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CASE REPORT

Two Cases of Retroperitoneal Fibrosis During Anti-programmed Cell Death 1 Antibody Treatment

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ABSTRACT —— ***Background.*** Retroperitoneal fibrosis is characterized by fibrosis around the abdominal aorta and iliac arteries. Two-thirds of reported cases had idiopathic causes. Idiopathic retroperitoneal fibrosis is thought to result from a local inflammatory reaction to antigens in the atherosclerotic plaques of the abdominal aorta. Therefore, it is thought that idiopathic retroperitoneal fibrosis may be a manifestation of a systemic autoimmune or inflammatory disease. In contrast, anti-programmed cell death 1 (anti-PD-1) antibodies may overexpress innate immunity. There have been only two case reports on retroperitoneal fibrosis during anti-PD-1 antibody treatment. We encountered two cases of retroperitoneal fibrosis during anti-PD-1 antibody treatment. ***Cases.*** Case 1 involved a 57-year-old man who experienced recurrence of squamous cell lung carcinoma after resection. More than 75% of his cancer cells were positive for programmed cell death ligand 1 (PD-L1). He experienced urinary urgency after one year and six months of nivolumab treatment. Computed tomography revealed a homogeneous plaque that was isodense with muscle surrounding the abdominal aorta and iliac arteries. Positron emission tomography revealed the accumulation of fluorodeoxyglucose at the same site. The serum IgG4 level was normal. Although a biopsy specimen was not obtained, the patient was diagnosed with retroperitoneal fibrosis. The patient was treated with steroids. Case 2 involved a 64-year-old man with pulmonary large cell carcinoma. An analysis of the cancer cells revealed that 50-74% of the cells were positive for PD-L1. Lower back pain appeared after one year and 11 months of pembrolizumab treatment. Computed tomography revealed right hydronephrosis and homogeneous plaque on the right side of the abdominal aorta. Although a biopsy specimen was not obtained, the patient was diagnosed with retroperitoneal fibrosis. The patient improved once with steroids but relapsed. ***Conclusion.*** We hypothesized that the administration of anti-PD-1 antibodies may have affected the onset of retroperitoneal fibrosis.

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KEY WORDS —— Retroperitoneal fibrosis, Anti-programmed cell death 1 (anti-PD-1) antibody, Nivolumab, Pembrolizumab

INTRODUCTION

Retroperitoneal fibrosis is characterized by fibrosis around the abdominal aorta and iliac arteries, as well as occasional ureteral involvement. One-third of reported cases had secondary causes (e.g., neoplasm, collagen disease, infection, surgery, radiotherapy, and drugs). Two-thirds of reported cases were idiopathic. Idiopathic retroperitoneal fibrosis is thought to result from a local inflammatory reaction to antigens in the atherosclerotic plaques of the abdominal aorta. Therefore, autoimmune diseases that involve other organs are frequently associated with retroperitoneal fibrosis. This suggests that it might be a manifestation of systemic autoimmune or inflammatory disease.[1] In contrast, anti-programmed cell death 1 (anti-PD-1) antibodies may overexpress innate

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immunity.[2] There are only two case reports of retroperitoneal fibrosis during anti-PD-1 antibody treatment. We encountered two cases of retroperitoneal fibrosis during anti-PD-1 antibody treatment.

