

Case Report

# Exceptional Regression of Malignant Pleural Mesothelioma with Pembrolizumab Monotherapy

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## Keywords

Immune checkpoint inhibitor · Immune-related endocrinopathy · Malignant pleural mesothelioma regression · Programmed cell death ligand 1 expression · Pembrolizumab monotherapy · Therapeutic biomarkers

## Abstract

The lead author with clinical stage I malignant pleural mesothelioma, epithelioid type, highly programmed cell death ligand 1 (PD-L1) positive, and BAP1 negative, experienced a prompt and exceptionally favorable response to pembrolizumab monotherapy. After cessation of treatment due to immune-related endocrinopathies, complete metabolic response on interim PET/CT scan was achieved. Two years after initial diagnosis, unifocal tumor reactivation was addressed with successful pembrolizumab monotherapy rechallenge. Immunotherapy, typically not used as frontline treatment for malignant pleural mesothelioma, may provide an effective and durable response for some patients. Based on this single case study, epithelioid type tumors with strongly positive PD-L1 and BAP1-negative immunohistochemical markers may be well suited for treatment with immune checkpoint inhibitors such as pembrolizumab.

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## Introduction

Pembrolizumab, a programmed cell death 1 (PD-1)-blocking antibody, is being used with increasing frequency for solid tumors positive for the programmed cell death ligand 1 (PD-L1) biomarker. There have been reports of antitumor activity in several malignancies with increased

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PD-L1 expression, including non-small-cell lung cancer. While recent reports [1, 2] have shown remarkable clinical improvement from salvage immunotherapy in cases of advanced malignant pleural mesothelioma (MPM), the present case demonstrates an exceptional response to frontline pembrolizumab in a patient with early-stage MPM and strong PD-L1 tumor labeling.

### Case Presentation

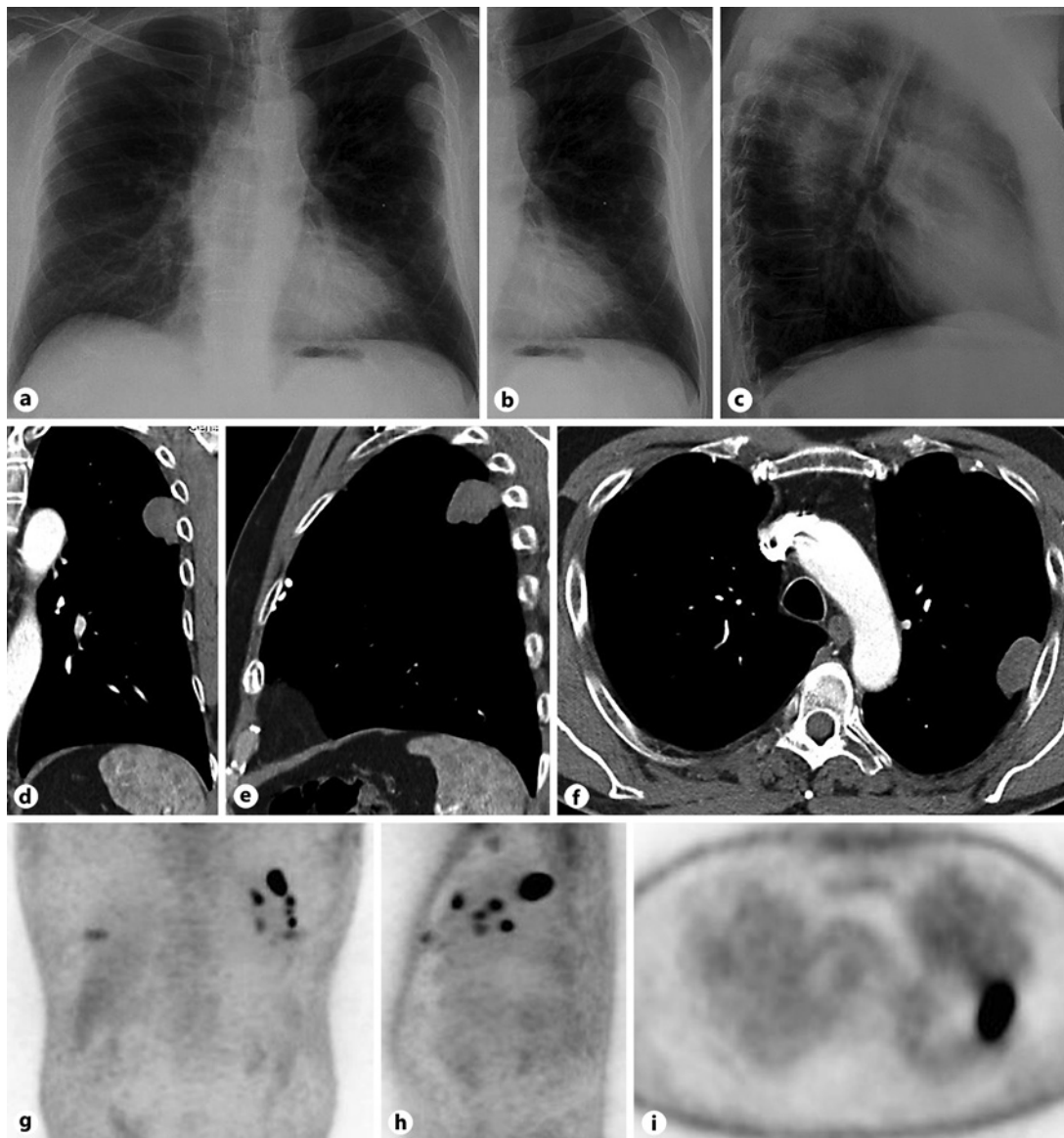
A 66-year-old male orthopaedist experienced sudden onset of episodic left upper chest pleuritic pain when blowing his nose and intermittent cough for 1 year without other constitutional symptoms or medical comorbidities. Nearly 50 years ago, he was exposed to asbestos when he worked as a pipe fitter during college summer hiatus. Initial workup included chest radiographs, computed tomography (CT) scan, and positron emission tomography (PET) scan. Interpreted by one of us (K.N.R.), the latter demonstrated 6 pleural-based masses confined to the left hemithorax (Fig. 1).

