Urology Case Reports 39 (2021) 101843

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Avelumab plus axitinib therapy for renal cell carcinoma in a patient with pulmonary alveolar proteinosis: A case report

Nobuaki Shimizu [a,*], Masaru Hasumi [a], Kazumichi Muramatsu [a], Yusuke Tsuji [a,b], Youtarou Takaku [c]

[a] Department of Urology, Gunma Cancer Center, Ota, Japan
[b] Department of Urology, Shibukawa Medical Center, Shibukawa, Japan
[c] Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, Kumagaya, Japan

ARTICLE INFO

Keywords:
Avelumab
Axitinib
Pulmonary alveolar proteinosis
Renal cell carcinoma

ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the abnormal accumulation of surfactant-derived substances in the lungs. To the best of our knowledge, the successful treatment of metastatic renal cell carcinoma in patients with PAP has not been reported. Here, we describe such treatment of a patient via avelumab plus axitinib therapy. After four courses of treatment, computed tomography showed size reduction of the pulmonary metastatic nodule and improvement of PAP. This study highlights that avelumab plus axitinib therapy is a safe and effective treatment option for metastatic renal cell carcinoma, even in patients with PAP.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the abnormal accumulation of surfactant-derived substances in the alveoli and terminal bronchi caused by the overproduction or impaired degradation of surfactants.[1]

Immune checkpoint inhibitors (ICIs) have recently been used in the treatment of metastatic renal cell carcinoma (RCC). However, its use in patients with PAP has not been reported.

Here, we describe the successful treatment of a patient with metastatic RCC and PAP via avelumab plus axitinib therapy.

2. Case presentation

A 61-year-old man with a two-year history of PAP presented with macroscopic hematuria. Bronchioalveolar lavage revealed a creamy white fluid. Histopathologic examination of transbronchial biopsy specimen stained with periodic acid-Schiff reagent showed proteinaceous components. These findings were consistent with a definitive diagnosis of PAP. Moreover, serologic tests revealed the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies, suggestive of an autoimmune etiology of PAP.

As the patient had a normal lung function, no treatment was administered to the patient for PAP.

Abdominal CT scan revealed 3.5 × 3.4 cm tumor in the middle of the right kidney (Fig. 1a). Chest CT showed ground-glass opacities, septal reticulations and parenchymal consolidation, forming a ''crazy paving'' pattern characteristic of PAP (Fig. 1b).

The patient underwent a laparoscopic radical nephrectomy without any complication. Histopathologic examination of the resected tumor confirmed the diagnosis of clear cell carcinoma.

Nine months later, CT scan showed several lung nodules which were suspected to be lung metastases or inflammation. However, after one month, the nodules increased in size (Fig. 2a), suggestive of metastatic RCC. The chest CT at that time showed a so-called crazy pave pattern, which was almost the same image as before nephrectomy (Fig. 2b). Based on the International Metastatic RCC Database Consortium risk classification, the patient was at an intermediate risk.

We initiated avelumab plus axitinib therapy. Avelumab was administered at a dose of 10 mg/kg as a 1-hour intravenous infusion every two weeks. Meanwhile, axitinib was given orally at a starting dose of 5 mg twice daily on a continuous dosing schedule. However, the patient presented with an increase in creatinine and urinary protein levels after the third course. As such, the dose of axitinib was reduced to 3 mg twice daily for five days a week in the fourth course of therapy.

After four courses of avelumab plus axitinib therapy, CT showed reduction of the pulmonary metastatic nodules and improvement of PAP (Fig. 3a, Fig. 3b).

* Corresponding author. Department of Urology, Gunma Cancer Center, 617-1Takabayashi-nishi, Ota, Gunma, 373-8550, Japan.
E-mail address: nshimizu@gunma-cc.jp (N. Shimizu).

https://doi.org/10.1016/j.eucr.2021.101843
Received 10 August 2021; Received in revised form 5 September 2021; Accepted 8 September 2021
Available online 9 September 2021

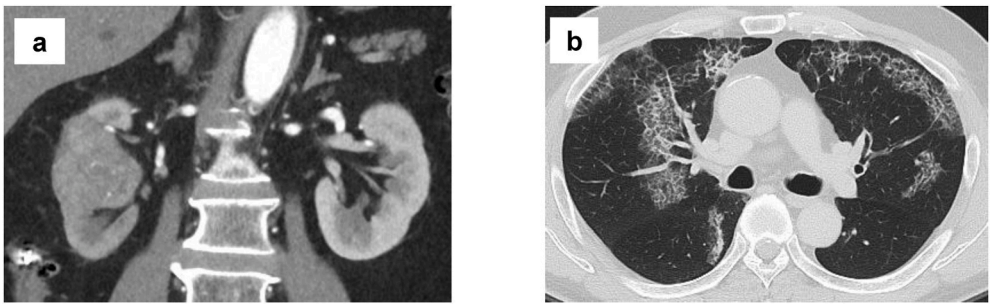

Fig. 1. Initial radiologic findings. (a) Abdominal computed tomography (CT) shows a 3.5 × 3.4 cm mass in the middle pole of the kidney. (b) Chest CT revealed ground-glass opacities, septal reticulations, and parenchymal consolidation, forming a crazy-paving pattern.

