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**Pembrolizumab as a novel therapeutic option for patients with refractory thymic epithelial tumor: A case report**

Wong-Chong J *et al*. Pembrolizumab for refractory thymic epithelial carcinoma

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**Abstract**

BACKGROUND

Thymic epithelial carcinomas are rare and have a poor prognosis. Treatment of thymic epithelial carcinoma is multimodal and includes surgery, post-operative radiation therapy, adjuvant and neoadjuvant chemotherapy, or exclusive chemotherapy based on disease resectability. However, there is currently no standard treatment regimen for metastatic and recurrent thymic carcinoma.

CASE SUMMARY

A 45-year-old Caucasian male, with no past medical history, presented with hepatalgia and a cervical mass. A computed tomography (CT) scan showed multiple suspect lesions in the lungs, liver, and anterior mediastinum associated with mediastinal and cervical adenopathy. CT-guided percutaneous biopsies of the liver lesions and anterior mediastinal mass were performed, confirming the histopathology of thymic epithelial carcinoma. Management consisted of several chemotherapy regimens and radiation therapy, administered between April 2016 and December 2018. The patient achieved complete metabolic response. Fluorodeoxyglucose positron emission tomography/CT performed in June 2019 showed disease relapse, with reappearance of a large hypermetabolic hepatic mass and involvement of mediastinal and axillary lymph nodes. Intravenous pembrolizumab (200 mg, every 3 wk) was administered after two prior systemic therapies. The patient’s response to treatment was last documented on March 5, 2020.

CONCLUSION

Pembrolizumab was successful in treatment of a patient with programmed death-ligand 1-negative metastatic thymic carcinoma, pretreated with chemotherapy.

**Key Words:** Thymic epithelial carcinoma; Programmed death-ligand 1 negative; Pembrolizumab; Immune checkpoint; Metastasis; Case report

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**Core Tip:** Thymic epithelial carcinomas are rare and have poor prognosis. The overall 5-year survival rate for patients with thymic carcinoma is about 30%-50%. We present the case of a 45-year-old Caucasian male who presented with hepatalgia and a cervical mass, and was diagnosed with programmed death-ligand 1-negative metastatic thymic carcinoma. The patient underwent pretreatment with platinum-based chemotherapy, after which pembrolizumab was administered as salvage therapy and complete metabolic response was achieved.

**INTRODUCTION**

Thymic epithelial carcinomas are rare and have a poor prognosis. The worldwide incidence is currently estimated to be 1.3 to 3.2 cases *per* million[1,2] and only 0.35 *per* 100000 persons-years in France[3]. Unfortunately, the overall 5-year survival rate is low as well, reportedly 30%-50%[4], and the risk factors are unknown. Epidemiologic studies have indicated that thymic carcinomas mainly occur between 40 and 60 years of age but show no sexual disparity[4,5]. The known symptoms are thoracic in nature and include chest pain, dyspnea, coughing, phrenic nerve palsy, and superior vena cava syndrome. Patients can also be asymptomatic, diagnosed incidentally on routine imaging. Paraneoplastic disorders, such as myasthenia gravis and autoimmune diseases, can be present but to an extent of association much less than with thymoma[6].

The initial assessment and staging of thymic carcinomas is carried out by computed tomography (CT) and/or magnetic resonance imaging and/or positron emission tomography (PET) scan. While these imaging modalities can differentiate thymic carcinomas from thymomas, confirmation of the entity requires histopathology. For the latter, it is recommended that both the Masaoka-Koga classification and Tumor-Node-Metastasis classification (8th edition) be used for proper staging[7]. Treatment is multimodal and includes surgery, postoperative radiation therapy, adjuvant and neoadjuvant chemotherapies, or exclusive chemotherapy based on disease resectability[7,8].

There is currently no standard treatment regimen for metastatic and recurrent thymic carcinoma. Second-line treatment options, including etoposide, ifosfamide, pemetrexed, fluorouracil, gemcitabine, and paclitaxel[9], as well as anti-vascular endothelial growth factor agents, such as sunitinib[10], and immune checkpoint inhibitors [anti-programmed cell death protein 1/programmed death-ligand 1 (PD-L1) antibodies] have provided promising results but further data are required to confirm their efficacy and safety profiles[11-13]. We report herein the successful use of the humanized antibody pembrolizumab as salvage therapy in a patient with a PD-L1-negative metastatic thymic carcinoma, following pretreatment with platinum-based chemotherapy.

