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Successful Treatment of Pembrolizumab-Induced Severe Capillary Leak Syndrome and Lymphatic Capillary Dysfunction

Haixia Qin, MD, PhD; Brittany Vlaminck, CNP; Itunu Owoyemi, MBBS; Sandra M. Herrmann, MD; Nelson Leung, MD; and Svetomir N. Markovic, MD, PhD

Abstract

Although capillary leak syndrome has a high mortality rate, its trigger, diagnosis, and treatment remain a challenge to clinicians because of the poor understanding of its mechanism and lack of treatment guidelines. With the extended use of immune checkpoint inhibitors in modern oncology, immune checkpoint inhibitor–associated immune-related adverse events have also expanded. We present a case of pembrolizumab-induced capillary leak syndrome and lymphatic capillary dysfunction in which the patient had an excellent clinical response to a tailored treatment strategy.

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From the Department of Medicine (H.Q., B.V.), Division of Nephrology and Hypertension (I.O., S.M.H., N.L.), and Division of Oncology (S.N.M.), Mayo Clinic, Rochester, MN.

Capillary leak syndrome (CLS) is a rare disease process characterized by loss of protein-rich fluid from intravascular to interstitial space with associated generalized edema, hemoconcentration, and hypoalbuminemia in the absence of albuminuria. Unlike primary CLS, secondary CLS is associated with other disease, treatment, and medications. To our knowledge, we report the first verified case of pembrolizumab-induced secondary CLS with successful treatment.

REPORT OF CASE

A 54-year-old man was first diagnosed as having malignant nodular melanoma on his right calf with metastasis to right inguinal lymph nodes (stage IV, T4aN2bM1c) in December 2017 after basic resection of the primary lesion. He received therapy with pembrolizumab and talimogene laherparepvec, with injection to his involved inguinal lymph node from January 2018 to July 2019. He underwent a partial right inguinal lymphadenectomy in April 2019 that was complicated by postoperative seroma requiring drainage and a wide resection of the primary lesion in June 2019, after which he achieved complete remission of his melanoma. A month after completing treatment, the patient experienced polydipsia, dyspepsia, anorexia, loose stools, fatigue, abdominal pain, scrotal and bilateral lower extremity edema, and an acute weight gain that progressed over the course of 2 months to about 15 kg above his original weight. These symptoms prompted a prolonged hospitalization in August 2019 at an outside hospital for progressive anasarca, symptomatic ascites, and bilateral pleural effusion. A complete cardiac work-up yielded unremarkable findings. Results of cytologic examination of specimens from both thoracentesis and paracentesis were negative for malignancy. He was given corticosteroids for presumed immunotherapy-related colitis without improvement. Colonoscopy with biopsies revealed normal-appearing mucosa of the terminal ileum and colon. Because of worsening anasarca and the associated decline in mobility, the patient was transferred to our facility at the end of August 2019.

Presentation and Diagnosis

On admission, the patient's blood pressure averaged 90/60 mm Hg. He had diffuse

well-defined macular lesions on his back, noticed by his wife soon after starting pembrolizumab. He also had generalized anasarca, diminished breath sounds, and ascites (positive fluid wave test result). Blood tests revealed mild leukocytosis (leukocyte count, 12.4×10^9/L), hemoconcentration (hemoglobin, 168 g/L; hematocrit, 49.7%), acute kidney injury (creatinine, 1.34 mg/dL [baseline, 0.7-0.9 mg/dL; to convert to μmol/L, multiply by 88.4]), bland urine sediment on microscopy with no evidence of albuminuria, decreased serum albumin level (28 g/L), and normal findings on liver function tests. He did not have monoclonal gammopathy on serum and urine electrophoresis. Positron emission tomography revealed no evidence of recurrent metastatic melanoma. A drain was placed in the right inguinal lymphocele to alleviate symptoms. He continued to have anasarca and respiratory compromise due to bilateral pleural effusion and ascites. Body fluid work-up revealed chylothorax (triglycerides, 2.01 g/L) and chylous ascites (triglycerides, 20.29 g/L), raising the concern that his anasarca was due to systemic CLS or lymphatic capillary dysfunction possibly related to prior immune therapy for melanoma. Results of a work-up for the inflammatory process of CLS included normal anti−vascular endothelial growth factor (VEGF) level, elevated interleukin (IL) 6 at 0.5992 IU/mL (reference range, ≤0.1926 IU/mL), and normal levels of α_1-antitrypsin, IgA1, IgA2, and IgG. Diagnostic lower extremity lymphangiography (Figure 1A and B) revealed typical linearity with extensive eventual leakage of contrast medium from the lymphatics into the adjacent tissues, suggesting diffusely abnormal lower extremity lymphatics. Further discussions of appropriate diagnostic testing led to upper and lower extremity lymphoscintigraphy, performed 2 weeks later (Figure. 2). It showed no central lymphatics visualized within the abdomen or pelvis, suggesting a primary abnormality of lymph drainage with perilymphatic extravasation. No radiotracer was seen to reach the central lymphatic system despite 24-hour delayed imaging, again suggesting lymphatic channel dysfunction. Based on these findings, CLS was diagnosed, primarily affecting lymphatic channels and attributed to prior immunotherapy (pembrolizumab and/or talimogene laherparepvec).

