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Case Report

Primary Pleural Angiosarcoma Treated with Nivolumab and Ipilimumab: A Case Report

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Abstract
Primary pleural angiosarcoma (PPA) is a rare and clinically fatal pleural tumor originating from vascular endothelial cells. Herein, we presented the case of a 73-year-old man who was referred to our emergency room with complaints of right chest and back pain for a few days. Chest computed tomography revealed massive pleural effusion and a large mass in the right chest cavity. Thoracoscopic examination demonstrated a large hemorrhagic tumor on the parietal pleura whose pathological analysis indicated PPA. The patient received immunotherapy combined with nivolumab and ipilimumab. A cycle of nivolumab and ipilimumab improved his hemorrhagic anemia and reduced the pleural effusion and tumor size. This treatment outcome suggests that nivolumab and ipilimumab comprise a vital treatment option for PPA.

Introduction

Angiosarcoma is a rare malignant tumor of vascular endothelial origin and has high mortality. It can develop in any portion of a soft tissue structure or viscera, accounting for approximately 2% of all soft tissue sarcomas [1]. The most common sites include the skin, especially of the head and neck, followed by the breast, extremities, and liver [1]. Primary

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pleural angiosarcoma (PPA) is extremely rare and has high malignancy. To the best of our knowledge, only 46 case reports have been published in the literature till 2020 [2].

Owing to its rarity, there is no consensus regarding the treatment of PPA. Current treatment methods, including surgery, chemotherapy, and radiotherapy, are based on case reports and angiosarcoma treatment guidelines. Regardless of the treatment approach, the usual prognosis of PPA is not good. Approximately 80% patients die because of PPA within 10 months of diagnosis, and the 2-year survival rate is approximately 4.4% [3].

Herein, we reported a rare case of a patient with PPA who was treated with nivolumab and ipilimumab. To the best of our knowledge, this report was the first to report that nivolumab and ipilimumab are effective for PPA.

Case Presentation

A 75-year-old man presented to our emergency room with complaints of right chest and back pain. At baseline, he could walk 8 km daily. However, over the past 1 week, his pain had gradually worsened with movements, rendering him unable to move independently. The patient had a history of diabetes mellitus and hypertension, which was under regular medical control. Moreover, he was an ex-smoker (a pack daily for the past 38 years, quitting 15 years ago). Furthermore, the patient had been exposed to asbestos when he was an engineer in an auto parts factory. At initial evaluation, the SpO_2 level in room air, blood pressure, and heart rate of the patient were 93%, 160/50 mm Hg, and 126 beats/min in sinus rhythm, respectively. Physical examination revealed that the breath sounds of the right lung were decreased. Laboratory parameters showed that the hemoglobin, hematocrit, and white blood cell levels were 10.1 mg/dL, 30.7%, and 19,500 cells/μL (with 89.2% neutrophils and 5.7% lymphocytes), respectively. The serum protein, albumin, and C-reactive protein levels were 5.8 g/dL, 2.6 g/dL, and 8.23 mg/dL, respectively. Other biochemical parameters, such as creatinine, were normal. For coagulation parameters, the activated partial thromboplastin time and prothrombin time international normalized ratio were 20.5 s and 1.11, respectively. Contrast-enhanced computed tomography (CT) of the chest revealed a large mass in the right lung, which was complicated with hemorrhagic pleural effusion and passive atelectasis in the right lung (Fig. 1a, c). Conversely, the CT showed no pulmonary thrombosis. Diagnostic thoracentesis revealed that the pleural effusion was hemorrhagic on gross inspection. The cytological examination of the pleural effusion was not helpful.

Thoracoscopy was performed for diagnosis (Fig. 2), which revealed that the large tumor on the parietal pleura in the dorsal region of the right lung was fragile and bleeding. The tumor had not invaded the lung and was suspected to be a pleural tumor or an organized hematoma. The intraoperative rapid pathological diagnosis suspected poorly differentiated carcinoma or malignant mesothelioma. Histological findings based on hematoxylin and eosin staining revealed that the tumor comprised sheets of epithelioid cells with enlarged hyperchromatic nuclei and prominent nucleoli. Vascular lumen-like structures, including abundant red blood cells, were scattered across the tumor (Fig. 3a). Immunohistochemistry demonstrated that the tumor cells were strongly positive for CD31, a vascular endothelial marker (Fig. 3b). Other endothelial markers (CD34, factor VIII, and claudin 5) were focally positive. Furthermore, the tumor cells were positive for pan-cytokeratin (CAM5.2) and negative for calretinin (Fig. 3c), thyroid transcription factor 1, carcinoembryonic antigen, and epithelial cell adhesion molecule. Based on these histological and immunohistochemical analysis results, the patient was diagnosed with PPA. Programmed cell death-ligand 1 (PD-L1; clone 22C3) was diffusely positive in the tumor cells (Fig. 3d).