At a cancer center of excellence, percutaneous core needle biopsy of the largest lesion revealed MPM, epithelioid type with immunohistochemical stains positive for calretinin and WT1, but negative for TTF1, p40, claudin-4, CD117, and polyclonal CEA. BAP1 (clone C4) nuclear labeling was lost in the tumor and mesothelin (clone 5B2) was positive in 70% of tumor cells. There was strong membranous labeling with PD-L1 (clone E1L3N) in 80% of cells, comparable to the diagnostic standard PD-L1 antibody (clone 22C3). Without further diagnostics, he was judged to have clinical stage I disease and was offered standard trimodal treatment comprised of pleurectomy/decortication, followed by platinum/pemetrexed chemotherapy, followed by intensity-modulated radiation therapy. The patient declined this standard protocol and consulted one of us (D.F.M.) to discuss alternative treatment options.

Based on a clinical trial of pembrolizumab for resectable MPM (NCT02707666), prior successful use of the drug for advanced disease [3], and highly positive PD-L1 tumor labeling, he began off-label treatment with pembrolizumab 200 mg Q3W in the hope of reinvigorating his immune system without the suppressive effects of prior chemotherapy. After only 3 treatment cycles, his chest pain and sense of well-being improved. Interim imaging studies showed remarkable reduction in size and 18F-fluorodeoxyglucose (FDG) avidity of all tumor masses (Fig. 2).

After 5 additional infusions resulted in progressive fatigue, further evaluation by one of us (G.C.E.) revealed new-onset autoimmune endocrinopathies. Primary hypothyroidism was treated with levothyroxine, and type 1 diabetes mellitus was treated with insulin and diet modification. These immune-related adverse effects (IrAE) led to suspension of immunotherapy to preserve some possibility of pancreatic recovery. Interim PET/CT scan 8 months after cessation of treatment revealed absence of FDG avidity, indicating complete metabolic response (CMR) to pembrolizumab monotherapy. Elevated lymphocyte and eosinophil counts persisted for months after pembrolizumab was discontinued (Table 1), indicating ongoing immunogenic effects of the treatment.

At subsequent follow-up 2 years after diagnosis and 18 months after suspending treatment, the PET/CT showed that 1 pleural-based pericardial nodule had modestly increased in size and FDG uptake (Table 1). Owing to these interim changes, pembrolizumab monotherapy was resumed. After 4 infusions of the 6-cycle rechallenge, PET/CT revealed decreased size of the pericardial nodule and no significant metabolic activity. Four months after the rechallenge and 33 months after diagnosis, repeat PET/CT showed no evidence of active disease. No surgical treatment, chemotherapy, or radiation therapy was used during the course of treatment to control tumor progression.