**CASE PRESENTATION**

***Chief complaints***

A 45-year-old Caucasian male presented with hepatalgia and a cervical mass. CT scan at admission showed multiple suspect lesions in the lungs, liver, and anterior mediastinum associated with mediastinal and cervical adenopathy.

***History of present illness***

The patient had three episodes of severe right hypochondrium pain.

***History of past illness***

The patient’s medical history was unremarkable.

***Personal and family history***

The patient’s family history was unremarkable.

***Physical examination***

Cardiovascular, abdominal, urinary, hematological and neurological examinations were performed. The cardiovascular, neurological and urinary examinations were normal. The patient presented sensitivity to hepatic palpation and various cervical adenopathies were found.

***Laboratory examinations***

Our histopathology sample was negative for nuclear protein in testis (NUT) protein staining, and no *NUT* gene rearrangement was found by fluorescence *in situ* hybridization. Thus, the patient was not diagnosed with NUT midline carcinoma[14]. PD-L1 assessment was not performed on the histological sample, but it was performed on biopsies at diagnosis (see below) and the PD-L1 status was negative (PD-L1 = 0%). Tumor mutational burden (TMB) was not assessed.

***Imaging examinations***

CT-guided percutaneous biopsies were obtained from the liver lesions and anterior mediastinal mass detected in the initial CT scan. Subsequent histopathological analysis demonstrated epidermal differentiation, suggestive of thymus carcinoma, and thus confirmed the biopsied tissues to be thymic epithelial carcinoma. Follow-up was performed by fluorodeoxyglucose (FDG)-PET scans.

**FINAL DIAGNOSIS**

Thymic epithelial carcinoma.

**TREATMENT**

The patient was administered combination chemotherapy with intravenous cyclophosphamide (500 mg/m2), doxorubicin (50 mg/m2), and cisplatin (50 mg/m2) every 3 wk[15] for six cycles (April to September 2016). CT scan and FDG-PET scan showed a partial morpho-metabolic response after the six cycles, with complete regression of the pulmonary and hepatic hypermetabolic foci but persistent uptake in mediastinal and cervical lymph nodes.

Disease recurrence occurred after 9 mo of surveillance (September 2016 to June 2017), with the appearance of a new mediastinal lymphadenopathy and a single liver metastasis. Second-line platinum-based chemotherapy regimen, consisting of paclitaxel (225 mg/m²) and carboplatin (area under the curve of 6 mg/mL), was administered every 3 wk[16] for six cycles (August to November 2017).

FDG-PET/CT performed in November 2017 assessed dissociated responses and showed complete metabolic response of the cervical and mediastinal lymphadenopathy and the liver metastasis but appearance of a previously undetected right upper latero-cervical hypermetabolic lymphadenopathy. Thus, radiation therapy of the hypermetabolic lymph node with subsequent platinum-based chemotherapy by paclitaxel was planned.

The patient discontinued treatment and presented to the medical oncology unit after 6 mo in July 2018, with complaint of dyspnea due to enlargement of the leftcervical lymph nodes. Re-evaluation by FDG-PET/CT confirmed disease recurrence on the anterior mediastinal mass, superior and inferior diaphragmatic lymph nodes, and single hepatic mass (located between the sixth and seventh hepatic segment). The lungs were clear of any lesion (Figure 1). Radiation therapy (30 Gy in 10 fractions of 3 Gy *per* fraction) was performed urgently on the left cervical lymph nodes with acceptable toxicity in August 2018. Weekly administration of paclitaxel-carboplatin chemotherapy was resumed on August 29, 2018 (1 wk after radiotherapy).

FDG-PET/CT performed in December 2018 showed a durable complete metabolic response after three cycles (Figure 2). Severe grade III peripheral neuropathy led to the discontinuation of both paclitaxel and carboplatin. FDG-PET/CT performed in February 2019 confirmed a complete metabolic response (Figure 3).

FDG PET/CT performed in June 2019 showed disease relapse with the reappearance of several hypermetabolic lesions (Figure 4A). The patient then received intravenous pembrolizumab (200 mg, every 3 wk)[11] after two prior systemic therapies. A dissociated response was obtained after four cycles of pembrolizumab, with a significant increase in FDG uptake of the single liver metastasis. Complete metabolic responses were achieved on some cervical lymph nodes, while other responses were hypermetabolic (Figure 4B). After four additional cycles, a complete metabolic response was observed on the hepatic mass and cervical lymphadenopathy, with stability of metabolism of the superior clavicular and right axillary lymph nodes (Figure 4C) (Figure 5).