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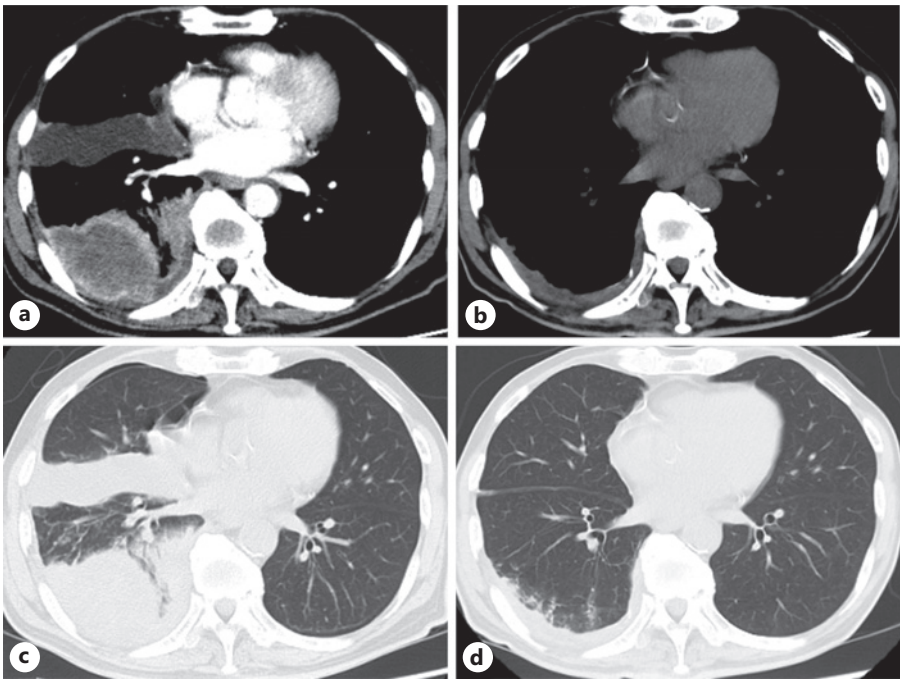

Fig. 1. Chest computed tomography (CT) images throughout the course of the treatment. **a**, **c** Chest contrast-enhanced CT axial view following the drainage of the right pleural effusion before chemotherapy on day 11. A large mass is detected in the right thoracic cavity with contrast enhancement. Pleural effusion is found in the right-sided chest cavity and passive atelectasis in the right lung. **b**, **d** Chest CT axial view after 37 days of chemotherapy, showing a remarkable reduction of the tumor size and pleural effusion.

Accurately diagnosing this disease is imperative to ensure the delivery of adequate chemotherapy; however, we had insufficient time to wait for the final diagnostic report. The patient received repeated blood transfusions (total volume: 2,520 mL) because of the persistent bleeding from the tumor and an urgent treatment was warranted to rescue him. Based on the preliminary results of the intraoperative rapid pathological diagnosis that suspected the tumor to be poorly differentiated carcinoma or malignant mesothelioma, we decided to treat him with immunotherapy combined with nivolumab (360 mg every 3 weeks) and ipilimumab (1 mg/kg every 6 weeks), a standard treatment for malignant mesothelioma. As the treatment progressed, the anemia of the patient improved and he did not require further blood transfusions (Fig. 2). CT showed reduction in the tumor size and pleural effusion (Fig. 1b, d). He received the second dose of nivolumab on day 21 following the first dose; however, a second cycle of nivolumab and ipilimumab was not administered as the patient had developed acute myocardial infarction (AMI) on day 37 following the first dose of nivolumab and ipilimumab. The patient unfortunately died of pulmonary infection despite his good response to the treatment.

