case reports

Metastatic Malignant Perivascular Epithelioid Cell Tumors With Microsatellite Instability Within Lynch Syndrome Successfully Treated With Anti-PD1 Pembrolizumab

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INTRODUCTION

Soft tissue sarcomas (STSs) consist in a highly heterogeneous group of malignancies of mesenchymal origin primarily classified according to their line of differentiation.[1] Among them, perivascular epithelioid cell tumors, also known as perivascular epithelioid cell tumors (PEComa), is a recognized entity composed of mesenchymal tumor cells of epithelioid or fusiform morphology expressing smooth muscle and melanocytic markers.[2] PEComa belong to the heterogeneous group of ultra rare STSs, with an estimated incidence of approximately 0.3 per 1,000,000.[3,4] PEComa include a variety of histologies with different behaviors (from benign tumors to high-grade malignant sarcomas), including for example angiomyolipoma, lymphangioleiomyomatosis, abdominopelvic sarcoma with perivascular epithelioid cells, and other rare tumor subtypes.[5] Over the past decades, advances in the molecular dismantlement of mesenchymal tumors have led to the identification of two main molecular subclasses of PEComa. Recurrent inactivating mutations and loss of heterozygosity of *TSC1*/*TSC2* genes have been identified in up to 60% of PEComa,[6-8] and PEComa can develop in the context of hereditary tuberous sclerosis complex syndrome that results from germline pathogenic variation of those genes.[9] Inactivation of *TSC1*/*TSC2* leads to increase mammalian target of rapamycin (mTOR) signaling pathway and ultimately to cell proliferation and tumor development,[10] which is the rationale for the activity of mTOR inhibitors in advanced PEComa.[11,12] In patients lacking *TSC1*/*TSC2* inactivation, recurrent *TFE3* rearrangements have been described involving various fusion partners.[13,14] The prognostic impact of these mutually exclusive alterations remains unknown.[15] Apart from *TSC1*/*TSC2* mutations and *TFE3* fusions, other rare molecular alterations have been described in individual patients and small series; however, their prevalence and oncogenic role in PEComa development remains to be determined.[16]

In this report, we describe for the first time the case of a 50-year-old patient with Lynch syndrome who was diagnosed with metastatic malignant PEComa and successfully treated with anti-PD1 pembrolizumab.

CASE PRESENTATION

A 50-year-old man referred to our institution for suspicion of metastatic sarcoma.

His personal medical history included a right hemicolectomy 10 years before for colon adenocarcinoma. His familial history included localized colon adenocarcinoma in his father and in his paternal grandmother and localized endometrial carcinoma in a paternal aunt. All familial tumors had developed in the context of a Lynch syndrome confirmed by a germline heterozygous deletion of exons 4-5 of *MLH1* identified in the patient as well as in his paternal branch. After treatment of his colon carcinoma, the patient had undergone regular colonoscopy surveillance without sign of relapse or new colorectal malignancy.

He presented to our institution with rapid altered performance status, thoracic pain, dyspnea, and gastroesophageal reflux. Chest x-ray and computed tomography (CT) scan revealed a 7-cm large solid mass centered on the right superior and apical bronchi with apical lung segment atelectasis, compressing the superior vena cava and encasing the upper right pulmonary artery (Figs 1A and 1B). Abdominal CT scan identified a 2-cm large hypodense solid nodule within the pancreatic body (Fig 1C). 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography CT showed significant uptake in both thoracic and pancreatic lesions (Fig 1D) without other distant metastases.

Thoracic and pancreatic biopsies were performed during bronchoscopy and pancreatic echoendoscopy,

