

Case Report

Ipilimumab and Pembrolizumab Mixed Response in a 41-Year-Old Patient with SMARCA4-Deficient Thoracic Sarcoma: An Interdisciplinary Case Study

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Keywords

SMARCA4 · SMARCA4-deficient thoracic sarcoma · Pembrolizumab · Ipilimumab · Checkpoint inhibitor

Abstract

SMARCA4-deficient thoracic sarcoma is a newly described entity of thoracic sarcomas with a poor prognosis, defined by poorly differentiated epithelioid to rhabdoid histomorphology and SMARCA4 gene inactivation. We present a case of a SMARCA4-deficient thoracic sarcoma in a 41-year-old male with a smoking history who presented with an upper anterior mediastinal mass, after seeking medical evaluation for increasing thoracic pain, odynophagia, and dizziness. The biopsy confirmed a large cell tumor with an epithelioid to rhabdoid histomorphology, positive for EMA, CD99, vimentin, TLE1, INI1, PAS-positive cytoplasmic granules, and PD-L1 (100% of tumor cells). High TMB and HRD scores were displayed in the tumor. The histology and immunophenotype of the mass were in line with the diagnosis of SMARCA4-deficient thoracic sarcoma. In the course of his treatment, the patient showcased a partial response to pembrolizumab and the combination of pembrolizumab and ipilimumab. This case report highlights the importance of recognizing SMARCA4-deficient thoracic sarcoma as an individual entity and supports the importance of checkpoint inhibition therapy for SMARCA4-deficient thoracic sarcomas, particularly in cases with a high TMB and PD-L1 expression.

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Introduction

SMARCA4 (Switch/sucrose-nonfermenting related [SWI/SNF], matrix associated, actin dependent regulator of chromatin, subfamily a, member 4)-deficient thoracic sarcoma, an aggressive and rare malignancy that presents with rapidly progressive masses involving the lung, mediastinum, and pleura, is a newly proposed histomorphological and molecular entity that was initially described by Sauter et al. [1]. It predominantly affects males with a median age of 48 with a history of smoking. The prognosis is poor, with a median survival of 6–7 months; direct comparison with prognostic data of thymic carcinoma patients reveals a considerably shorter 2-year survival rate (12.5 vs. 64.4%) [1–5]. Since then several case studies reporting this entity have been described in the literature [1, 6–9].

Histologically, the tumors consist of poorly differentiated epithelioid to rhabdoid cells with high mitotic rates, and present an immunohistochemical loss of the proteins BRG1 (Brahma-related gene-1; the protein encoded by the *SMARCA4* gene) and BRM (Brahma), with an intact expression of INI-1 (integrase interactor 1) [2, 4, 10].

BRG1, BRM, and INI-1 are subunits of the SWI/SNF chromatin remodeling complex. SWI/SNF plays an important role in transcription, replication, DNA repair and recombination, regulation of gene expression, and cell cycle regulation [10]. Due to its direct influence on chromatin accessibility and remodeling, both inactivation as well as overexpression of SWI/SNF subunits may have carcinogenic potential [10]. BRG1 and BRM are encoded by the genes *SMARCA4* and *SMARCA2* [4]. Inactivation of *SMARCA4* as well as *SMARCA2* co-deficiency are characteristic for the tumor profile of *SMARCA4*-deficient thoracic sarcoma [4]. Generally, mutations in SWI/SNF subunits or associated proteins have been found to be present in approximately 20% of all human cancers, among them non-small cell lung cancer (NSCLC), medulloblastoma, Burkitt's lymphoma, small cell ovarian carcinoma, hypercalcemic type (SCCOHT), dedifferentiated endometrial carcinoma, sinonasal undifferentiated carcinoma, pediatric rhabdoid tumors, and other cancers [4, 10, 11]. *SMARCA4* mutations specifically have also been found in cases of thymic carcinoma, NSCLC, and SCCOHT [3, 12–14].

Interdisciplinary Case Presentation

Initial Presentation and Diagnostics

A 41-year-old man was admitted to our hospital in June 2018 with increasingly worsening thoracic pain, odynophagia, and dizziness that had been lasting for a week. Lab results showed elevated lactate dehydrogenase (408 U/L) and increased CRP (19.7 mg/L). Computerized tomography (CT) of the thorax and abdomen and a consecutive positron emission tomography/CT-fusion (PET/CT) revealed a mass of conglomerated lymph nodes, measuring 5.7 × 12 × 10 cm in the upper anterior mediastinum encompassing infracarinal and hilar lymph nodes, encasing supra-aortic vessels leading to compression of the innominate vein and superior vena cava (Fig. 1).

