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Case Report

Clinical activity of pembrolizumab in refractory *MDM2*-amplified advanced intimal sarcomas

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***Abstract*:** Intimal sarcoma (InS) is an ultra-rare and aggressive subtype of soft tissue sarcoma (STS). It usually arises in large mediastinal arteries and the heart. In the advanced setting, sequential cytotoxic chemotherapy is often used, mainly based on retrospective studies and case series but with modest benefit. The use of immune checkpoint inhibitors is a promising strategy for some STS, but identifying biomarkers of response remains challenging due to disease rarity and heterogeneity. A reactive and pro-inflammatory tumor microenvironment (TME) is believed to be associated with better outcomes for patients receiving anti-PD-1-based regimens, generating the rationale to explore this strategy in malignancies with this characteristic, such as InS. We report three cases of advanced InS patients experiencing partial response to pembrolizumab-based therapy despite low tumor mutational burden and absence of mismatch-repair deficiency. We hypothesize that TME-related characteristics such as PD-L1 expression and the presence of tertiary lymphoid structures might explain this phenomenon.

Plain language summary

Pembrolizumab in advanced intimal sarcomas

Intimal sarcomas are ultra-rare and highly aggressive malignant tumours that most frequently arise in mediastinal arteries or the heart. Besides arising in challenging areas of the thoracic cavity, their rarity directly interferes with the development of new therapies, which negatively impacts patients' prognosis, especially after disease progression on chemotherapy regimens. We reported three cases successfully treated with immunotherapy (represented by pembrolizumab-based regimens), as well as a potential explanation for their outcomes.

Keywords: checkpoint inhibitor, immunotherapy, intimal sarcoma, pembrolizumab, tertiary lymphoid structure, vascular tissue neoplasm

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Background

Intimal sarcoma (InS) is an ultrarare high-grade sarcoma that commonly arises from the subendothelial space of large mediastinal vessels or the heart, where it is also known as undifferentiated cardiac sarcoma.[1] Most InS display overexpression of cell-cycle regulators such as MDM2 and CDK4, owing to frequent amplifications in the 12q12-15 region. While *MDM2* amplifications may be considered a molecular hallmark of InS,

MDM2-negative InS exists, and may show amplifications involving *MDM4* and *CDK6*.[2–4]

Due to their aggressive biological behavior and development in critical anatomic locations, InSs carry a poor prognosis regardless of clinical stage. In the largest real-world series of MDM2-positive InS patients ever published, Frezza *et al*. reported median progression-free survival (PFS) and overall survival for those with advanced disease undergoing frontline anthracycline-based chemotherapy of 7.7 and 21.8 months, respectively, with a 38% response rate.[2] Gemcitabine, pazopanib, and other agents seem to have limited activity in this disease, with little contribution to an already narrow therapeutic arsenal.[2]

Checkpoint inhibitors (CPI) which disrupt the PD-1/PD-L1 axis have shown clinical activity in selected subtypes of soft-tissue sarcoma (STS),[5] even leading to the approval of atezolizumab for alveolar soft-part sarcoma (ASPS) by the U.S. FDA. However, data regarding the efficacy of CPI in InS remain scarce and limited in the context of disease with microsatellite instability (MSI), justifying the importance of additional reports of this nature.[6,7] We herein report the outcomes of our three MDM2-positive pretreated InS patients who received pembrolizumab after failing standard cytotoxic chemotherapy regimens.

Case report

Case 1

A 33-year-old male patient presented in January 2022, with a history of headaches and left complete hemiparesis. MRI brain revealed a 30 mm right frontal brain lesion, suspicious for metastasis. A CT chest demonstrated a pulmonary vein lesion measuring 38 mm, with a necrotic aspect, extending along the right lower lobe bronchus, as well as bilateral lung metastases. Retrospectively, it was thought the pulmonary vein lesion may have been present about a year ago when the patient presented with nonspecific pulmonary symptoms, albeit the lesion was much more subtle.