**OUTCOME AND FOLLOW-UP**

The response to treatment was last documented on March 5, 2020. The patient experienced symptoms of fatigue, sleepiness, and residual chemotherapy-induced sensory neuropathy. No immune-related adverse events (irAEs), and notably no thyroiditis, hepatitis, or paraneoplastic syndrome occurred.

**DISCUSSION**

High expression of PD-L1 (> 50%) is known to provide a better response to immune checkpoint inhibitors than low or no PD-L1 expression in thymic carcinoma[5]. The successful use of pembrolizumab, a checkpoint inhibitor targeting PD-L1, was described in two open-label single-arm phase II trials[11,12] and case reports[13,17]. Nivolumab, another checkpoint inhibitor that blocks PD-L1, is routinely used as salvage therapy to treat refractory thymic epithelial carcinoma[18-20].In a post-hoc analysis on patients treated by pembrolizumab, Giaccone *et al*[11] showed that progression-free survival was longer in patients with high PD-L1 expression (PD-L1 ³50%) than in those with low (PD-L1 1%-49%) or no expression (median survival: 24 mo *vs* 2.9 mo). Overall survival was also longer in patients with high expression than in those with low or no expression [median survival (50% of patients still alive at end of study): Not reached *vs* 15.5 mo].

Regarding irAEs, Cho *et al*[12] discouraged the use of immune checkpoint inhibitors in patients with thymoma and/or history of autoimmunity. Fatal AEs have been reported in that population. Most patients with thymoma (71.4%, 7 of 11 patients) presented with grade 3 or 4 irAEs such as myocarditis, hepatitis, myasthenia gravis, thyroiditis, colitis, conjunctivitis, and nephritis. By contrast, only 15.4% (4 of 26 patients) with thymic carcinoma report grade 3 or 4 irAEs including hepatitis, myasthenia gravis, and subacute myoclonus. Most patients who discontinue treatment due to irAEs recover. Some patients receive a combination of high-dose corticosteroids and immunosuppressive agents[15]. Reported cases of polymyositis and myocarditis are managed by high-dose corticosteroids but also require the placement of pacemakers[5]. Thus, the management of grade 3 or 4 irAES is challenging and should involve multidisciplinary teams.

The patient in our case report had a very good response to immunotherapy despite the absence of PD-L1 expression. PD-L1 is highly expressed in normal thymic epithelial cells. PD-L1 immunostaining is typically performed on liver biopsies to avoid confounders of that predictive biomarker, but this is not the standard practice for histopathological analysis of thymus biopsies[20]. Thus, the biopsies were performed at diagnosis, prior to the initiation of chemotherapy. As mentioned above, the PD-L1 status was negative (PD-L1 = 0%). However, PD-L1 immunostaining is an imperfect predictor of response, and it should not be used as a definitive biomarker for the selection of immunotherapy[21]. First, false negatives may arise when biopsy material is insufficient or archived, as the expressed protein can degrade over time. Second, PD-L1 expression may be focally heterogeneous at the target sites and can be missed if the biopsy is too small[22]. It can also vary according to anatomical site in an individual[23]. Third, prior platinum-based chemotherapy may exert immunomodulatory effects on the tumor microenvironment, leading to the up-regulation of PD-L1 expression in tumor cells[24], which would justify repeating biopsy collection and analysis before each new line of therapy is initiated. It is important to note that in our case, no repeat biopsy was performed to confirm those hypotheses. Finally, the scoring method for evaluating PD-L1 immunostaining is subjective and lacks standardization, with the use of multiple antibodies that may not be validated[25] and the use of variable thresholds for positivity[26].However, a durable objective response has been reported in epithelial carcinoma and other solid tumors, regardless of PD-L1 status[26,27].

Other biomarkers, such as the combined positive score (CPS), are currently being evaluated[28]. CPS takes into account tumor-infiltrating immune cells, which represent a positive prognostic feature[21] and may be more relevant clinically and more reproducible. Immune pathways are complex and still need to be understood, including the clinical relevance of PD-L2- in PD-L1-negative status of patients[21,29].

**CONCLUSION**

We report herein the successful use of pembrolizumab in a patient with PD-L1-negative metastatic thymic carcinoma, pretreated with platin-based chemotherapy. Additional clinical trials are required to evaluate the role of immunotherapy in a first-line setting when considering the promising results and excellent tolerance of immunotherapy as second-line treatment. Research is also needed to develop more reliable predictive biomarkers and better understand immune pathways and their implications for cancer immunotherapy.