Subsequently performed lymph node biopsy displayed a monomorphic large cell tumor with an epithelioid to rhabdoid morphology (Fig. 2). Immunohistochemical analyses excluded germ-cell tumor, lymphoma, melanoma, mesothelioma, histiocytic sarcoma, myeloid sarcoma, angiosarcoma, rhabdoid tumor, epithelioid sarcoma, nitrogen regulatory protein 1 (NUT)-positive carcinoma, anaplastic lymphoma kinase (ALK)-rearranged malignoma, rhabdomyosarcoma, and mast cell sarcoma. The tumor showed positivity for epithelial membrane antigen (EMA), CD99, vimentin, transducing-like enhancer of split 1 (TLE1), and INI1, and periodic acid Schiff (PAS)-positive cytoplasmic granules. Programmed death-ligand 1 (PD-L1) staining revealed positivity in 100% of tumor cells (Fig. 2). The tumor presented with considerably high tumor mutation burden (TMB) (674 single nucleotide variants [SNV] and 47 indels) and homologous recombination deficiency (HRD) scores (loss of heterozygosity [LOH])

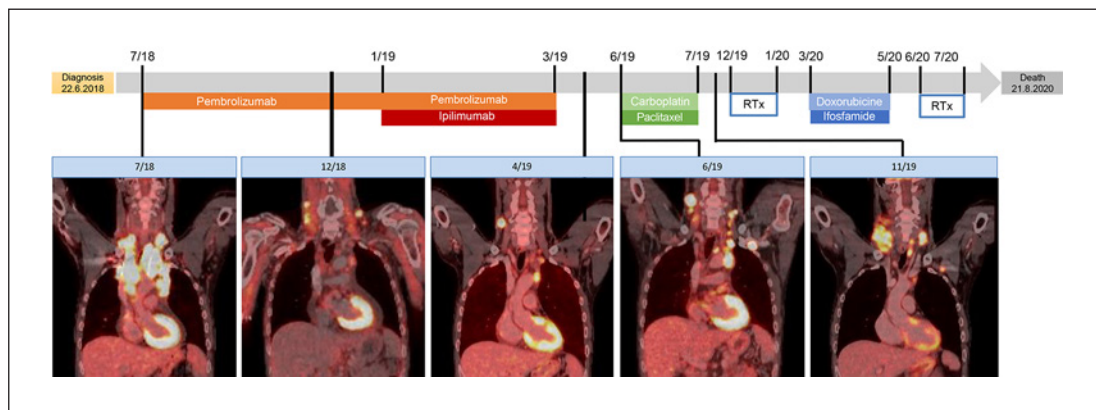


Fig. 1. Treatment timeline and therapeutic response PET-CT follow-ups in a patient with SMARCA4-deficient thoracic sarcoma. Pembrolizumab monotherapy as well as pembrolizumab and ipilimumab combination generated a mixed response (see PET-CT 12/18 and 4/19, respectively). Follow-up from June 2019 onwards showed signs of progressive disease in mediastinal and cervical lymph nodes despite receipt of chemotherapy and radiotherapy. See main text for individual regimens.