The patient underwent surgery for symptomatic brain metastasis, followed by adjuvant stereotactic radiosurgery (SRS) to the resection bed, with a total dose of 27.5 Gy (5 fractions) plus a 2.5 Gy boost. The pathology report revealed a poorly differentiated malignancy composed of the spindle to pleomorphic and anaplastic cells, with immunostaining and fluorescence in situ hybridization (FISH) confirming *MDM2*-amplified InS. He was subsequently treated with single-agent doxorubicin, experiencing progression of disease (PD) after six cycles of chemo [best response of stable disease (SD)]. This patient then underwent single-agent abemaciclib, ultimately developing drug-induced colitis that prompted treatment discontinuation in November 2022, after 4 months on CDK4/6 inhibition (best response SD).

From November 2022 to April 2023, the patient received third-line pembrolizumab 200 mg q3w, with evidence of unconfirmed partial response (uPR) represented by tumor reduction in the mediastinum and lungs after three cycles [RECIST 1.1 Δ −30.8%, Figure 1(a)–(d)], along with excellent tolerance to treatment. In May 2023, he experienced asymptomatic PD of his brain and lung disease, leading to treatment discontinuation. Retrospectively, we identified high PD-L1 expression on the core biopsy of his lung metastasis [combined positive score (CPS) 80%]. There was no evidence of lymphoid aggregates, although the biopsy was limited with minimal representation of the tumor:lung interface. Molecular profiling obtained using the Illumina TruSight Oncology 500 (TSO500) panel (Table 1) disclosed low tumor mutational burden (TMB -4.7 muts/Mb), microsatellite stable, *H3C3* p.Leu101fsTer8 mutation, *ATP5MJ-ERG* fusion, and amplification in the following genes: *CCND3* (CN = 4), *CDK4* (CN = 12), *EGFR* (CN = 3), *ERBB3* (CN = 5), *KRAS* (CN = 4), *MDM2* (CN = 9), and *PDGFRA* (CN = 32).

Case 2

A previously healthy 35-year-old male patient was diagnosed with a 3-cm left atrial mass in August 2018, after a syncopal episode during extraneous exercises. The lesion partially obstructed the mitral valve, and an urgent partial resection was performed. The pathology report described a high-grade spindle cell neoplasm with positive immunostaining for vimentin and SMA, patchy positivity for MDM2/CDK4, and negative staining for desmin, AE1/AE3, CD34, and S100; the final diagnosis was FNCLCC grade 3 primary InS. Due to evidence of residual disease, the patient underwent systemic treatment with five cycles of doxorubicin, ifosfamide and mesna (AIM regimen – best response PR), followed by a complete resection in January 2019, remaining on surveillance thereafter.

