR1-ATF1 fusion, but no other relevant findings. Tumor mutational burden was unable to be determined.

The peritoneal cancer index at diagnostic laparoscopy was 26. Positron emission tomography scan revealed markedly increased metabolism in the omentum and peritoneum, internal mammary, and right supraclavicular fossa nodes (Fig. 2). Excisional biopsy of two right-sided supraclavicular lymph nodes favored reactive changes only.

The patient underwent a cytoreductive peritonectomy with hyperthermic intraperitoneal chemotherapy with cisplatin and mitomycin. The intraoperative peritoneal cancer index was 34. Epithelioid mesothelioma was confirmed to involve the umbilicus, right and left diaphragmatic peritoneum, spleen, and widespread omental involvement. Vascular invasion was noted. None of the 15 lymph nodes found were involved by mesothelioma. Programmed death-ligand 1 (clone SP263) stained 1% of immune cells and 1% of tumor cells (membranous staining).

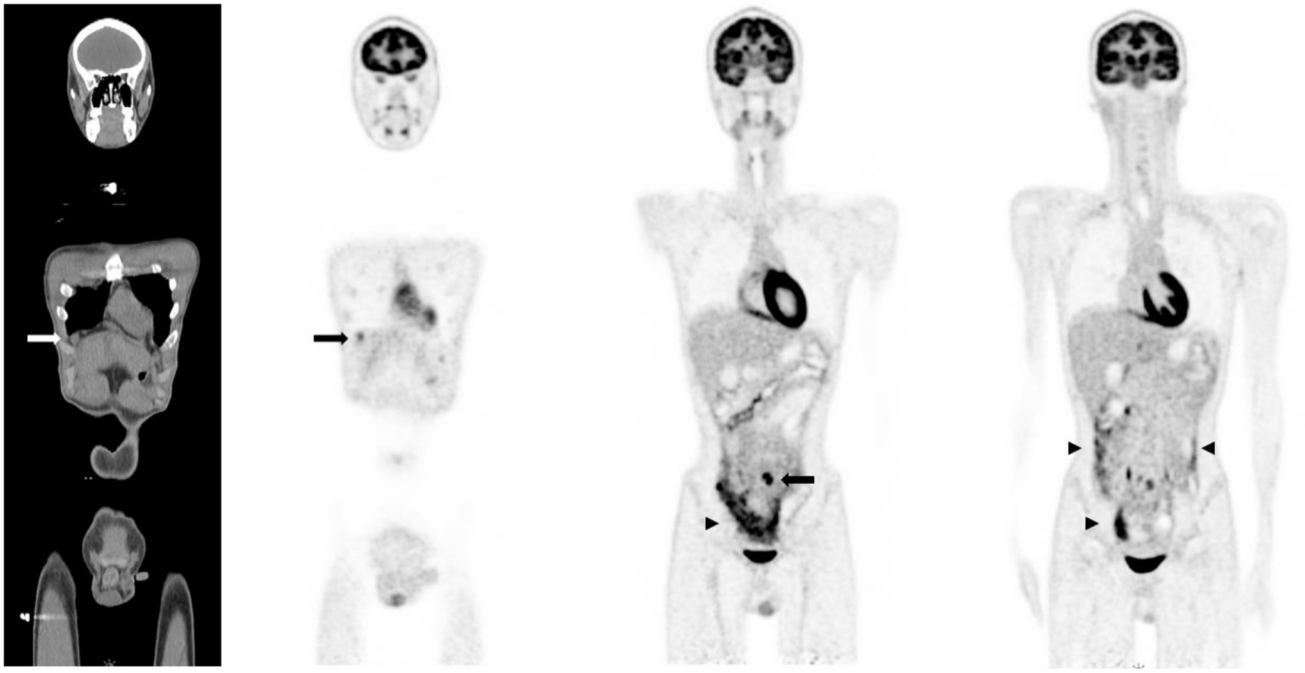

Figure 2. A coronal CT and corresponding PET image are illustrated in the left two panels; sequential anteroposterior coronal PET images are illustrated in panels 3 and 4. Long arrows reveal solid sites of disease overlying the liver (panels 1 and 2) and in the mesentery in the lower abdomen (panel 3) in which $SUV_{max} = 17.1$. Arrowheads indicate disease in the peritoneum, omentum, and over the surface of the bowel ($SUV_{max} = 10.9$). CT, computed tomography; PET, positron emission tomography; SUV_{max}, maximum standardized uptake value.