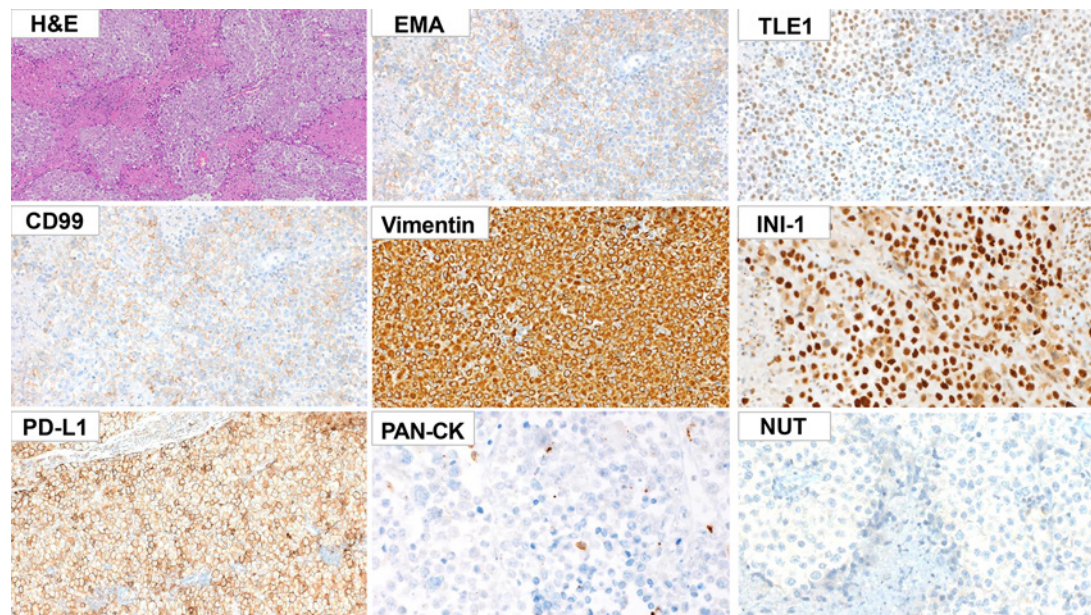


Fig. 2. Microscopic findings of SMARCA4-deficient thoracic sarcoma. Monomorphic, poorly differentiated, large cell tumor with an epithelioid to rhabdoid morphology, strongly positive for EMA, TLE1, CD99, vimentin, INI-1, and focally positive for PAN-CK. PD-L1 was found to be expressed in 100% of tumor cells. The stain for (I) NUT was negative, excluding NUT carcinoma. Magnification, $\times 100$ for H&E, EMA, TLE1, CD99, PD-L1, and vimentin; magnification, $\times 200$ for INI-1, PAN-CK, and NUT.

of 20, telomeric-allelic imbalance [TAI] of 22, and large-scale state transitions [LST] of 11). Subsequently performed massive parallel sequencing utilizing the OncoPrint™ Comprehensive Panel Version 3 revealed pathogenic terminating (deleterious) frameshift mutations in *Cyclin Dependent Kinase Inhibitor 2A* (*CDKN2A*) (p.T18fs) and *SMARCA4* (p.K1334fs).