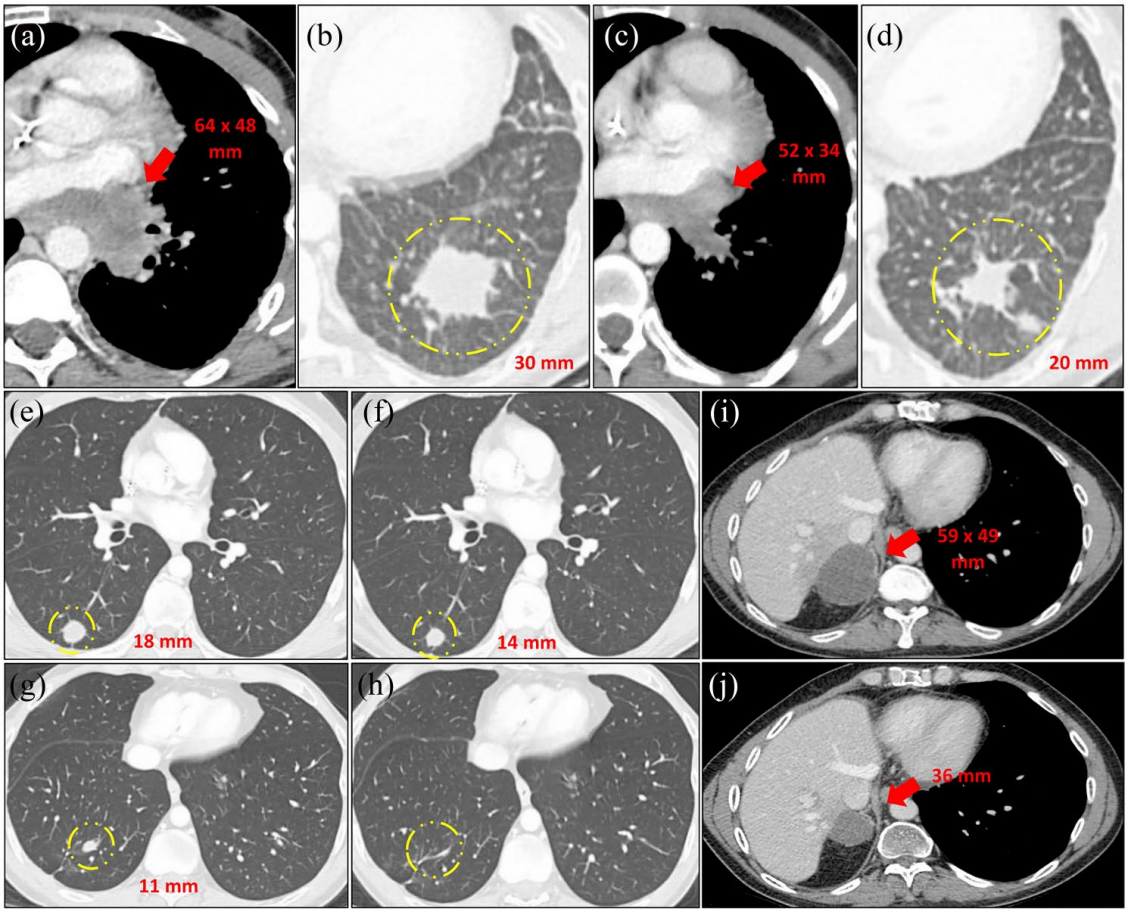

Figure 1. Illustration of *MDM2*-amplified InS with RECIST 1.1 objective response to anti-PD-1-based therapy. (a) and (b) Baseline CT scans of a 34-year-old patient (Case 1) diagnosed with metastatic InS to the bones, lungs (yellow circle), and lymph nodes (red arrowhead) – November 2022. (c) and (d) Evidence of uPR (–30.8%) following three cycles of pembrolizumab 200 mg q3w – January 2023. (e) and (f) Baseline CT scans of a 40-year-old patient (Case 2) diagnosed with metastatic InS to the lungs (yellow circle) and bones – May 2023. (g) and (h) Evidence of PR (–51.7%) following two cycles of pembrolizumab 200 mg q3w – June 2023. (i) Baseline CT scan of a –50-year-old patient (Case 3) diagnosed with metastatic InS to the bones and adrenal glands (red arrowhead) – December 2021. (j) Evidence of PR (–41.6%) following eight cycles of pembrolizumab 200 mg q3w plus investigational compound – May 2022.
InS, intimal sarcoma; MSI, microsatellite instability; PR, partial response; uPR, unconfirmed partial response.

Table 1. NGS (Illumina TSO500) and PD-L1 immunohistochemistry data for all three patients treated with pembrolizumab-based therapies.

Genomic findings	Patient 1	Patient 2	Patient 3
TMB (muts/Mb)	4.7	5.5	2.4
MSS status	Stable	Stable	Stable
Sequencing variants	*H3C3* p.Leu101fsTer8	None identified	None identified
Fusions	*ATP5MJ-ERG*	None identified	*MET-CAV1*
Amplifications (CN)	*CCND3* (CN = 4), *CDK4* (CN = 12), *EGFR* (CN = 3), *ERBB3* (CN = 5), *KRAS* (CN = 4), *MDM2* (CN = 9), *PDGFRA* (CN = 32)	*CDK4* (CN = 6) *MDM2* (CN = 35)	*CCNE1* (CN = 4), *EGFR* (CN = 6), *KIT* (CN = 9), *MDM2* (CN = 38), *MYC* (CN = 5), *PDGFRA* (CN = 11), *RICTOR* (CN = 4)
PD-L1 (IHC – CPS)	80%	7%	0

CN, copy number; CPS, combined positive score; TMB, tumor mutational burden; IHC, immunohistochemistry; MSS, microsatellite stability status; NGS, next generation sequencing; PD-L1, programmed death-ligand 1.

