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Fatal adverse events in two thymoma patients treated with anti-PD-1 immune check point inhibitor and literature review

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ABSTRACT

Objectives: Thymomas, as well as thymic carcinomas, are extremely rare tumors that arise from the thymus. The management of these tumors is primarily the complete surgical resection, however when there is tumor progression or metastatic unresectable disease, palliative platinum-based chemotherapy is the standard of care. On this setting, alternative options are emerging including immune checkpoints inhibitors. Based on that, PDL-1 expression was measured in thymic tumors as a potential predictive biomarker of response to anti-PD1 and anti-PDL1 immune inhibitors. Our objective is to report the first two cases of fatal toxicity due to anti- PD1 therapy in thymoma patients.

Materials and Methods: Here, we report two cases of metastatic B2/B3 thymomas refractory to initial standard chemotherapy treatment, with high PDL1 expression (> 50%), that were treated with the anti-PD1 agent, pembrolizumab.

Results: The administration of anti- PD1 immune check point inhibitor resulted in a storm of immune related adverse events including myositis, myocarditis and myasthenia gravis and death after administration of the first treatment cycle.

Conclusion: In thymomas, the administration of PD1 inhibitors seems to be associated with a high percentage of severe immune related adverse events, thus requiring special caution on the usage of these agents in thymomas.

1. Introduction

Thymic epithelial tumors (TETs) are rare tumors that arise from the thymus gland [1]. The management of these tumors is primarily surgical resection, however in metastatic disease, platinum-based chemotherapy is the standard of care [2]. On this setting, alternative options are emerging including immune checkpoints inhibitors (ICIs).

Herein, we report two cases of metastatic thymomas refractory to platinum chemotherapy, with high PDL1 expression (> 50%), treated with the anti-PD1 agent, pembrolizumab which resulted in fatal immune-related adverse events (iRAEs) after administration of first cycle.

2. Case 1

A 58-year old woman with a history of metastatic thymoma with pleural metastases received pemrolizumab after disease progression that occurred 10 months after the last cycle of CAP (Cyclophosphamide, Doxorubicin, Cisplatin). She had been diagnosed with ocular myasthenia with *positive anti-acetylcholine receptor (AchR)* antibodies due to mixed B2/B3 thymoma eleven years ago, which had fully regressed after an R0 surgical excision of her tumor. As immunohistochemical examination on the tumor revealed a high PDL1 expression in 80% of tumor cells (e-Fig. 1d), she was treated with the anti-PD1 inhibitor, pembrolizumab.

One week after the first pembrolizumab administration, she presented with fever and a rash in the extremities and oral mucosa. She had increased transaminases and raised inflammatory markers. Her ECG showed no dynamic changes and troponin was negative.

Biopsies of the skin rash confirmed Stevens Johnson rash and she was administered prednisolone 1 mg/kg, broad spectrum antibiotics

Abbreviations: AchR, anti-acetylcholine receptor; iRAEs, immune related adverse events; ICU, Intensive Care Unit; TETs, thymic epithelial tumors; PD-1, programmed cell death protein 1

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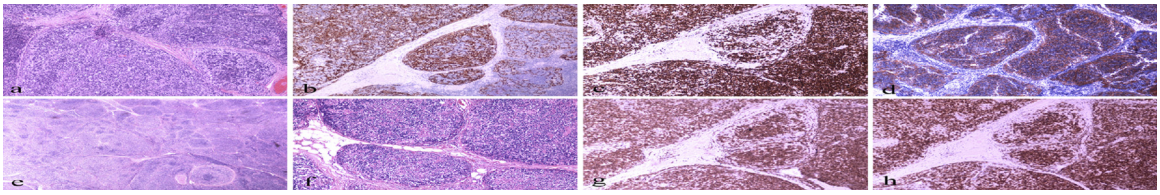