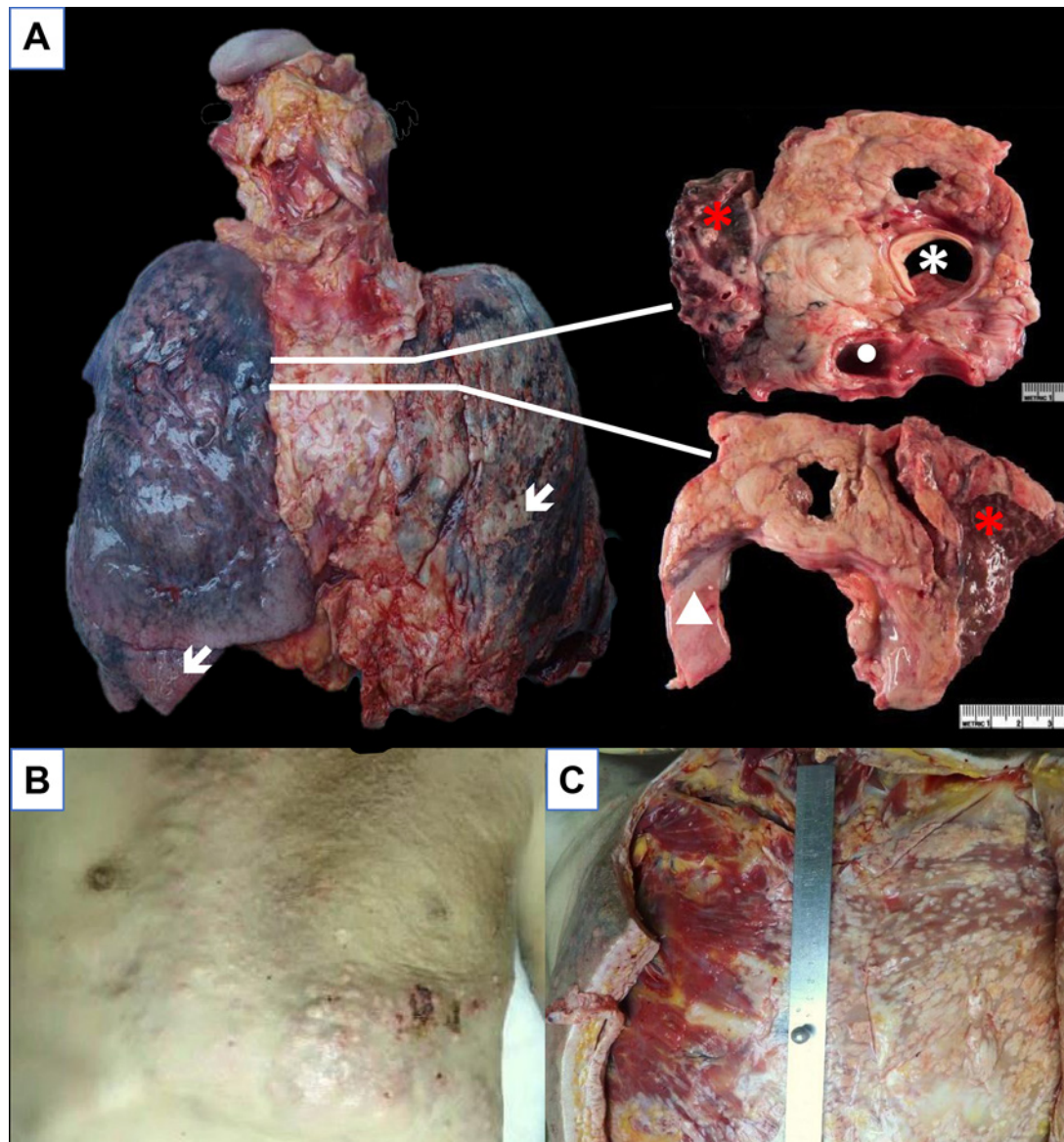


Fig. 3. Gross findings of SMARCA4-deficient thoracic sarcoma at autopsy. **A** Primary tumor mass (20 × 10 × 7 cm) in the anterior mediastinum, with diffuse pericardial infiltration (white triangle), per-continuitatem involvement of the left bronchus (white circle) and pulmonary trunk (white asterisk), and diffuse infiltration into the lung parenchyma (red asterisk). Bilateral pleural metastases (white arrows), left > right. **B, C** Widespread miliar cutaneous and subcutaneous metastases encompassing pectoral muscles of the chest.

Therapeutic Measures and Follow-Up

Figure 1 provides an overview of the therapeutic timeline. In line with the positive PD-L1 status, the patient received 8 cycles of pembrolizumab 200 mg (absolute) and showed a mixed response, with disease progression in cervical lymph nodes and regression in mediastinal lymph nodes. He proceeded to receive 4 cycles of pembrolizumab 200 mg (absolute) and ipilimumab 1 mg/kg of body weight, which similarly showed a mixed response with progression of the supraclavicular lymph node metastasis and persisting disease in the mediastinal lymph nodes. Three months after receipt of checkpoint inhibitor therapy, palliative

chemotherapy with 2 cycles of carboplatin AUC and 6 paclitaxel 175 mg/m², q3 was initiated. Five months later, the patient received palliative radiotherapy for painful lymph node metastases of the cervical and paraclavicular region bilaterally with 18 × 2.66 Gy. Due to a significant increase in lymph node swelling (tumor progression vs. pseudo-progression), the treatment volume was expanded after 4 fractions. This was followed by palliative chemotherapy with 6 cycles of doxorubicin 75 mg/m², d1, ifosfamide 1,500 mg/m², d1-5, and G-CSF d7, q3 and a second series of palliative radiotherapy (18 × 2.66 Gy) for pain relief. Following that, the treatment volume was expanded after 6 fractions due to increased swelling.

In August 2020, the patient presented with progressive dyspnea, flank pain, and edema of the left arm and ankles. Bronchoalveolar lavage (BAL) excluded an infectious etiology. The patient subsequently developed progressively worsening renal and respiratory failure and died in August 2020.