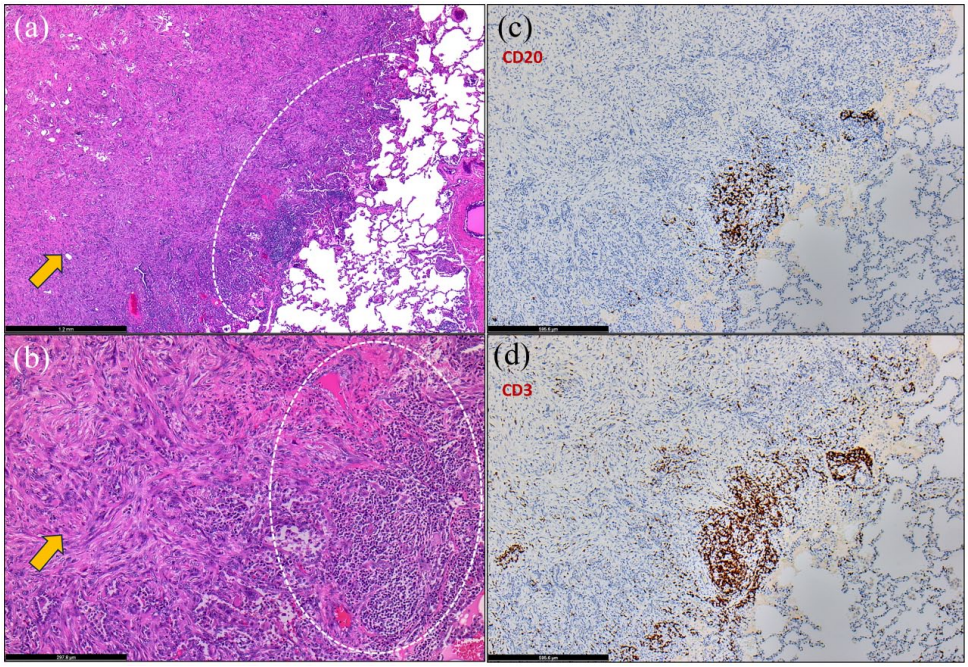

Figure 2. Illustration of peritumoral lymphoid aggregates in a specimen of lung metastasectomy (case #2). (a) Microscopic assessment of case #2 pulmonary wedge resection specimen disclosing a high-grade spindle cell neoplasm (yellow arrow) with lymphoid aggregates at the tumor periphery (white dashed circle). Hematoxylin/eosin, 5×. (b) Hematoxylin/eosin, 10×. (c) CD20-positive immunostaining disclosing predominance of B-cell population in the center of a peritumoral lymphoid aggregate. (d) CD3-positive immunostaining disclosing abundant T-cell population across the entire peritumoral area, overlapping with B cells in its center.

In December 2020, surveillance PET-CT scan showed evidence of a right lower lobe lung metastases, along with two lytic lesions on the right iliac bone and left tibia. He was treated with stereotactic body radiation therapy (SBRT) 3500 cGy in five fractions for the bony disease and from February 2021 to February 2023, he received six cycles and gemcitabine plus docetaxel, followed by maintenance gemcitabine (best response SD). He underwent a video-assisted wedge resection for a solitary oligoprogressive lung lesion in February 2022.