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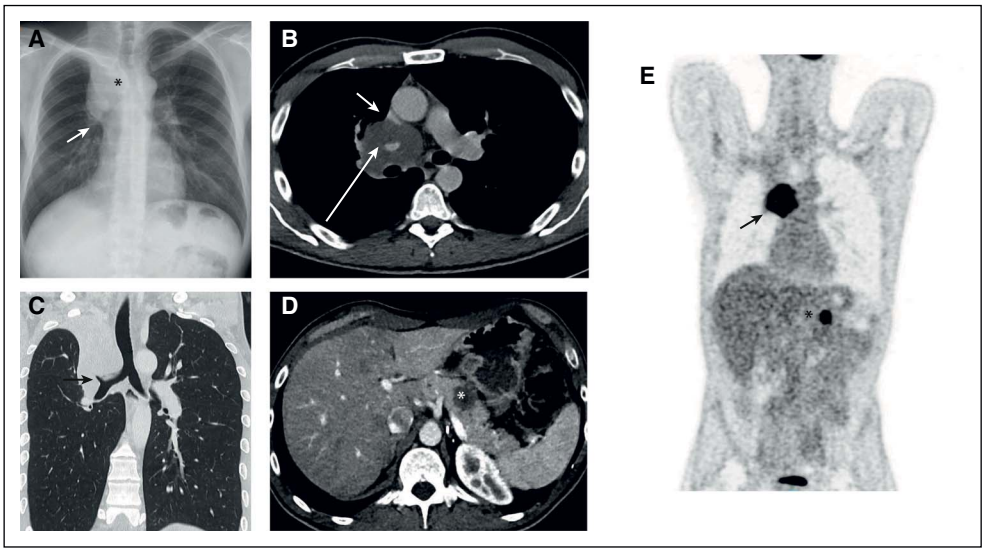


FIG 1. Imaging features at diagnosis. (A) Chest x-ray at diagnosis showing a right hilar and mediastinal enlargement (white arrow) with tracheal deviation (black star). (B and C) Chest CT after iodine contrast showing a solid mass (33/50 precontrast and postcontrast HU) centered on the right superior and apical bronchi (black arrow), compressing the superior vena cava (short white arrow) and encasing of the upper right pulmonary artery (long white arrow). (D) Abdominal CT (arterial phase) showing a hypodense (33/58 precontrast and postcontrast HU) solid nodule within the pancreatic body (white star). (E) 18F-FDG positron emission tomography showing significant uptake of both thoracic (black arrow) and pancreatic (white star) lesions (SUVmax 12 and 15, respectively). CT, computed tomography; HU, Hounsfield Unit; SUVmax, maximum standard unit value; 18F-FDG, 18F-fluorodeoxyglucose.