Autopsy Findings

An autopsy was performed, revealing a partly necrotic white mass, measuring 20 × 10 × 7 cm in the anterior mediastinum, with diffuse pericardial infiltration and per-continuitatem immurement of the left bronchus and pulmonary trunk (Fig. 3a). Metastases were found in cervical, hilar, aortic arch, infrarenal para-aortic, and right retroperitoneal lymph nodes. Pleural carcinomatosis and malignant pleural effusion, in lieu with lymphangiosis carcinomatosa of the pulmonary parenchyma with a few interstitial metastases were present bilaterally. Subcutaneous tubercular metastases of the skin were present on the left side of the neck, chest (55 × 30 cm), and left arm with accompanying lymphedema and diffuse infestation of the left pectoral muscle (Fig. 3b–c). Distant metastases included infiltration of the right renal hilus, both adrenal glands, the greater omentum, and jejunal mesothelium.

Discussion

The patient was a 41-year-old man with a history of smoking and a survival time of 2 years after initial diagnosis, in compliance with the typical epidemiology of *SMARCA4*-deficient thoracic sarcoma [1, 4]. Along with the *SMARCA4* mutation, the rhabdoid morphology as well as immunohistochemical profile of the described tumor corresponded to observations from previously conducted studies, histomorphologically and molecularly setting this subgroup apart from non-sarcomatoid *SMARCA4*-deficient NSCLC. Previously conducted immunohistochemical profiles of thoracic sarcomas demonstrate similarities with our case, particularly in the absence of BRG1 and NUT and positivity for EMA, vimentin, and CD99 [9, 15].

The diagnosis of thoracic sarcomas often poses a challenge, typically warranting high expertise. Recent years have witnessed an increased utilization of next-generation sequencing assays as a potential tool for sub-entity recognition, diagnosis, and classification. Mediastinal sarcomas are thus a notable illustration of interdisciplinary diagnostics by means of genomics and morphology. Current data on treatment strategies for this new and challenging tumor entity is fragmented [16, 17]. Although surgical resection has reportedly shown survival benefit, a considerable fraction of cases initially presents with locally advanced or metastatic disease. The roles of radiotherapy and adjuvant therapy are still unclear [18, 19]. Importantly, our patient had showcased a mixed response to treatment with pembrolizumab monotherapy and similarly in combination with ipilimumab that deserves discussion. Previously conducted clinical trials and case studies have shown promise for programmed cell death protein 1 (PD-1) antibody treatment in thymic carcinoma [20]. Two studies on respective patients showed improvement after pembrolizumab treatment in instances with

a high (>50%) PD-L1 expression [21, 22]. Although data on sarcomatoid mediastinal tumors is scarce, numerous trials have failed to prove consistent clinical efficacy of immune checkpoint inhibitors (ICI) [23]. In two cases of *SMARCA4*-deficient thoracic tumors, there have been isolated reports of a marked treatment response to pembrolizumab despite heterogeneity of PD-L1 expression: in one of the cases, the tumor displayed immunohistochemical negativity for PD-L1, while in the other, 60% of tumor cells expressed PD-L1 [24, 25]. This discrepancy between PD-L1 expression and treatment response implies a more complex situation respecting prediction of ICI efficacy in *SMARCA4*-deficient tumors, which warrants further investigation [26].

There is considerable clinical evidence of responses to anti-PD-1 agents in a broad spectrum of other *SMARCA4*-deficient tumor entities. In four cases of *SMARCA4*-deficient SCCOHT, prolonged responses to nivolumab and pembrolizumab have been reported [27]. In a case of *SMARCA4*-deficient lung adenocarcinoma, negative for PD-L1, the patient received nivolumab and showcased a marked reduction of the lung metastases for 14 months [28]. In vitro evidence has suggested plausible pathophysiological rationale regarding this phenomenon. Mutations in the polybromo-associated BAF (*PBAF*) form of the SWI/SNF complex were reported to increase tumor cell line sensitivity to interferon- γ , resulting in enhanced secretion of chemokines essential for effector T-cell chemotaxis [29]. Another study reported an interaction between the SWI/SNF complex gene AT-rich interaction domain 1A (*ARID1A*) and MutS homolog 2 (*MSH2*), implying aberrant mismatch repair and generally increased genomic instability that may generate a higher TMB, which potentiates a more effective immunotherapy response [30]. Our patient, too, had an extremely high TMB; moreover, in several studies where patients had received ICI therapy, a higher survival benefit has been observed in patients with a higher TMB, compared to those with a lower TMB [31, 32]. This was also demonstrated in cases of patients treated with a combination of two ICIs, again, independently of PD-L1 expression [33, 34]. The use of combined ICIs in various cancers may result in an improvement of overall survival [35]. Cytotoxic T-lymphocyte-associated protein 4 (*CTLA4*) is associated with T-cell proliferation regulation in the early stages of an immune response occurring in lymph nodes, while PD-1 is thought to play part in later stages occurring in the tumor microenvironment [36]. Amplified disease response to dual ICI therapy compared to single ICI therapy has been observed in advanced melanomas, metastatic renal cell cancers (RCC), small-cell lung cancers (SCLC), and NSCLC [37, 38].