From March to May 2023, he was treated with third-line pazopanib, ultimately developing further lung disease manifested as bilateral metastases. In June 2023, he was started on pembrolizumab 200 mg q3w, and restaging scans following two cycles showed a PR of his lung metastases [RECIST 1.1: Δ −51.7%, Figure 1(e)–(h)]; the patient has been tolerating the treatment well overall, with only grade 1 fatigue reported after eight cycles so far. We performed additional immunohistochemical studies on the pulmonary wedge resection specimen, disclosing multiple lymphoid aggregates in the tumor periphery [Figure 2(a) and (b)], characterized by CD20+ lymphocytes [Figure 2(c)] admixed with numerous CD4+/CD8+ T cells [Figure 2(d)], as well as alveolar and intratumoral macrophages; the PD-L1 CPS staining was 7%; this specimen was also tested using the NGS Illumina TSO500 assay (Table 1), displaying amplifications in *CDK4* (CN = 6) and *MDM2* (CN = 35), 5.5 muts/Mb, absence of MSI status, but no sequence variants/fusions identified. Collectively, these findings suggest the presence of tertiary lymphoid structures (TLS) which may explain this patient's response to pembrolizumab.

Case 3

A 48-year-old male patient who presented to the emergency department (ED) with worsening chest pain and dyspnea was found to have an 11-cm large mediastinal and right-sided pulmonary artery mass, prompting hospital admission for investigation. A CT-guided biopsy revealed a high-grade malignancy involving the pulmonary artery and its branches, infiltrating as sheets and fascicles of round to ovoid cells exhibiting pleomorphic and hyperchromatic nuclei, admixed with extensive necrosis, and frequent mitotic

figures (60 per 10 HPF). There was positive immunostaining for CD31 and ERG, but negative staining for CD34; FISH confirmed *MDM2* amplification. In November 2019, the patient underwent a right pneumonectomy with negative margins and no evidence of nodal involvement, starting on follow-up thereafter.

In August 2020, due to solitary metastasis in the small bowel, he underwent a metastasectomy and remained on surveillance. In September 2021, due to the evidence of limited bone and right adrenal gland metastases, the patient received SBRT followed by two cycles of doxorubicin and ifosfamide (AIM regimen), discontinuing treatment due to toxicity (best response SD). The patient was subsequently enrolled in a clinical trial assessing the efficacy and safety of a combination of pembrolizumab 200 mg every 21 days with a novel investigational agent, starting his second-line treatment in December 2021. Following eight cycles of pembrolizumab-based therapy, he experienced PR [RECIST 1.1 Δ −41.6%, Figure 1(i)–(j)], remaining on treatment with excellent tolerance for a total of 12 months (18 cycles). Due to clear PD in December 2022, we switched his systemic therapy to gemcitabine and docetaxel.

Of note, an NGS assay Illumina TSO-500 performed using his small bowel metastasis specimen (Table 1) revealed amplifications in *CCNE1* (CN = 4), *EGFR* (CN = 6), *KIT* (CN = 9), *MDM2* (CN = 38), *MYC* (CN = 5), *PDGFRA* (CN = 11), *RICTOR* (CN = 4), as well as a MET-CAV1 fusion, stable MSI status, and TMB of 2.4 muts/Mb. We retrospectively evaluated for TLS and PD-L1 expression on the bowel metastasis, both negative (CPS of 0 and scarce lymphocytic infiltrate).

Discussion

InS is a challenging ultra-rare sarcoma to treat especially in the advanced or metastatic disease. Current practices employ doxorubicin-based regimens with modest benefits at best. The rarity of this tumor has hampered the ability to better understand its genomic profile and tumor microenvironment (TME), and to identify therapeutic vulnerabilities that could bring novel treatments instead of cytotoxic chemotherapy use.[1,2] We presented three cases of advanced InS patients who experienced PR to pembrolizumab-based regimens with variable duration and, possibly, distinct mechanisms of response (PD-Ll hyperexpression, presence of TLS).