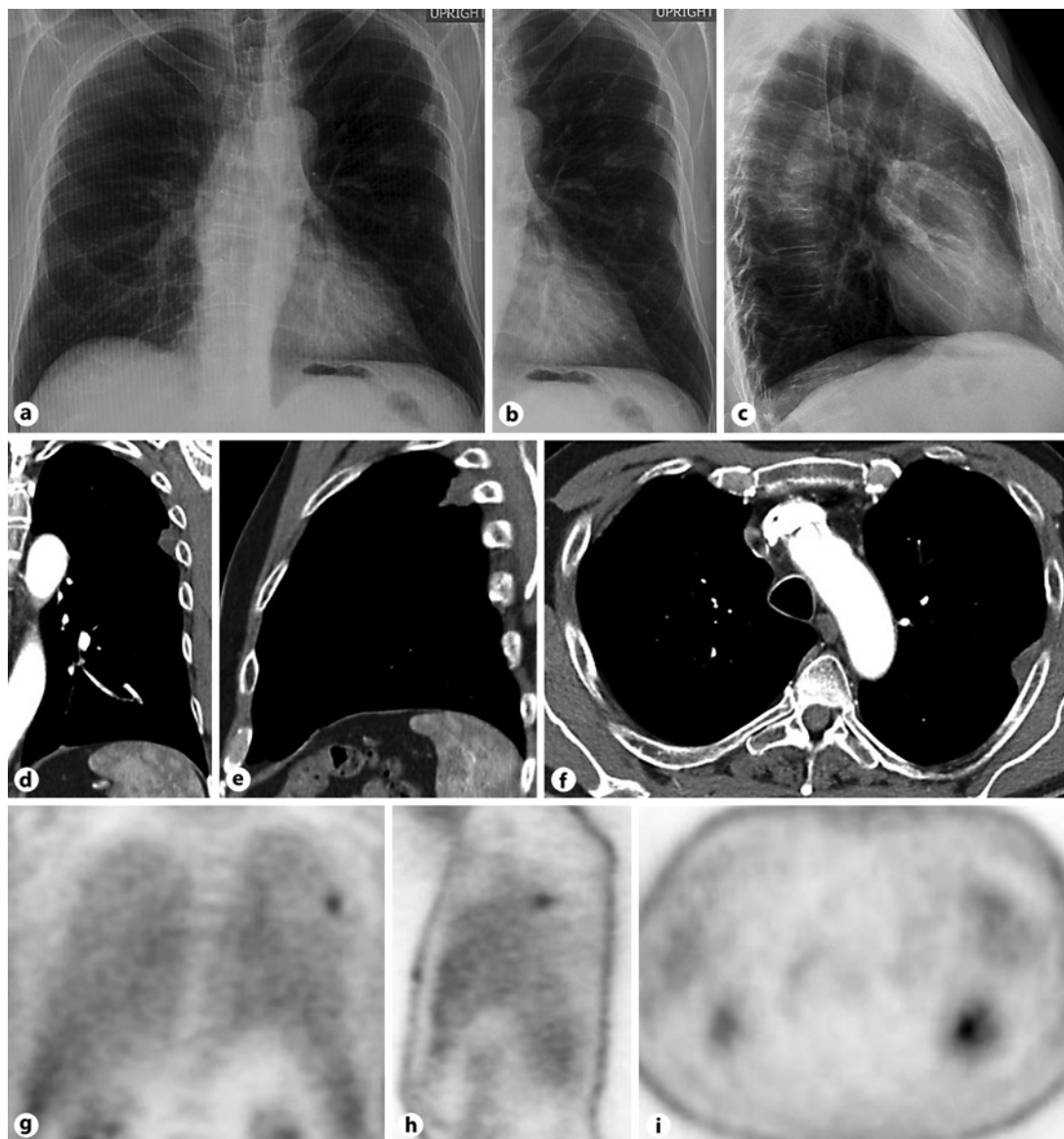


**Fig. 1.** Baseline imaging. Posteroanterior (a), left hemithorax (b), and lateral (c) chest radiographs showing upper lateral chest wall soft tissue mass. Coronal (d), sagittal (e), and axial (f) CT scan images revealing a 3.3 × 2.0 × 2.6 cm solid pleural-based mass at the periphery of the left upper lobe. Coronal (g), sagittal (h), and axial (i) PET scan images demonstrating multiple pleural-based 18F-FDG-avid nodules in the left hemithorax. The largest mass measured 3.4 × 1.9 × 2.9 cm wherein the maximum standardized uptake value was 10.3.