Fig. 1. Mixed mediastinal thymoma of B2/B3 type, H&E stain (a). The epithelial cells are highlighted with the immunohistochemical stain Cam 5.2 (b) and the immature lymphocytes with TdT stain (c). Programmed cell death ligand 1 (PD-L1) demonstrated positivity (membrane stain) in 80% of cells (d), magnification X100. Pleural relapse of above thymoma, H&E stain, magnification X40 (e) and X100 (f). Immunostains for CD1a (g) and CD3 (h) that shows the immature T lymphocytes, magnification X100.

and intravenous hydration. Two days later, the rash was improving, but her liver function tests were increasing. A routine daily ECG showed an extensive anterior myocardial infarction with high troponin level (> 50). She was transferred to the Cardiology *Intensive Care Unit* (CICU) with thoracic pain and shortness of breath. An echocardiogram showed acute heart failure with a left ventricular ejection fraction less than 30% and diffuse hypokinesia of the heart. The coronary angiogram was normal. She received treatment with b-blocker, antiarrhythmics, and mycophenolate mofetil for acute autoimmune myocarditis caused by pembrolizumab, but despite aggressive management, it led to decompensated heart failure, ventricular arrhythmia and death five days following admission to CICU.

3. Case 2

The second patient was a 30-year old female who suffered from de novo metastatic B3 thymoma since 2010 (Fig. 2 a–d). She was resistant to multiple previous lines of therapy. She did not have any history of autoimmunity. Her tumor was MMR-deficient and had PDL1 expression 60% on cancer cells.

Pembrolizumab was administrated and three days later, she developed acute chest pain and proximal muscle weakness. She was diagnosed with myositis/myocarditis syndrome due to ischemic changes in ECG leads II, III, aVR, and rising levels of CPK and troponin I and was initially put on prednisolone 2 mg/kg. Two days later, she developed unilateral eyelid drop, diplopia, hypercapnic respiratory failure and had acute increase in her liver transaminases. Anti-AchR antibodies were positive. She was put on NIPPV, but eventually, she was intubated. She stayed in the ICU for 30 days and received, along with corticosteroids and pyridostigmine, a course of immunoglobulin (400 mg/kg for 5 days), without any improvement. Subsequently, she was treated with weekly rituximab 375/m^2 as in refractory cases of myasthenic crisis [9]. One week after the rituximab administration it was possible to be successfully weaned from ventilation and put on NIPPV. She was transferred back to the oncology ward, where she received two more weekly administrations of rituximab showing signs of gradual improvement. However, on her 54th day of hospitalization she developed septic shock and was transferred again back to the ICU, where she died 10 days later.

4. Discussion

Herein we present two cases of metastatic B2/B3 thymomas, both treated with pembrolizumab, resulting in a storm of *iRAEs*.

In a retrospective study of 496 skin cancer patients who received anti-PD1 treatment, 242 i*RAEs* were reported, including neurological (11.5%) and cardiac (3.6%) events. Grade 3–4 iRAEs were observed in 24%, including one grade 4 seronegative myasthenia gravis (MG) 10 weeks after initiation of treatment [3]. Macarious reported 23 cases of immune checkpoint inhibitors inducing MG of which 13 were de novo presentations and 10 were exacerbations of MG, but only 9 had positive anti-AchR antibodies. The average time of onset was 6 weeks after initiating immunotherapy whereas 30.4% were fatal despite immediate management [4]. In the biggest retrospective study of 10,277 patients receiving nivolumab for various tumors but none for thymoma, 12 developed nivolumab-related MG and among them, 10 had positive anti-AchR antibodies. According to that study, 2 deaths were observed due to myocarditis and myasthenic crisis [13]. Furthermore, Johansen et al systematically reported 85 patients with neuromuscular events (including MG, myositis etc) following administration of anti-PD1 treatment. Surprisingly, AchR- antibody status was available in 43 patients of whom half were positive. Additionally, mortality was high despite immediate management, including steroids, whereas more than 30% of patients with MG developed cardiac events [14].