The underlying mechanisms of response to immune checkpoint inhibition (ICI) in STS are diverse and not completely understood, which makes adequate patient selection a challenging task, especially for the ultra-rare subtypes. Henick *et al.* reported one case of pembrolizumab-sensitive InS in the setting of MSI/mismatch repair deficiency post-progression to first-line doxorubicin and olaratumab[6]; conversely, Mounai *et al.* observed mixed response with frontline pembrolizumab in a patient with high disease volume and background of Lynch Syndrome whose tumor harbored MSI-high status, TMB of 69 muts/Mb, and a PD-L1 tumor proportion score (TPS) of 90%.[7] These reports suggest not only that MSI status and TMB might play a role in InS antitumor immune response but also the existence of a more complex interplay between these biomarkers, PD-L1 expression, and immune cell infiltrates. This is highlighted by the fact that none of our three responding patients had tumors with high TMB/MSI-high status, and our only patient with strong PD-L1 immunostaining (CPS 80%) had the shortest duration of response. We acknowledge the fact that, as with other solid tumors, the clinical value of high PD-L1 expression in sarcomas, as well as the best reading method (CPS *versus* TPS), remains unknown. In addition, data on anti-PD-1 antibody performance for InS patients can also be obtained by analyzing studies of immunotherapy that included this sarcoma subtype (though usually poorly represented); Paoluzzi *et al.* reported SD on nivolumab in one InS patient, with PFS of roughly 8 months, whereas the only InS patient included in the basked phase II trial AcSe experienced PD on pembrolizumab.[8,9]

The role of TLS in predicting better outcomes for STS patients undergoing immunotherapy has recently gained the spotlight. These structures consist of CD20+/CD3+ ectopic lymphoid aggregates arising in non-lymphoid tissues under chronic inflammatory states (e.g. auto-immune conditions, cancer), being most likely involved in tumor antigen presentation, T-cell priming/activation and, consequently, elaboration of an antitumor immune response.[10,11] Italiano *et al.* reported superior efficacy outcomes with pembrolizumab plus low-dose cyclophosphamide in a patient cohort with documented TLS in the phase II trial PEMBROSARC. The 6-month non-progression rate and objective response rate (ORR)

for the TLS cohort were, respectively, 40% and 30%, when compared with 4.9% and 2.4% for the all-comers.[11] These clinical findings are supported by the biomarker analysis of the phase II trial SARC028, showing that patients whose tumors highly expressed immune-checkpoint-related genes, such as those encoding PDL1, PDL2, CTLA4, and TIM3 (aka SIC E) more frequently presented TLS; patients on pembrolizumab for SIC E tumors in that study had the diagnosis of undifferentiated pleomorphic sarcomas or dedifferentiated liposarcomas, and experienced superior PFS and ORR when compared with those in other 'cold' TME categories.[12,13] The presence of TLS in our case #2 could potentially justify a response to pembrolizumab regardless of weak PD-L1 and low TMB.

Our report suggests that InS patients might derive benefit from immune checkpoint blockade, possibly driven by an immune 'hot/inflamed' TME.[14] The inclusion of advanced InS patients in ICI-based early-phase studies and multi-institutional collaborations may be helpful to start exploring the efficacy of this treatment modality in an underrepresented population while enabling translational research focused on the identification of predictive biomarkers of response. As with the ASPS example,[5] a clinical-research-oriented approach to managing InS may prove, soon, to be more successful in raising the bar for these challenging diseases than insisting on sequential cytotoxic chemotherapy solely supported by retrospective data.

Conclusion

Anti-PD-1 therapies might play a role in the management of chemotherapy-refractory advanced InS patients, as suggested by the outcome of our three InS patients treated with pembrolizumab-based regimens. Prospective studies enabled by multi-institutional collaborations and the identification of predictive biomarkers are key to providing further clarification about the role of immunotherapy for these ultra-rare sarcomas.

Declarations

Ethics approval and consent to participate

As per the University Health Network (UHN) Research Ethics Board (REB) policy, case studies that involve three or fewer patients do not require an ethics review.

Consent for publication

Patients or their next-of-kin provided verbal and written informed consent for this publication.

Author contributions

Mauricio Fernando Ribeiro: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Elizabeth G. Demicco: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – review & editing.

Albiruni Ryan Abdul Razak: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

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Competing interests

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Availability of data and materials

Data are to be provided upon request to the corresponding author.

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