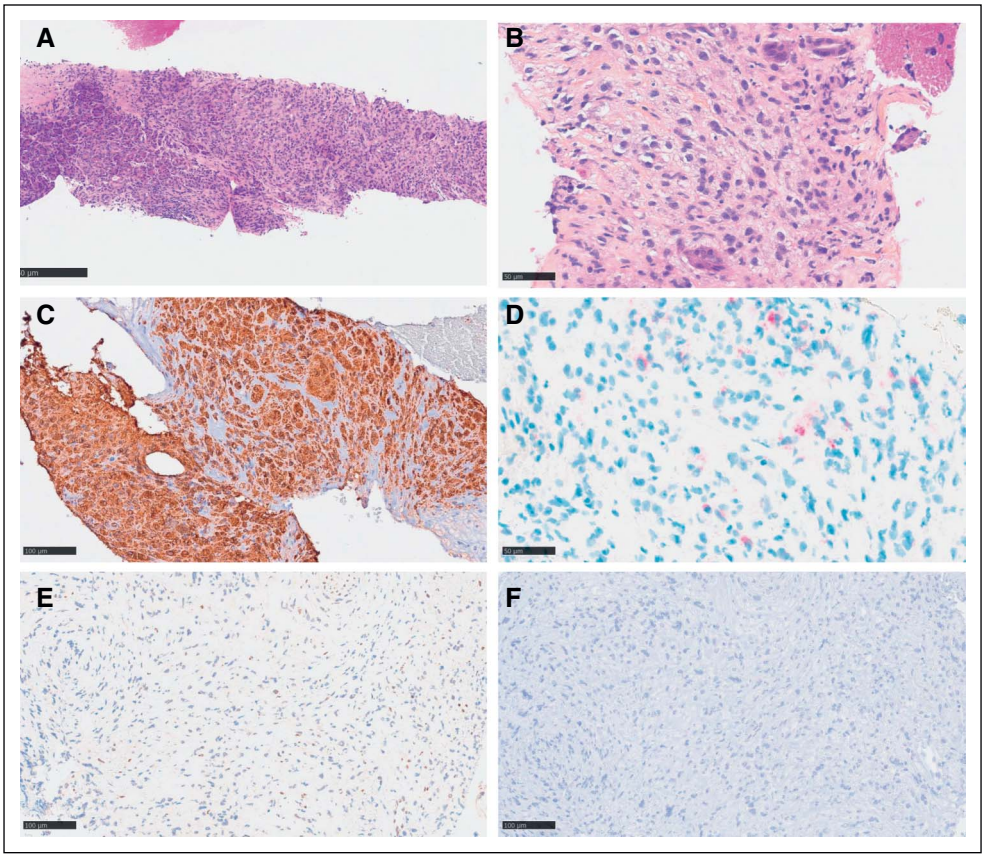
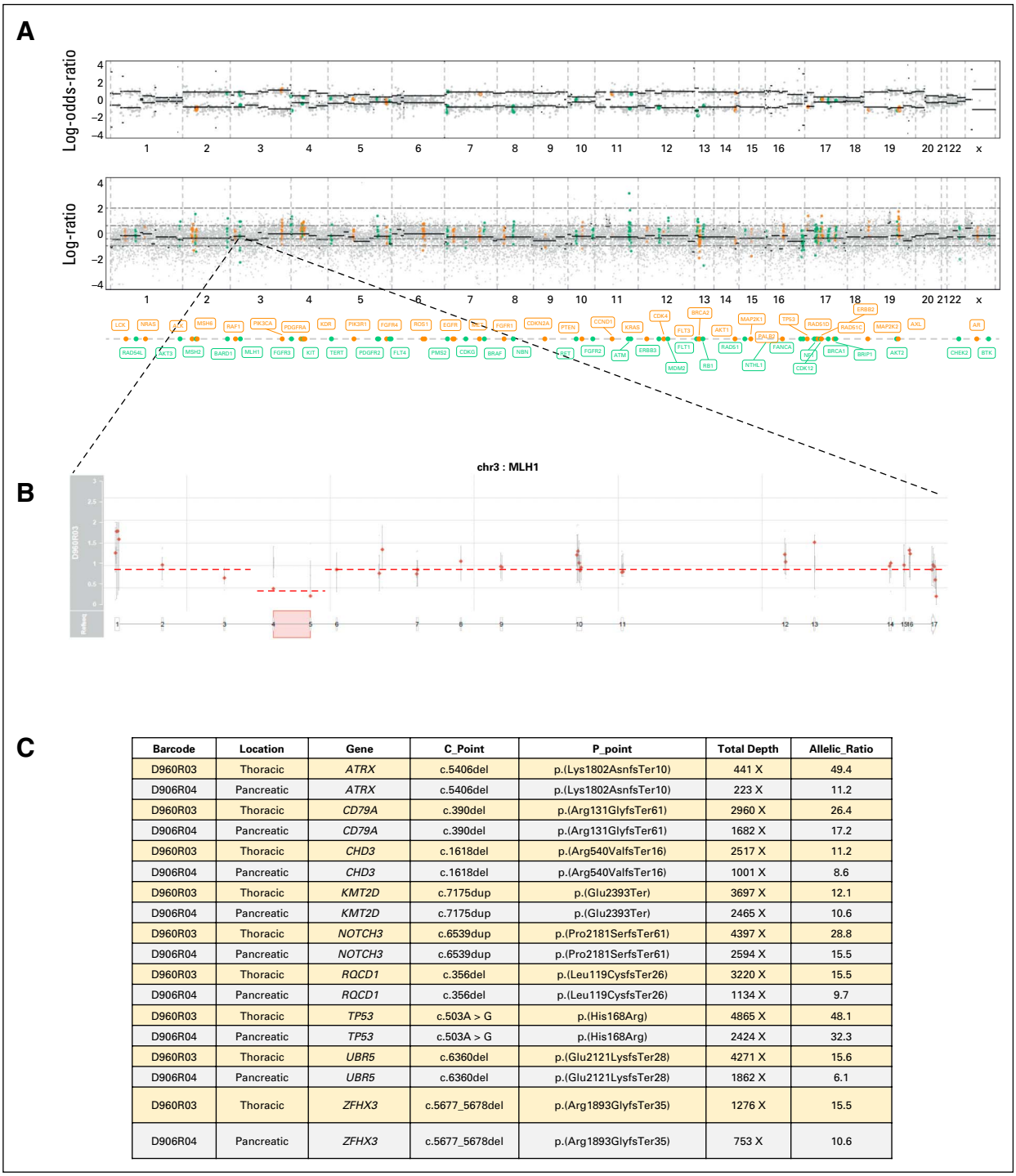


FIG 2. Pathological presentation. (A) H&E staining on the pancreatic biopsy showing sheets and nests of tumor cells infiltrating the pancreatic parenchyma, with foci of tumor necrosis. (B) Noncohesive epithelioid cells with moderate atypia and clear to eosinophilic cytoplasm. (C) By immunohistochemistry, tumor cells showed diffuse and intense expression of SMA. (D) HMB 45 was focally expressed in a minority of tumor cells. (E and F) Subtotal loss of MLH1 expression (E) and total loss of PMS2 expression (F) in tumor cells. H&E, hematoxylin and eosin; SMA, sequential multiple analysis.