There are few data evaluating ICIs in thymomas. *J*. Cho et al included twenty-six patients with thymic carcinomas and seven with thymomas who had relapsed on platinum chemotherapy. Patients with active autoimmune disease were excluded from the trial. 24.2% achieved partial response (PR) and 51.5% had stable disease (SD). Severe iRAEs included hepatitis (12.1%), myocarditis (9.1%) and MG(6.1%).Five patients with thymoma and three with thymic carcinoma discontinued treatment due to toxicity [5]. In a phase I trial, avelumab was administered to seven patients with thymoma and one with thymic carcinoma. All responding patients experienced iRAEs, including myositis. Grade 3–4 iRAEs were observed in 38% and 25% of patients, respectively, whereas five patients discontinued treatment due to toxicity [6]. In a phase II trial, pembrolizumab was administered in 41 patients with thymic carcinoma. Eight (20%) achieved PR and twenty-one (53%) SD. Six (15%) patients developed grade 4 iRAEs including two with myocarditis and no one with MG (e- Table 1) [7]. No treatment related deaths were recorded in the above trials [5–7].

During normal T cell maturation, immature T lymphocytes pass through the thymus cortex and interact with the epithelial cells stationed there and those that survive this interaction pass in the thymic medulla. There they interact with the dendritic cells and the autoreactive cells either undergo apoptosis or they fall into anergy [8].

A possible mechanism of autoimmunity in both patients described in this report is that in thymomas the neoplastic thymic epithelium has the potential to induce differentiation of immature $CD4^+CD8^+CD3^+$ lymphocytes into $CD4^+CD8^-$ or $CD4^-CD8^+$ autoreactive lymphocytes [8,9]. The autoreactive T cells that result from this interaction do not pass through the thymic medulla for a second quality control by the

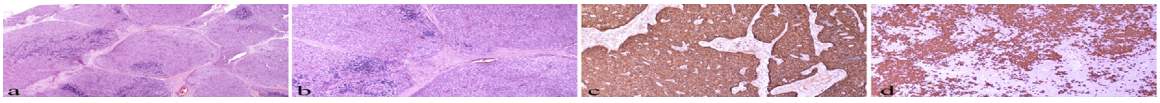

Fig. 2. Panoramic view (X40) of mediastinal thymoma type B3 (a). Higher magnification (X100) of the same case (b). MNF-116 highlights the epithelial component (c) and TdT immunohistochemical stain (d) that shows the immature lymphocytic population, magnification X100.

Table 1
Clinical trials of PD1/PDL1 inhibitors for thymomas and thymic carcinomas. N: number of patients, T: Thymoma, TC: Thymic carcinoma, ORR: Overall response rate, IRAE: Immune related adverse events.

STUDY	N	PD1/PDL1	PTS WITH T/TC	ORR	Grade ¾ IRAEs IN T/TC
Cho et al(Phase II)	33	PEMBROLIZUMAB	7/23	24%	71%/11.5%
Rajan et al(Phase I)	8	AVELUMAB	7/1	24%	71%/0%
Giaccone et al(Phase II)	41	PEMBROLIZUMAB	0/41	22.50%	0/15%