Discussion

Herein, we reported a rare case of PPA treated with nivolumab and ipilimumab. PPA is an extremely rare disease, and hence, its pathogenesis and etiology have remained uninvestigated. Several risk factors of PPA that have been reported include prior radiotherapy, history of tuberculous pyothorax, and exposure to asbestos [2]. Herein, the patient had been exposed to asbestos earlier in life, with PPA taking at least 13 years to develop since the patient's last exposure to asbestos.

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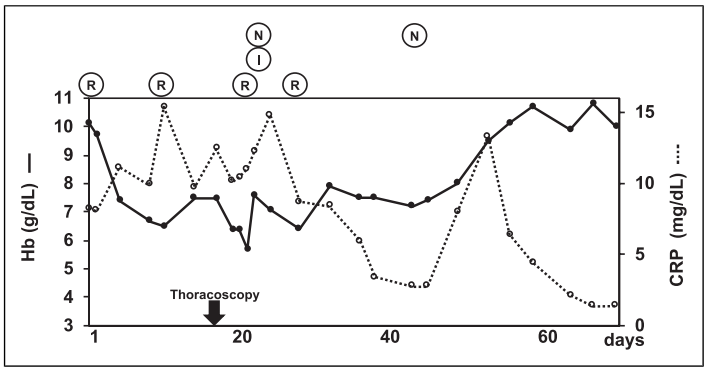

Fig. 2. Levels of hemoglobin (Hb) (solid line) and serum C-reactive protein (CRP) (dashed line) throughout the treatment course. R with a circle denotes red blood cell transfusion, N with a circle denotes nivolumab administration (360 mg), and I with a circle denotes ipilimumab administration (1 mg/kg). Following admission, several red blood cell transfusions were required because of progressive anemia. However, owing to chemotherapy, anemia improved, and blood transfusions were no longer required. The CRP level also reduced with treatment.

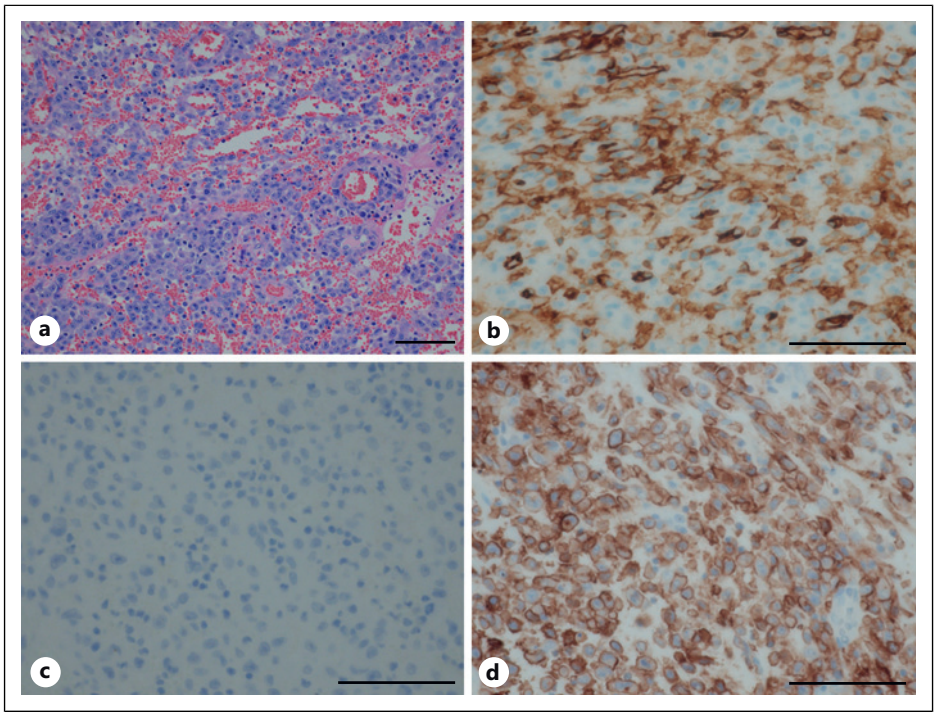

Fig. 3. Histological results of the specimen obtained via thoracoscopy. The bars show 100 μm. **a** Photomicrograph of hematoxylin and eosin staining (× 200 magnification). Epithelioid cells with enlarged hyperchromatic nuclei and prominent nucleoli composed the sheets. The tumor contained vascular lumen-like structures with abundant red blood cells scattered. Immunohistochemistry results (× 400 magnification): (**b**) CD31, (**c**) calretinin, and (**d**) PD-L1. The tumor cells were positive for CD31, negative for calretinin, and diffusely positive for PD-L1.