CASE REPORTS

Case 1

A 57-year-old man presented with retroperitoneal fibrosis. He had no remarkable medical history. The patient had a 35 pack-year smoking history. In January 2014, right upper lobectomy combined with chest wall resection was performed for squamous cell carcinoma of the right lung. More than 75% of the cancer cells were positive for anti-programmed cell death 1 (anti-PD-1) [immunohistochemistry using PD-L1 IHC 22C3 pharmDx (Dako, Inc.)]; postoperative irradiation of the chest wall was added. In January 2016, positron emission tomography (PET) revealed metastasis of the right pulmonary hilar and axillary lymph nodes and pleural dissemination. Four courses of chemotherapy with cisplatin and gemcitabine were administered. Thereafter, from May 2017, nivolumab (3 mg/kg) was administered 40 times at two-week intervals. In October 2018, the patient suffered urinary urgency. In January 2019, computed tomography (CT) revealed homogeneous plaque that was isodense with muscle. The plaque surrounded the abdominal aorta and iliac arteries (Figure 1A). The accumulation of fluorodeoxyglucose (FDG) was observed on PET at the same site (Figure 1B). Left hydronephrosis was observed. His serum IgG and IgG4 levels were normal. His serum WBC count was normal at 7330/μl. His CRP level was slightly high at 2.87 mg/dl. The erythrocyte sedimentation rate at one hour was high at 35 mm. The serum carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA), and squamous cell carcinoma antigen levels were within the normal limits. Antinuclear antibodies were also normal. The urinary leukocyte count was between 10 and 19 per high-power field (HPF), and the urinary erythrocyte count was between 50 and 99 per HPF. No other abnormalities, including autoimmune diseases, were recognized. In January 2019, due to the suspicion of retroperitoneal fibrosis, nivolumab was discontinued. The patient did not give his consent for a biopsy. In March 2019, prednisolone (PSL; 40 mg) was administered. At one month after the initiation of internal use, the homogeneous plaque had disappeared. The dose of PSL was gradually decreased and PSL was terminated in April 2020. Nivolumab has not been readministered as of May 2022, and no recurrence of the tumor has been observed.

Case 2

A 64-year-old man presented with retroperitoneal fibrosis. The patient had diabetes and angina pectoris, and a 28 pack-year smoking history. In 2005, a stent was placed in the right common iliac artery due to arteriosclerosis obliterans. In May 2016, chest CT revealed a 1.7 cm nodule on the pulmonary left upper lobe and an enlarged mass of the paraaortic lymph node. Contrast-enhanced magnetic resonance imaging revealed a 5 mm abnormal imaging effect that was suspected to be a brain metastasis of the left frontal lobe. The abnormal imaging feature shrank naturally after one month. In July 2017, large cell carcinoma was diagnosed by thoracoscopic partial resection of the lung, and the PD-L1 positivity rate of the tumor cells was determined to be 50-74%. Beginning in July 2017, 2 mg/kg of pembrolizumab was administered 28 times at three-week intervals. In June 2019, lower back pain was reported. CT re-

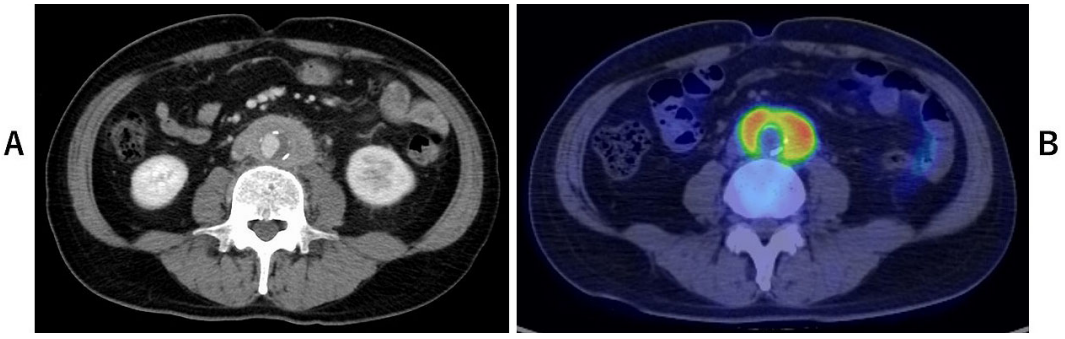

Figure 1. **(A)** CT shows a homogeneous plaque that is isodense with muscle around the abdominal aorta. **(B)** PET shows the accumulation of FDG in the plaque.