Barcode	Location	Gene	C_Point	P_point	Total Depth	Allelic_Ratio
D960R03	Thoracic	*ATRX*	c.5406del	p.(Lys1802AsnfsTer10)	441 X	49.4
D906R04	Pancreatic	*ATRX*	c.5406del	p.(Lys1802AsnfsTer10)	223 X	11.2
D960R03	Thoracic	*CD79A*	c.390del	p.(Arg131GlyfsTer61)	2960 X	26.4
D906R04	Pancreatic	*CD79A*	c.390del	p.(Arg131GlyfsTer61)	1682 X	17.2
D960R03	Thoracic	*CHD3*	c.1618del	p.(Arg540ValfsTer16)	2517 X	11.2
D906R04	Pancreatic	*CHD3*	c.1618del	p.(Arg540ValfsTer16)	1001 X	8.6
D960R03	Thoracic	*KMT2D*	c.7175dup	p.(Glu2393Ter)	3697 X	12.1
D906R04	Pancreatic	*KMT2D*	c.7175dup	p.(Glu2393Ter)	2465 X	10.6
D960R03	Thoracic	*NOTCH3*	c.6539dup	p.(Pro2181SerfsTer61)	4397 X	28.8
D906R04	Pancreatic	*NOTCH3*	c.6539dup	p.(Pro2181SerfsTer61)	2594 X	15.5
D960R03	Thoracic	*RQCD1*	c.356del	p.(Leu119CysfsTer26)	3220 X	15.5
D906R04	Pancreatic	*RQCD1*	c.356del	p.(Leu119CysfsTer26)	1134 X	9.7
D960R03	Thoracic	*TP53*	c.503A > G	p.(His168Arg)	4865 X	48.1
D906R04	Pancreatic	*TP53*	c.503A > G	p.(His168Arg)	2424 X	32.3
D960R03	Thoracic	*UBR5*	c.6360del	p.(Glu2121LysfsTer28)	4271 X	15.6
D906R04	Pancreatic	*UBR5*	c.6360del	p.(Glu2121LysfsTer28)	1862 X	6.1
D960R03	Thoracic	*ZFHX3*	c.5677_5678del	p.(Arg1893GlyfsTer35)	1276 X	15.5
D906R04	Pancreatic	*ZFHX3*	c.5677_5678del	p.(Arg1893GlyfsTer35)	753 X	10.6

FIG 3. Molecular characterization. (A) The whole-genome copy number (lower profile) and allelic profile (upper profile) assessed by panel sequencing show many losses of heterozygosity including the locus of *MLH1* at chromosome 3p22. (B) Zoom of the *MLH1* gene showing the homozygous deletion of exon 4 to 5 (enclosed in red). (C) Nucleotidic variants of both thoracic and pancreatic tumors, sequenced by our panel exhibit a lot of indels in homopolymeric sequences and a pathogenic mutation of *TP53*. All variants presented in the table are found in both tumors, which enables to establish a clear filiation between the pancreatic and the thoracic lesions.

respectively. Both biopsy specimens demonstrated a similar infiltrating tumoral proliferation of mainly epithelioid cells, arranged in nests or sheets (Fig 2A). Tumor cells showed irregular nuclei with moderate anisocaryosis. Mitotic activity was evaluated at 4 mitoses/10 HPF in the pancreatic tumor. The cytoplasms were eosinophilic or clear in places, with indistinct limits (Fig 2B). The stroma was rare, fibrous or myxoid, with mild to moderate