## Discussion

The unfavorable prognosis of MPM, even with the latest trimodal therapy [4], has prompted some patients to seek clinical trials and alternative treatment options. In the present case, 3 cycles of frontline pembrolizumab resulted in prompt regression of the multiple MPM tumors in the left hemithorax, obviating the need for surgical resection which had been anticipated prior to treatment.

Using this immune checkpoint inhibitor as primary treatment appeared to be an attractive option to the physician-patient (B.F.H.), in contrast to an onerous 9-month trimodal regimen



**Fig. 2.** Interim imaging after the third pembrolizumab infusion, 7 weeks after the first treatment cycle. Posteroanterior (a), left hemithorax (b), and lateral (c) chest radiographs showing marked size reduction of the lateral chest wall mass. Coronal (d), sagittal (e), and axial (f) CT scan images confirming size reduction of the largest pleural-based nodule. Coronal (g), sagittal (h), and axial (i) PET scan images demonstrating significant interval regression of all 18F-FDG-avid masses. Residual hypermetabolic activity remained in only the largest mass where the maximum standardized uptake value was 2.6, indicating a remarkable 75% reduction in intensity.

with its potential for severe morbidity. Moreover, the favorable response of MPM to pembrolizumab was durable after the drug was discontinued, as previously demonstrated for patients with melanoma [5]. After a period of quiescence, unifocal tumor reactivation was again promptly controlled with pembrolizumab rechallenge.

PD-1 is a complex protein on activated T lymphocytes which serves as an inhibitory receptor. When these receptors are engaged by corresponding ligands (PD-L1) expressed on tumor cells, tumor-specific T effector cells are inhibited, causing tumor tolerance. Pembroliz-



**Table 1.** PET/CT and serum biomarker changes during pembrolizumab monotherapy

Parameter	Dec 17	Mar 18	Jun 18	Oct 18	Feb 19	Aug 19	Dec 19	Mar 20
Pembrolizumab cycles completed	0	3 of 8	8 of 8	hiatus	hiatus	hiatus	hiatus	4 of 6
PET/CT findings								
Peripheral nodule size, cm	3.4×2.9	decreased		1.6×0.6	1.3×0.5	1.3×0.6		
FDP avidity, SUV <sub>max</sub>	10.3	2.6	1.6	1.3	background	1.1	background	
Pericardial nodule size, cm	1.6×1.1	decreased				1.4×1.0	1.6×1.1	1.3×0.9
FDP avidity, SUV <sub>max</sub>	4.1	background	background			1.3	1.9	1.4
Serum biomarkers								
Lymphocyte count (normal, 25–33)		34	27	26	40	38	30	40
Eosinophil count (normal, 0–3)		6	10	22	12	6	4	7
SMRP (normal, 0–1.5)				0.7		0.7	0.4	0.3

PET/CT, positron emission tomography/computed tomography; FDP, 18F-fluorodeoxyglucose; SUV<sub>max</sub>, maximal standardized uptake value; SMRP, soluble mesothelin-related peptide; background, background mediastinal blood pool activity.

zumab, a humanized IgG4 antibody with high affinity for PD-1, blocks the inhibitory interaction of T cells at this immune checkpoint in the tumor microenvironment, thereby enhancing the antitumor response of the T cells [6].

Since PD-1 receptors are also present on pancreatic islet cells, blocking the PD-1 pathway with immune checkpoint inhibitors such as pembrolizumab prevents downregulation of autoreactive T cells which target the insulin-producing  $\beta$ -cells of the pancreas [7]. When 80% or more of pancreatic islet cells are subsequently destroyed, type 1 diabetes mellitus ensues as an IrAE of treatment. The treatment complications of diabetes and hypothyroidism, as well as an episodic urticarial rash initially seen within hours of his first infusion, are all manifestations of immune system response, which serve as therapeutic biomarkers.