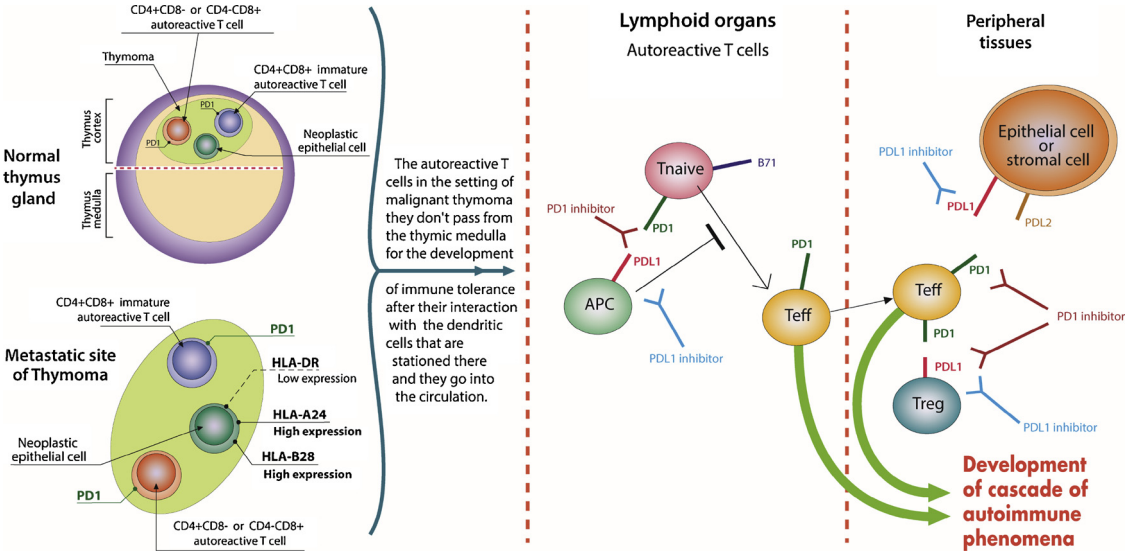

Fig. 3. Mechanism of development of an autoimmunity cascade in patients with thymoma that are administered a PD1/PDL1 inhibitor.

dendritic cells [9]. Moreover, neoplastic thymocytes have increased levels of HLA-A24 and HLA-B8, which have been shown to be associated with an increased risk of autoimmunity development in patients with thymomas [9]. Due to the intrinsic capability of the thymic neoplastic epithelium to induce differentiation in $CD4^+CD8^+$ lymphocytes and the absence of a functional thymic medulla in thymomas, these autoreactive T cells escape in the circulation inducing autoimmune phenomena. The presence of immature T lymphocytes seems to be crucial for the development of autoimmunity in thymic malignancies, and this is supported by the fact that thymic carcinomas, which lack these immature immune cells, have less capability to induce autoimmunity compared to thymomas [10,11].The PD1/PDL1 axis has an important role in the development of immune tolerance in peripheral lymphoid organs and tissues [12] (e-Fig. 3). However, the model described above is a putative explanation, yet the precise mechanism underlying the development of autoreactive T cells in thymomas remains to be elucidated.

Despite that the administration of ICIs in patients with thymoma has shown promising activity, it is associated with high rates of toxicity, which can be attributed to the intrinsic ability of these malignancies to induce autoimmunity [5,6,8]. However, this may not be true for thymic carcinomas and considering the aggressive nature and the lack of effective treatment, the administration of pembrolizumab in patients with pure thymic carcinomas could be an option [7]. Moreover, despite that PDL1 level is a biomarker in patients receiving ICIs, these data should not be extrapolated for patients with thymoma, since PDL1 is constitutively expressed at high levels in the normal thymic epithelium, as part of normal T lymphocyte maturation process [11,12]. Additionally, as both patients had positive anti-AchR antibodies, it would be reasonable to test for these antibodies before the commencement of anti-PD1 treatment in thymoma patients and avoid treatment due to high risk of toxicity if positive anti-AchR antibodies are found. Lastly, there are no other fatal events reported to date caused by anti-PD1 treatment in thymoma patients.

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Contribution

Dimitrios Mavroudis had the conception.

Dimitrios Mavroudis, Konstantina Thomopoulou and Konstantinos Rounis contributed to the design of the case series.

Konstantina Thomopoulou and Konstantinos Rounis did the analysis, interpretation and drafting of the data.

Eleni Lagoudaki and Anastasios Koutsopoulos and Anastasia Mala contributed to the interpretation of the data.

Ioannis Souglakos, Sofia Agelaki and Dimitris Mavroudis did the critical revision of the article.

Dimitrios Mavroudis did the final approval of the article.

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