The most common clinical symptoms of PPA include chest pain (47.5%), followed by dyspnea (35%), and hemoptysis (27.5%). Pleural effusion (70%), focal or diffuse pleural thickening (40%), and mass lesions (approximately 50%) are frequently observed on radiological evaluation [2]. Similar to the case in a previous report, our patient exhibited a large

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mass in the right lung and massive pleural effusion. As the clinical symptoms and radiological signs are not specific, they are difficult to distinguish from other pleural tumors, such as mesothelioma. Therefore, pathology is essential for diagnosing PPA. As noninvasive biopsy, surgical biopsy without direct vision, and nontargeted biopsy are not useful, tumor resection or biopsy performed using video-assisted thoracoscopy surgery are the most helpful diagnostic approaches for PPA [2]. Herein, the specimen collected via video-assisted thoracoscopy surgery led to the diagnosis of PPA.

A general consensus regarding PPA treatment is yet to be established. Current treatment approaches of PPA refer to case reports and/or angiosarcoma guidelines. Regarding the clinical outcome of patients with angiosarcomas treated with chemotherapy, primarily taxanes, the response rate, and progression-free survival range from 18% to 89% and 4–9.5 months, respectively [4–7]. A report showed that PPA responded well to nanoparticle albumin-bound paclitaxel [8]. Immunotherapy has been established as an effective treatment approach for various cancers including melanoma and non-small lung cancer. Anticancer immunotherapy, including programmed cell death-1 (PD-1)/PD-L1 antibodies, plays an important role in cancer treatment and is reportedly also effective for angiosarcoma [9–11]. Wagner et al. [9] reported that nivolumab and ipilimumab were effective for metastatic or unresectable angiosarcoma. The objective response rate (ORR) was 25% for angiosarcoma not including PPA, and the ORR was 60% for primary cutaneous scalp or face angiosarcoma [9]. PD-L1 expression indicates a better response rate in tumors [12]. In Wagner's report, 1 patient who achieved partial response had a tumor proportion score of 30% (22C3 antibody was used for the analysis) [9]. A case report showed that anti-PD-1 therapy has an effect on PPA whose positivity of PD-L1 with 22C3 pharmDx was 5% [13]. Herein, we described a patient with PPA who responded well to nivolumab and ipilimumab. The proportion of tumor cells expressing PD-L1 was high. To the best of our knowledge, this is the first reported case of PPA treated with nivolumab and ipilimumab. Further investigation is warranted to elucidate the efficacy of immunotherapy in patients with pleural angiosarcoma and its association with PD-L1 expression.

Finally, the patient experienced AMI 37 days following the first dose of nivolumab and ipilimumab. AMI might be a side effect of the treatment. In a previous case report, AMI occurred 10 days following the 4 cycles of nivolumab for melanoma [14]. It was suggested that nivolumab causes coronary artery disease as it is associated with the dysregulation of immune responses, such as enhanced T cell activity. However, AMI as a side effect of immune checkpoint inhibitors has been less documented compared with myocarditis, pericarditis, and heart block. Furthermore, in our patient, the period between the onset and the last dose of nivolumab was much longer than the other case report [14]. In addition, the patient exhibited numerous risk factors for coronary artery diseases, such as age and history of diabetes, hypertension, and smoking. Thus, we cannot determine whether AMI occurred owing to the administration of nivolumab and ipilimumab because of limited evidence; nevertheless, the risk for AMI should be considered when administering nivolumab and ipilimumab for angiosarcoma.

Conclusion

PPA is an extremely rare disease that has a high malignancy, and consequently, an effective treatment is yet to be established. This case report suggests that nivolumab and ipilimumab can have a substantial therapeutic effect on PPA, especially PD-L1-expressing PPA. The Care Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529447).

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Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report including images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed equally to the conceptualization of this article; M.N., K.W., and K.U. drafted this manuscript. M.N., K.W., T.N., K.Y., K.F., N.H., J.M., and K.U. contributed to the patient management. K.F., N.H., and J.M. provided the clinical input for the thoracoscopic examination. Y.M. and T.M. provided pathology input.

Data Availability Statement

All data supporting the findings of this case report was included in this article. Further inquiries can be directed to the corresponding author.

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