Prior clinical studies have confirmed the efficacy and safety of pembrolizumab in those with advanced MPM, many of whom have endured prior chemotherapy without improvement. Alley et al. [3], in the KEYNOTE-028 phase Ib trial, reported that 5 of 25 patients with PD-L1-positive MPM who had failed standard therapy had a partial metabolic response (PMR) to pembrolizumab, while 13 (52%) of the cohort had stable disease, implying a disease control rate (DCR) of 72%. No patient in the series experienced CMR. Metaxas et al. [8] reviewed an unselected group of 93 patients from Switzerland and Australia who received palliative treatment with frontline or second-line pembrolizumab for MPM. Sixteen patients in the study had PMR and 1 had CMR for an overall response rate of 18%. Though strong PD-L1 expression ( $\geq 50\%$ ) was significantly correlated with better overall response rate (44%) and increased DCR (89%), multivariate analysis failed to demonstrate a statistically significant association of PD-L1 labeling with either outcome measure. Reporting on phase II trial of pembrolizumab in an unselected population of 65 patients with malignant mesothelioma (56 with pleural involvement) and disease progression after platinum/premetrexed chemotherapy, Desai et al. [9] found 19% had PMR and 47% had stable disease for a DCR of 66%. Higher response rate and more durable progression-free survival were correlated with increasing PD-L1 expression.

Frontline anti-PD-1 therapy for MPM requires identifying patients for whom such therapy will be most effective and least morbid. In this case, specific biomarkers were used as guides before, during, and after treatment. Before initiating treatment, we recognized that epithelioid type mesotheliomas with BAP1 mutations are relatively well-differentiated lesions and may be associated with relatively prolonged survival [10]. Though the role of tumor PD-L1 labeling as a prognostic biomarker in MPM is uncertain [8], we suspect that highly PD-L1-positive tumors may be more likely to improve with anti-PD-L1 agents in treatment-naïve

patients than in those previously challenged with chemotherapy. Recently, increased soluble PD-L1 levels compared to baseline during anti-PD-L1 immunotherapy for MPM have been shown to be a prognostic biomarker for longer overall survival [11].

Despite their significant clinical implications, the IrAEs which occurred during treatment served as indicators of effective immune system activation. In melanoma patients, emerging evidence suggests that such pembrolizumab-induced events portend better recurrence-free survival [12]. Serum biomarkers indicative of a positive treatment response in this case included elevated lymphocyte and eosinophil [13] counts and consistently middle- to low-range normal soluble mesothelin-related peptide (SMRP) levels [14] observed after immunotherapy was suspended (Table 1). The best prognostic biomarker during and after treatment was the marked reduction in tumor FDG avidity on interim PET/CT scan (Fig. 2), which has been shown to correlate with progression-free survival and overall survival in MPM patients treated nonsurgically [15].

Though there are no randomized clinical trials supporting the use of immunotherapy for MPM, the durable response in this case suggests that pembrolizumab monotherapy may play a role in some clinical settings, particularly in view of the disappointing outcomes seen with standard treatment. Furthermore, his progression from PMR to CMR after therapy suspension indicates that prolonged immunotherapy may not be required in those who achieve an early good response. To the contrary, pausing treatment in such patients may help avert IrAEs, albeit resumption of immunotherapy may be required in the event of tumor reactivation. The effect of modifying drug dosage or frequency on clinical response and toxicity remains to be determined.

## Conclusions

Based on this case report, patients with early clinical stage MPM, epithelioid tissue type, strongly PD-L1 positive, and BAP1 negative, may be good candidates for pembrolizumab monotherapy. In our case, we found that lymphocytosis, eosinophilia, reduction in tumor FDG avidity on interim PET/CT scans, and IrAEs were favorable therapeutic biomarkers indicative of an effective immunogenic response during and after treatment. The exceptional response to immunotherapy in this case suggests that patients with early-stage MPM should be considered for frontline pembrolizumab, particularly if they are unwilling to accept the morbidity associated with standard multiple modality treatment.

## Statement of Ethics

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

## Conflict of Interest Statement

The authors have no conflicts of interest.

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### Author Contributions

B.F.H. compiled the clinical data and imaging studies, prepared the figures and table, drafted and edited the manuscript. K.N.R. interpreted the imaging studies and edited the manuscript for imaging content. G.C.E. reviewed and edited the manuscript for immune-related endocrinopathy content. D.F.M. conceptualized the project and revised the manuscript for oncology content. All authors read and approved the final version of the manuscript prior to submission.

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