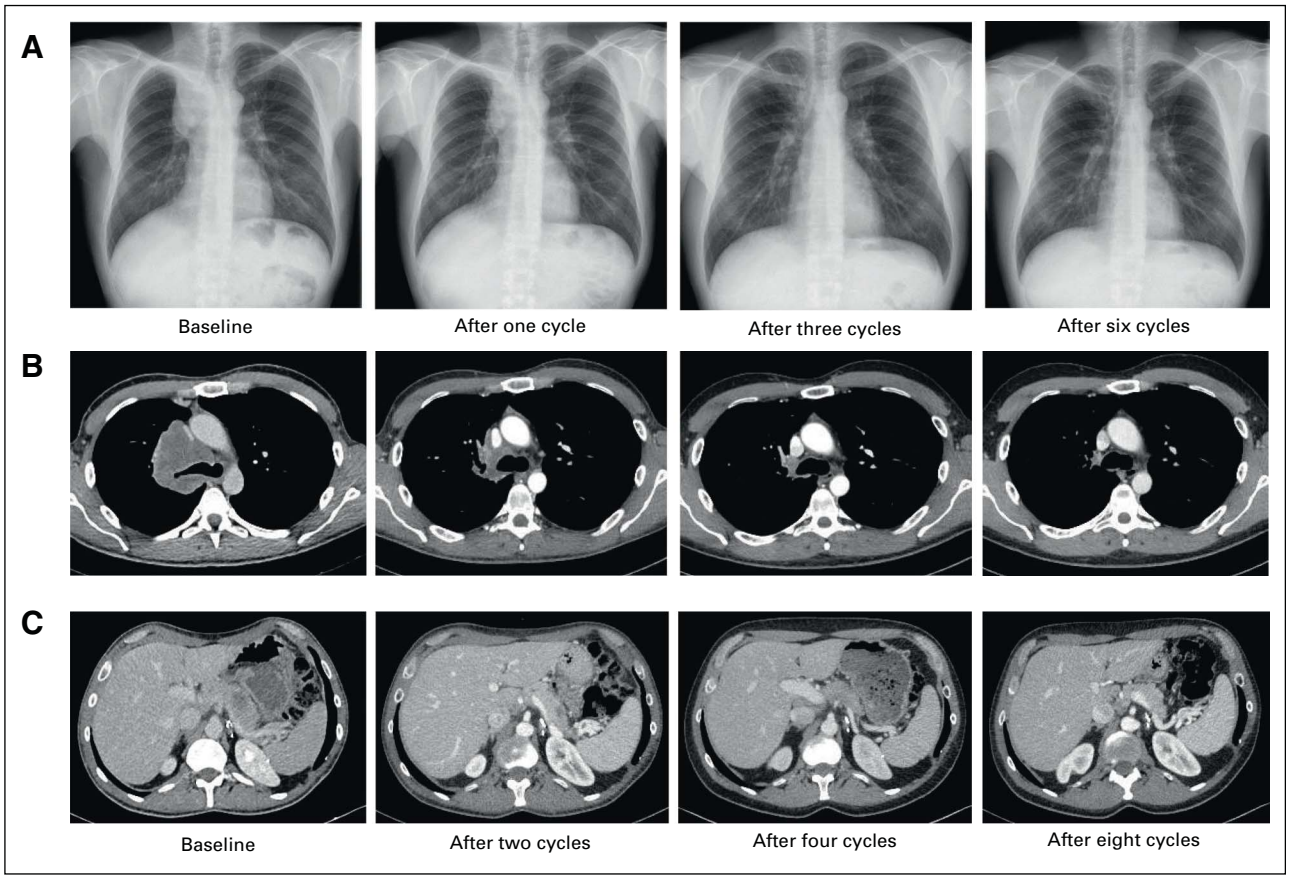


FIG 4. Response to pembrolizumab. (A) Chest x-ray at baseline and after one, three, and six cycles of pembrolizumab showing the rapid regression of the right apical mass and the disappearance of tracheal deviation under treatment. (B and C) Thoracic and abdominal CT at baseline and after two, four, and eight cycles of pembrolizumab. Major partial response was observed after only two cycles, and complete response was observed after eight cycles. CT, computed tomography.

lymphocytic infiltration, without evidence of mature tertiary lymphoid structures. Areas of tumor necrosis were present. In immunohistochemistry, tumor cells showed diffuse and intense expression of SMA, and HBM45 was focally expressed in a minority of tumor cells (Figs 2C and 2D). There was no expression of Melan-A, TFE3, desmin, caldesmon, MyoD1, S100, SOX10, CKAE1/AE3, CK8/18, PAX8, CDX2, CD45, CD138, CD23, SALL4, CD117, DOG1, CD34, ERG, MDM2, ALK, nor ROS1, and INI1 and BRG1 expression was conserved. KI67 was 40%. There was no expression of PD-L1 (QR1 clone). The lymphocytes were mainly T phenotype CD20– CD5+ CD3+. The microscopic and immunohistochemical profiles oriented toward the diagnosis of malignant PEComa. Tumor cells showed subtotal loss of MLH1 expression (> 95% unlabeled tumor cells) and total loss of PMS2 expression (Figs 2E and 2F), in favor of a Lynch syndrome–associated malignancy.