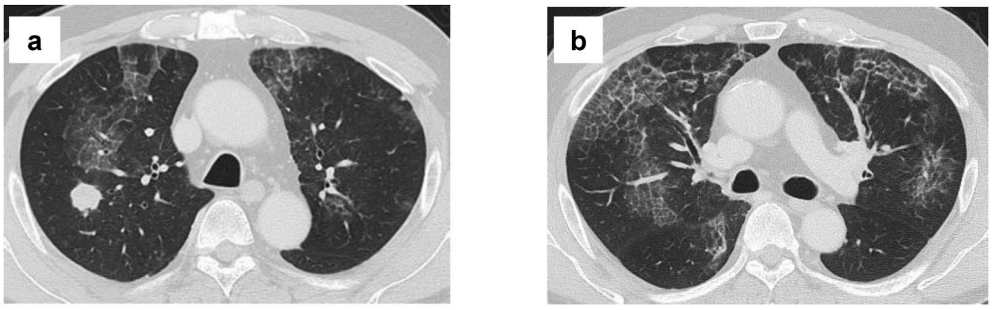

Fig. 2. Chest CT taken before avelumab plus axitinib therapy shows (a) a 2.1 × 1.7 cm lung nodule and (b) a so-called crazy pave pattern, which was almost the same image as Fig.1b.

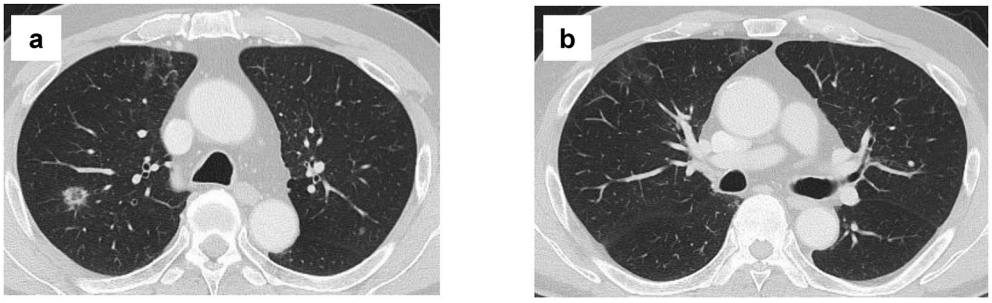

Fig. 3. Chest CT taken after six months of therapy shows (a) reduction of the nodule size to 1.3 × 0.9 cm and (b) improvement of the patient's pulmonary alveolar proteinosis.

3. Discussion

Based on pathogenesis, PAP can be divided into three main types: autoimmunity, secondary and congenital. Congenital PAP, usually caused due to genetic mutations, is especially common in children. In contrast, autoimmune PAP accounts for the majority of adult cases.

In adults, PAP is caused by decreased surfactant clearance due to impaired alveolar macrophage function. Attenuation of alveolar macrophage maturation is usually caused by inadequate GM-CSF signaling. GM-CSF is secreted by type II alveolar epithelial cells. The binding of GM-CSF to its receptors on immature alveolar macrophages facilitates maturation. In autoimmune PAP, alveolar macrophage maturation is inhibited by the presence of anti-GM-CSF antibodies, which block GM-CSF binding to its receptor.[1,2]

To the best of our knowledge, successful treatment of RCC in patients with autoimmune PAP has not been reported.

Currently, dual Immune checkpoint inhibitor therapy or combination therapy (i.e., ICI plus molecular-targeting drug) is considered the first-line treatment for metastatic RCC.

ICIs have been reported to cause immune-related adverse events (irAEs) such as myocarditis, thyroiditis, interstitial pneumonia and so on. The detailed mechanisms of irAEs are unknown, but they are thought to be caused by the activation of immunity by ICIs.[3] So far, it has been unclear how ICIs administration affect autoimmune type PAP.

In Japan, only three formulations (i.e., pembrolizumab plus axitinib, avelumab plus axitinib, and ipilimumab plus nivolumab) have been approved for the management of RCC.

The response rates of these treatments are approximately 50%, which is not significantly different from one another.[4,5]

Although overall adverse events (AE) were similar, avelumab plus axitinib had a lower discontinuation rate compared to the other approved formulations. Furthermore, the steroids usage rate due to immune-related AEs is considered low.[4,5]

In our case, the etiology of PAP was likely autoimmune. Hence, avelumab plus axitinib was selected due to the lower rates for immune-related AEs.

Fortunately, the patient did not present with serious AEs that prompted discontinuation of treatment. After four courses of therapy, the patient's PAP improved.

As spontaneous resolution of PAP has been reported in about 7–30%

of cases,[1] the exact efficacy of avelumab plus axitinib is still unclear. Further studies are necessary to determine whether avelumab plus axitinib is effective for the treatment of PAP.

4. Conclusion

We reported the successful treatment of RCC via avelumab plus axitinib therapy in a patient with PAP. Although the patient presented with minor AEs of treatment, improvement in metastatic RCC and PAP were observed. To the best of our knowledge, this is the first case to highlight the relative safety and efficacy of avelumab plus axitinib in the management of RCC, even in patients with PAP.

Consent

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

Sources of funding

This case report had no funding or sponsors.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. *Lancet Respir Med*. 2018;6(7):554–565. https://doi.org/10.1016/S2213-2600(18)30043-2.
2. Borie R, Danel C, Debray MP, et al. Pulmonary alveolar proteinosis. *Eur Respir Rev*. 2011;20(120):98–107. https://doi.org/10.1183/09059180.00001311.
3. Postow MA, Sidlow R, Hellmann MD, et al. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018 Jan 11;378(2):158–168, 10.1056.
4. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1103–1115. https://doi.org/10.1056/nejmoa1816047.
5. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277–1290. https://doi.org/10.1056/nejmoa1712126.