Limb arteriolar vasculitis induced by pembrolizumab plus chemotherapy in a patient with lung cancer

Kazuki Takada¹ · Motoharu Hamatake¹ · Kenichi Kohashi² · Shinichiro Shimamatsu¹ · Fumihiko Hirai¹ · Shun Ohmori³ · Tetsuzo Tagawa⁴ · Masaki Mori⁴

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Abstract

Immune-related adverse events (irAEs) associated with immune checkpoint inhibitors are becoming more common; however, irAEs involving blood vessels are rare. We report a patient with limb arteriolar vasculitis induced by pembrolizumab plus chemotherapy. He was 60-year-old man who received first-line treatment with pembrolizumab plus chemotherapy for postoperative lung cancer recurrence. Two weeks after the first administration, he experienced Raynaud's phenomenon. We initiated a vasodilator, but his symptoms worsened, and we considered an irAE. We initiated oral prednisolone, and his symptoms gradually improved. A few weeks later, we performed skin biopsies of both of the patient's feet, and pathological examination revealed arteriolar thrombosis with slight perivascular lymphocytic infiltration. Infiltration of neutrophils with karyorrhexis in the subendothelium was also seen. He also developed acute kidney injury, likely owing to thrombosis. Physical examination of bilateral fingers and toes in patients with lung cancer should be performed carefully after administering pembrolizumab therapy.

Keywords Immune-related adverse events · Lung cancer · Pembrolizumab · Raynaud's phenomenon · Vasculitis

Introduction

Immune checkpoint inhibitors (ICIs) are approved for non-small cell lung cancer [1–8]. Secondary immune-related adverse events (irAEs) are common [9], although irAEs involving blood vessels are rare. We report a patient with lung cancer with limb arteriolar vasculitis induced by pembrolizumab plus chemotherapy.

Case report

The patient was a 60-year-old man who received first-line treatment with pembrolizumab (200 mg/body) plus carboplatin (area under the concentration–time curve: 5) and pemetrexed (500 mg/m²) for postoperative recurrent lung pleomorphic carcinoma. He was antinuclear antibody- and rheumatoid factor-negative, with no history of autoimmune conditions. Moreover, his renal function was within normal range before the treatment initiation, and he did not have any past complication diseases such as hypertension, cardiovascular disease and diabetes. We did not check for thromboembolic factors and an echocardiogram was not conducted before the treatment initiation. Two weeks after first receiving pembrolizumab, he experienced color changes in his fingers and toes, with focal ischemia suggestive of Raynaud's phenomenon (Fig. 1). We prescribed a vasodilator, but his symptoms worsened, and we considered an irAE. We then prescribed oral prednisolone (1 mg/kg [60 mg/day], tapered), and his symptoms gradually improved. We subsequently performed skin biopsy of both feet, and pathological examination revealed arteriolar thrombosis with slight perivascular lymphocytic

✉ Kazuki Takada
k_takada@surg2.med.kyushu-u.ac.jp

¹ Department of Thoracic Surgery, Kitakyushu Municipal Medical Center, 2-1-1 Bashaku, Kokurakita-ku, Kitakyushu, Fukuoka 802-8561, Japan

² Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Fukuoka 812-8582, Japan

³ Department of Dermatology, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, Fukuoka 807-8555, Japan

⁴ Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Fukuoka 812-8582, Japan

Fig. 1 Images of the patient's fingers and toes

Fig. 2 Representative images of hematoxylin and eosin-stained skin biopsy specimens from both feet. **a** Arteriolar thrombosis with slight perivascular lymphocytic infiltration. **b** Arteriolar thrombosis with

infiltration of neutrophils with karyorrhexis at the subendothelium. Original magnification $\times 400$

infiltration (Fig. 2a) and infiltration of neutrophils with karyorrhexis at the subendothelium (Fig. 2b), suggestive of vasculitis. Approximately 3 weeks later, we prescribed oral prednisolone (55 mg/day), and his symptoms of limb arteriolar thrombosis slightly worsened. Moreover, he developed acute renal function deterioration (blood urea

nitrogen [BUN]: 124.4 mg/dl; creatinine [Cre]: 7.82 mg/dl), with extremely high urinary $\beta 2$ -microglobulin (8222 $\mu\text{g/l}$). He underwent hemodialysis three times, and renal function improved (BUN: 30.8 mg/dl; Cre: 1.32 mg/dl). His general condition also improved, and he was discharged after normalized BUN and Cre values.

Discussion

irAEs associated with ICIs are relatively common; however, irAEs involving blood vessels are very rare. Digital vasculitis induced by ipilimumab in a patient with melanoma has been reported as well as Raynaud's phenomenon induced by a combination of nivolumab and ipilimumab in a patient with non-small cell lung cancer [10, 11]. To the best of our knowledge, we report the first case of pembrolizumab plus chemotherapy inducing limb arteriolar vasculitis in a patient with lung cancer.

The most common vascular irAE is giant cell arteritis/temporal arteritis [12]. Watanabe et al. reported the molecular mechanism of ICI-induced vasculitis in large and medium vessels [13]. Vascular dendritic cells express low levels of programmed cell death-ligand 1 and fail to inhibit interacting T cells, most of which carry the programmed cell death-1 receptor [13]. The T cells produce proinflammatory cytokines and promote vessel wall restructuring by enhancing microvascular neoangiogenesis and accelerating intimal hyperplasia. ICIs may promote the process and induce vasculitis. Our patient developed acute kidney injury, and the cause was unclear, because we did not perform kidney biopsy. Thrombosis in small- and medium-sized kidney vessels may have been the cause, and oral prednisolone might be one of the factors associated with thrombosis. Therefore, oral prednisolone was not increased when the patient developed acute renal function deterioration.

As an important limitation, our patient was treated with both pembrolizumab and cytotoxic chemotherapy. Therefore, it is possible that the adverse events resulted from the cytotoxic chemotherapy. However, symptoms gradually improved after initiating oral prednisolone, and pathological examination revealed findings suggestive of vasculitis. Therefore, we are confident that this was a rare irAE.

To this end, physical examination of the fingers and toes in patients with lung cancer should be performed carefully after administering pembrolizumab.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The patient has provided informed consent for publication of this case report.

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