Imaging before and after adjuvant chemotherapy with platinum and pemetrexed revealed no residual disease. Unfortunately, asymptomatic peritoneal recurrence was discovered during stoma reversal 2 months after chemotherapy. Although there was no evidence of disease seen on a computed tomography scan performed at that time, within 8 weeks there was radiologic evidence of disease involving the serosal surfaces of the residual colon with accompanying gastrointestinal symptoms.

Treatment was commenced with ipilimumab 1 mg/kg every 6 weeks and nivolumab 3 mg/kg every 2 weeks. Imaging after 12 weeks confirmed further peritoneal disease progression causing hepatic duct dilatation and increased symptom burden.

The patient's individual preference was against local radiotherapy or further systemic chemotherapy. Because of reported activation of the *c-MET* gene by EWSR1-ATF1 fusions, third-line treatment with MET-inhibitor crizotinib 250 mg twice daily was commenced. Less than 2 months later, the patient was admitted with small bowel obstruction and mesenteric bleed. Active anticancer therapies were ceased. The patient died 18 months from diagnosis (10 months after recurrence).

Discussion

To the best of our knowledge, this is the first case report describing the clinical outcomes of EWSR1 rearrangement in peritoneal mesothelioma. Our case had consistent clinicopathological features with other reported cases of this very rare malignancy,[1] including young age, no asbestos exposure, and epithelioid subtype retaining BAP1 expression.

The recommended treatment for resectable malignant peritoneal mesothelioma is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy followed by adjuvant cisplatin and pemetrexed chemotherapy in high-risk disease,[2] with reported median survival between 30 and 92 months. There is also increasing interest in immune checkpoint inhibition after a trial reporting survival advantage over chemotherapy in pleural mesothelioma.[3] Unfortunately for our patient, his disease had an aggressive course with disease progression soon after chemotherapy, ipilimumab, and nivolumab, confirming little or lack of efficacy. There remains no clear guide for the role of chemotherapy or immunotherapy in patients with peritoneal mesothelioma with EWSR1-ATF1 fusion mutations.

EWSR1 has many fusion partners shared in morphologically and clinically unrelated malignancies.[4] The aberrant fusion of *EWSR1* with the cyclic adenosine monophosphate–regulated transcription factor ATF1 aberrantly activates MITF, which, in turn, activates the *c-MET* gene.[5] Although there is no specific targeted therapy for EWSR1 fusions, MET inhibitors have been proposed as biologically directed therapy. Response to crizotinib and pazopanib was reported in a patient with gastrointestinal

neuroectodermal tumor and EWSR1-CREB1 fusion.[6] Unfortunately, biologically directed therapy with crizotinib in our case did not yield a response.

It has been proposed that the partly shared genetics of EWSR1 fusions may lend sensitivity to chemotherapy regimens used for Ewing sarcoma. We found a single case report[7] of early and deep radiologic response to this chemotherapy in a patient with metastatic EWSR1-POU5F1 fusion myoepithelial carcinoma. To the best of our knowledge, there are no reports of a similar response in malignancies with an EWSR1-ATF1 fusion.

Conclusions

Primary peritoneal mesothelioma with EWSR1-ATF1 fusion is a very rare malignancy. Our case of a young patient with this malignancy highlights treatment resistance to standard chemotherapy, ipilimumab and nivolumab, and crizotinib, resulting in limited survival (18 mo). There are no known treatments currently available that target this driver mutation. More research is required in this rare subtype of peritoneal mesothelioma.

CRediT Authorship Contribution Statement

Helen Ke: Writing - original draft.

Anthony J. Gill: **Michael Fulham**: Writing - review & editing; Visualization.

Catriona McKenzie, James G. Kench, Renee C.F. Chan, **Nick Pavlakis**, **Cherry Koh**: Writing - review & editing.

Steven Kao: Writing - review & editing; Supervision.

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