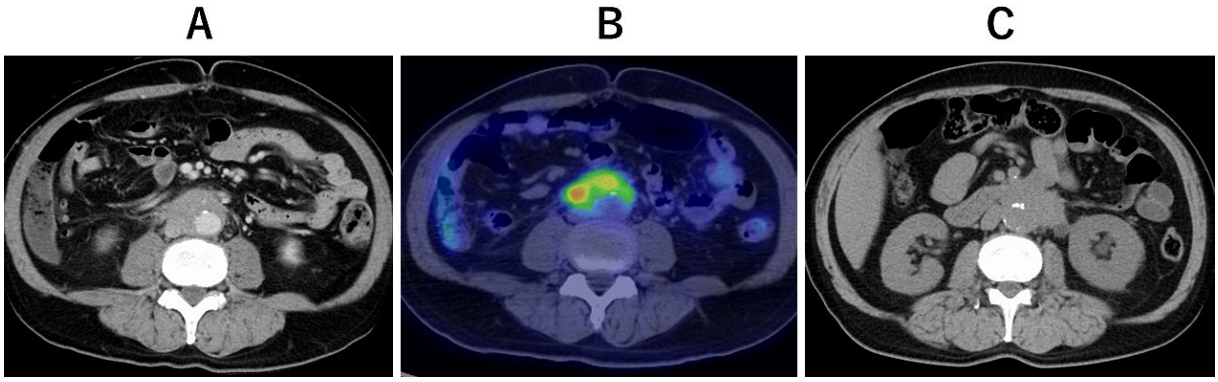

Figure 2. **(A)** CT reveals a homogeneous plaque on the right side of the abdominal aorta. **(B)** PET shows the accumulation of FDG in the plaque. **(C)** CT shows a homogeneous plaque on the left side of the abdominal aorta.

vealed right hydronephrosis and a homogeneous plaque on the right side of the abdominal aorta (Figure 2A), and PET showed the accumulation of FDG (Figure 2B). The serum WBC count was normal, at 8470/μl. The CRP level was slightly high at 1.64 mg/dl. His serum CEA and CYFRA levels were within the normal limits. His serum IgG and IgG4 levels were normal. Although a biopsy specimen was not obtained, the patient was diagnosed with retroperitoneal fibrosis. PSL was initiated at 40 mg, with the dose gradually decreased to 3 mg. In April 2020, an enlarged metastatic paraaortic lymph node was observed and was subsequently removed. Histologically, the lymph node was large cell carcinoma that was strongly positive for PD-L1, similarly to the primary lesion. In January 2021, lower back pain reappeared, and CT revealed a homogeneous plaque on the left side of the abdominal aorta (Figure 2C) and left hydronephrosis. The serum WBC count was normal at 9370/μl. The CRP level was slightly high at 1.29 mg/dl. The urinary leucocyte count was 5-9 per HPF. The patient was diagnosed with retroperitoneal fibrosis. The dose of PSL was increased to 40 mg and then gradually reduced to 5 mg. No recurrence of the tumor, including brain metastasis, has been observed as of May 2022.

DISCUSSION

As a mechanism of idiopathic retroperitoneal fibrosis, it is thought that the $CD4^+$ T cells in the aortic wall are activated by antigens, and IL-6 and eotaxin are secreted, thereby allowing fibroblasts to mature into myofibroblasts and secrete collagen.[3]

Regarding drug-related retroperitoneal fibrosis, there are many reports of ergot alkaloids used as migraine headache drugs. The pathogeneses include the profibrotic-reactive haptenic effect or feedback rebound release of serotonin. These induce the transforming growth factor-β (TGF-β)/Smads cascade, which enhances myofibroblast proliferation, and excessive production of extracellular matrix components, such as collagen, fibronectin, tenascin and glycosaminoglycan.[4]

An immune-related agent reported as the cause of retroperitoneal fibrosis is etanercept, a soluble tumor necrosis factor-α (TNF-α) receptor.[5] However, infliximab and adalimumab, monoclonal antibodies against TNF-α, have been reported to be effective in the treatment of retroperitoneal fibrosis.[6] It is hypothesized that this phenomenon may have arisen due to differences in drugs kinetics and mechanisms of action.