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**Footnotes**

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**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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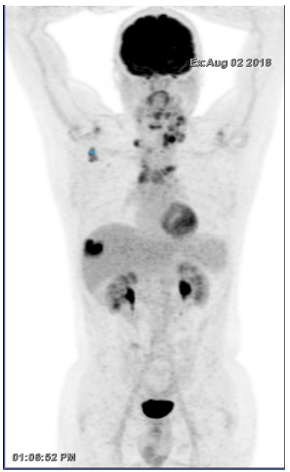
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Grade D (Fair): 0

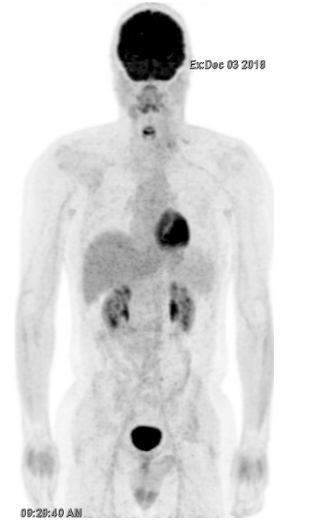
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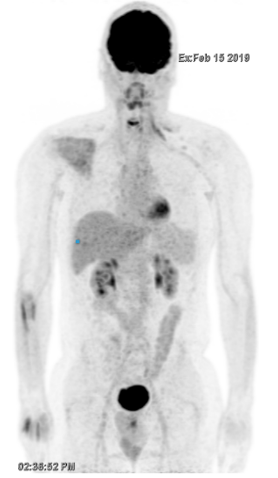
**Figure Legends**



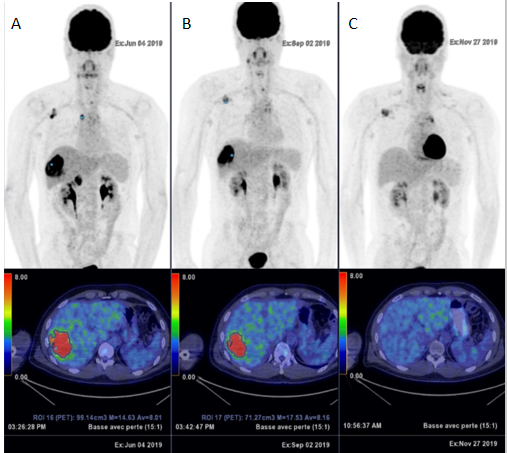
**Figure 1** **Disease recurrence with fluorodeoxyglucose-positron emission tomography/computed tomography** **showing cervical, right axillary, and mediastinal lymphadenopathies, and a single hepatic lesion (August 2018).**



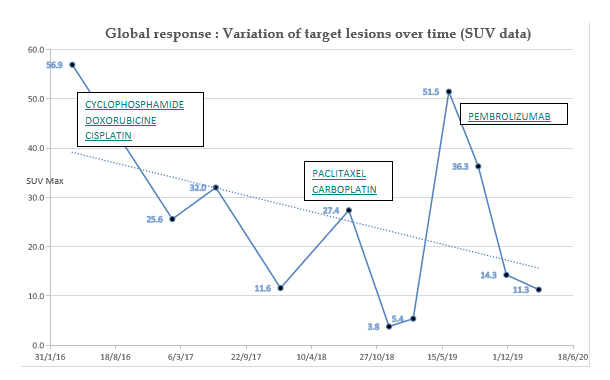
**Figure 2** **Response to palliative radiation therapy followed by three cycles of paclitaxel-carboplatin systemic therapy (December 2018).**



**Figure 3 Confirmation of complete metabolic response by fluorodeoxyglucose-positron emission tomography/computed tomography (February 2019).**



**Figure 4** **Disease progression.** A: Disease recurrence with a large hypermetabolic hepatic mass, mediastinal and axillary lymph nodes (June 2019); B: Dissociated response after four cycles of pembrolizumab with decrease in fluorodeoxyglucose (FDG) uptake on the axillary and mediastinal lymph nodes, but increase in FDG uptake on the liver metastasis (standardized uptake value: 14.63 to 17.53) (September 2019); C: Complete metabolic response of the liver mass and lymph nodes after eight cycles of pembrolizumab (November 2019).



**Figure 5 Global response: Variation of SUV of target lesions over time, from start of frontline systemic treatment to last follow-up.** The corresponding treatments are noted on the graph.



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