Recent in vitro studies have described synthetic lethality of ICI with cyclin-dependent kinase 4/6 (*CDK4/6*) inhibition associated with a downregulation of cyclin D1 in *SMARCA4*-deficient NSCLC, thus additionally introducing *CDK4/6* inhibitors such as palbociclib or abemaciclib as potential treatment options in *SMARCA4*-deficient tumors [39, 40]. Although no randomized controlled trials have been performed yet, a case study reported promising response of combination treatment with nivolumab and abemaciclib in SCCOHT. *SMARCA4*-deficiency leads to reduced *CDK4/6* kinase activity, which in turn leads to cytostasis and increased antigen presentation in tumor cells, whilst decreasing expression of inhibitory receptors and promoting chemokine secretion in immune cells, which propagates T-cell infiltration and their function as effectors [27, 41]. Combination of ICI and *CDK4/6* inhibitor therapy may thus possibly be an effective treatment alternative in *SMARCA4*-deficient malignancies, and may thus hold promise for the treatment of *SMARCA4*-deficient thoracic sarcoma [27]. *CDK4/6* inhibitors, furthermore, could demonstrate potential therapeutic efficacy in cancers with a mutation in *CDKN2A*, analogously present in our patient, since *CDKN2A* is a negative regulator of *CDK4/6*. Different cancers with *CDKN2A* loss have been found to show an intermediate level of sensitivity to *CDK4/6* inhibitors, displaying growth cessation, but not tumor regression [42–46]. In our

case, a CDK4/6 inhibitor therapy had been planned but was unable to be initiated as the patient had deteriorated too quickly.

Another promising treatment approach could also encompass a combination of poly (ADP-ribose) polymerase (PARP) inhibitors and ICI, which has shown promise in a study of patients with advanced solid tumors [47]. PARP inhibition leads to dysregulated DNA repair due to aberrant homologous recombination [48]. It furthermore restores an efficient Th1 immune response and promotes PD-L1 expression, which could benefit and increase the effectiveness of ICIs [49, 50]. PARP inhibitors monotherapy has also shown promise in the treatment of different cancers with high HRD scores [51–53].

New studies have introduced an inhibition of enhancer of zeste homolog 2 (EZH2), a histone methyltransferase, as a further emerging treatment possibility for tumors with defects in the SWI/SNF complex. EZH2 is a catalytic subunit of the polycomb repressor complex (PRC) that is involved in cancer proliferation and metastasis, while SWI/SNF regulates the action of PRC. Targeted EZH2 inhibition may thus downregulate the PRC complex and halt cancer growth. Currently, a clinical trial investigating the efficacy of EZH2 inhibitors in patients with *SMARCA4*-deficient thoracic sarcomas is underway [1, 54].

In conclusion, this is one of the few case reports delineating partial response to pembrolizumab/ipilimumab combination therapy in *SMARCA4*-deficient thoracic sarcoma. Our findings underline the importance of recognizing this subset of tumors as an individual disease entity, and support the inherent value of checkpoint inhibitor therapy particularly in cases with high PD-L1 expression and TMB. Further studies are warranted to characterize the histomorphological and genomic landscape of these aggressive thoracic tumors to optimize novel therapeutic approaches.

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Statement of Ethics

Written informed consent for publication of this case report and any accompanying images was obtained from the patient before his demise.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Nothing to declare.

Author Contributions

J.D.H. and A.T. conceived the work and provided the histological diagnosis and analysis for the patient. J.D.H. performed the autopsy. Manuscript by N.A. and J.D.H. N.A. collected clinical patient data and designed images. F.K. and A.-L.E. provided details of therapy regimens and clinical disease progression/management. Critical revision for intellectual content by J.D.H. and A.T. All authors read and approved the final manuscript.

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