The association between anti-PD-1 and retroperitoneal fibrosis is considered to be as follows. Tumors treated with anti-PD-1 exhibit the increased expression of genes (S100A4, vimentin, α-smooth muscle actin) associated with the activation of TGF-β signaling.[7] In contrast, in patients with IgG4-related diseases, including retroperitoneal fibrosis, $CD4^+$ cytotoxic T lymphocytes infiltrate the lesion and secrete cytokines involved in fibrosis, namely TGF-β1 and IL-1β.[8] From the above, it is considered that the activation of cytokines involved in fibrosis, such as TGF-β, by the administration of anti-PD-1 may be one of the causes of retroperitoneal fibrosis.

Our search of the relevant literature revealed two cases of retroperitoneal fibrosis in patients treated with anti-PD-1 antibodies. One case was of a 59-year-old man diagnosed with lung adenocarcinoma. Lower back pain and abdominal discomfort appeared two years after the initiation of pembrolizumab treatment. The patient was

curatively treated with steroids.[9] Another case involved a patient with lung adenocarcinoma who developed retroperitoneal fibrosis two years after the initiation of nivolumab treatment and who was curatively treated with steroids.[10] In the cases presented in this report, case 1 was a 57-year-old man who developed retroperitoneal fibrosis one year and six months after the initiation of nivolumab treatment and who was curatively treated with steroids. Case 2 was a 64-year-old man, who developed retroperitoneal fibrosis one year and 11 months after the initiation of pembrolizumab treatment; he improved once with the steroid treatment but his condition relapsed. All four cases developed after approximately two years of anti-PD-1 antibody treatment. All patients were curatively treated with steroids, although one relapsed. Histological findings were not obtained in any of the four cases.

We cannot exclude the possibility that our two cases of retroperitoneal fibrosis that developed during anti-PD-1 antibodies treatment were idiopathic and developed by chance. However, anti-PD-1 antibodies may have affected the onset of retroperitoneal fibrosis. The accumulation of further cases is required.

CONCLUSION

We hypothesized that the administration of anti-PD-1 antibodies may have affected the onset of retroperitoneal fibrosis.

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REFERENCES

1. Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. *Lancet*. 2006;367:241-251.
2. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockage. *N Engl J Med*. 2018;378:158-168.
3. Vaglio A, Maritati F. Idiopathic retroperitoneal fibrosis. *J Am Soc Nephrol*. 2016;27:1880-1889.
4. Alberti C. Drug-induced retroperitoneal fibrosis: short aetiopathogenetic note, from the past times of ergot-derivatives large use to currently applied biopharmacology. *G Chir*. 2015;36:187-191.
5. Couderc M, Mathieu S, Dubost JJ, Soubrier M. Retroperitoneal fibrosis during etanercept therapy for rheumatoid arthritis. *J Rheumatol*. 2013;40:1931-1933.
6. Catanoso MG, Spaggiari L, Magnani L, Pipitone N, Versari A, Boiardi L, et al. Efficacy of infliximab in a patient with refractory idiopathic retroperitoneal fibrosis. *Clin Exp Rheumatol*. 2012;30:776-778.
7. Zhao F, Evans K, Xiao C, DeVito N, Theivanthiran B, Holtzhausen A, et al. Stromal fibroblasts mediate anti-PD-1 resistance via MMP-9 and dictate TGFβ inhibitor sequencing in melanoma. *Cancer Immunol Res*. 2018;6:1459-1471.
8. Mattoo H, Mahajan VS, Maehara T, Deshpande V, Della-Torre E, Wallace ZS, et al. Clonal expansion of $CD4^+$ cytotoxic T lymphocytes in patients with IgG4-related disease. *J Allergy Clin Immunol*. 2016;138:825-838.
9. Moreau A, Giraudet AL, Mognetti T, Kryza D. Retroperitoneal fibrosis in on-going anti-PD-1 immunotherapy detected with [^{18}F]-FDG PET/CT. *Eur J Nucl Med Mol Imaging*. 2019;46:1758-1759.
10. Daoussis D, Kraniotis P, Kalofonou F, Kalofonos H. Anti-PD-1 associated retroperitoneal fibrosis. *Rheumatology*. 2021;60:e329-e330.