A large next-generation sequencing (NGS) DNA panel was performed on both bronchial and pancreatic lesions to better characterize this unusual tumor. This panel enables the detection of genomic variants in more than 500 genes involved in oncogenesis, copy number variations, tumor mutation burden, and microsatellites status. NGS analyses on both biopsies revealed a microsatellite instability-high (MSI-H), associated with multiple Insdel variations, and a pathogenic c.503A>G/p.(His168Arg) *TP53* mutation. The known deletion of exon 4-5 of *MLH1* was associated to a loss of heterozygosity of the gene on chromosome 3, leading to its complete inactivation in tumor cells (Figs 3A and 3B). There was no pathogenic alteration on *TSC1*, *TSC2*, or *PI3KCA* genes. The tumor mutation burden was slightly elevated (21.4 mutations/Mb). The comparative analysis of the pancreatic and bronchial tumors showed the same genomic alterations and enabled to establish a clear filiation between both tumors (Fig 3C).

The gold standard treatment for metastatic malignant PEComa usually relies on mTOR inhibitors. However, because of the absence of pathogenic *TSC1*/*TSC2* alteration and to the MSI-H status in the tumor, the choice was made to start anti-PD1 pembrolizumab (200 mg flat dose on day 1, every 3 weeks). The administration of the treatment was validated after multidisciplinary tumor board review. The treatment was funded by the institution. The patient was informed, agreed to receive pembrolizumab, and provided written consent for pathological analyses, NGS analyses, and participation to this manuscript. After only one dose of

pembrolizumab, the performance status of the patient dramatically increased, with a complete disappearance of thoracic pain, dyspnea, and fatigue. Follow-up imaging confirmed the significant regression of both thoracic and pancreatic lesions after two cycles, and complete response according to RECIST 1.1 criteria was seen after eight cycles of pembrolizumab (Figs 4A-4C). Pembrolizumab was well-tolerated with no significant adverse event and was maintained for a planned duration of treatment of 2 years. At the time of this report, the patient has been treated with pembrolizumab for 1 year, without any evidence of tumor progression. The consent for publication was obtained.

DISCUSSION

Over the past decade, MSI-H or mismatch-repair deficiency (MMRD) status has become one of the most successful biomarkers to predict efficacy of immune checkpoint inhibitors (ICIs) in both advanced and localized cancers, independent of tumor's origin.[17-20]

MMRD in STSs has been the matter of several studies, with the largest and most contemporary series evaluating its prevalence between 1% and 2%.[21,22] In these studies, the most frequent histological subtypes with MMRD were undifferentiated sarcomas and leiomyosarcomas, and MMRD most of the time resulted from deleterious mutations in *MLH1* or *MSH2* genes. The exact prevalence of germline MMR mutations in patients with MSI-H STSs remains unknown, mainly because of the rarity of the diseases and the heterogeneity of histological subtypes. STS developing within Lynch syndrome is exceedingly rare but have been reported in case reports and small series, particularly in patients with *MSH2* germline mutations,[23-26] and it is now acknowledged that STSs belong to the spectrum of rare histological subtypes that can arise within this syndrome.

Data concerning the response of advanced MMRD STSs to ICI remain scarce. The KEYNOTE-158 study evaluating the efficacy of pembroluzimab in patients with MSI-H/MMRD cancers of various origins enrolled 14 patients with sarcomas. Among them, 12 could be evaluated for tumor response, with one complete response, three partial responses, six stable diseases, and two progressive diseases.[27] Other small series or case reports have also reported heterogeneous responses to ICI in MSI-H/MMRD STSs[21,28]; however, these series did not include patients with known Lynch syndrome. Whether germline predisposition or specific histological subtypes are associated with increased efficacy of ICI in patients with MSI-H/MMRD STSs will require further investigation and larger cohorts. However, our case report suggests that ICI should be considered as frontline therapeutic option for these rare patients.

In conclusion, we report here the first case of a patient with metastatic malignant PEComa developed within Lynch syndrome who showed complete response to anti-PD1 pembrolizumab. This report increases the data on ICI in patients with MSI-H/MMRD STSs and highlights the need to constitute prospective cohorts of these patients to better determine their optimal therapeutic management.

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DATA SHARING STATEMENT

All data and material used in this case reports have been included in this manuscript.

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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: Nanobiotix
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