Treatment

Initially, a trial of tocilizumab (an IL-6 antagonist) and high-dose intravenous corticosteroids was given with no appreciable response. The patient also received albumin (25 g/d or every other day) along with intravenous furosemide (40 to 80 mg/d) with minimal effect. Once CLS was confirmed, he was given bevacizumab, which was abruptly discontinued because of development of acute deep venous thrombosis of his left lower extremity. A regimen of axitinib (5 mg twice a day) was initiated, along with 5 days of intravenous immunoglobulin (IVIG; 0.4 g/kg/d). His condition quickly stabilized, as evidenced by decreased peripheral edema and gradual weight loss. Hypotension was controlled with oral midodrine. After repeated therapeutic paracentesis, he was discharged in October 2019 with plans to continue weekly IVIG therapy (he eventually received 0.4 g/kg weekly for 10 consecutive weeks) and axitinib. He eventually required an abdominal drain catheter placement for ascites and octreotide injections (200 μg every 8 hours). Over time, he was able to be weaned from midodrine, with notable improvement of lower extremity edema and resolution of bilateral pleural effusions. He was referred to the outpatient nephrology service for continued management of anasarca, for which daily amiloride and bumetanide were prescribed as needed for diuresis. He self-discontinued axitinib in November 2019 because of a lack of appetite and fatigue. He soon noticed weight gain and increased chylous drainage from his abdominal drainage catheter and was admitted to the hospital for further evaluation. Abdominal magnetic resonance imaging at that time revealed portal vein thrombosis while he was receiving therapeutic doses of enoxaparin for his left lower extremity deep venous thrombosis. On consultation with the vascular medicine service, anticoagulation with enoxaparin was continued. His axitinib was resumed and gradually increased to 5 mg twice daily with good symptom control. The patient continues to improve 12 months later with gradual reduction in supportive care measures while still taking axitinib and octreotide and receiving

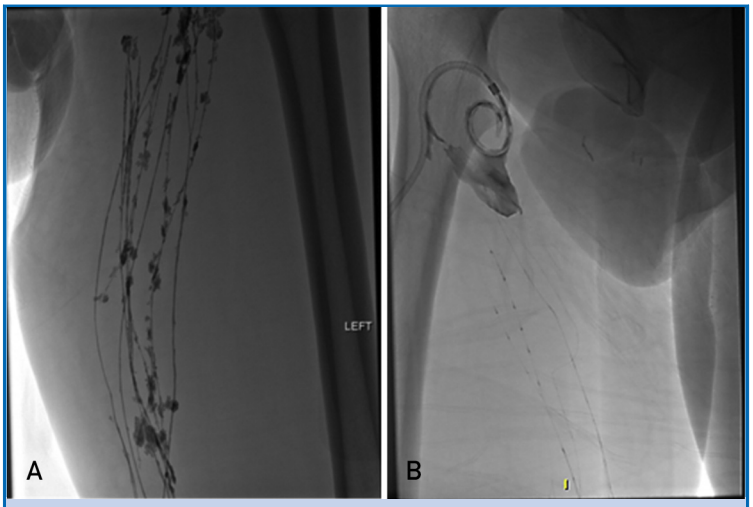

FIGURE 1. Diagnostic bipedal lymphangiogram showing typical linearity but extensive eventual leakage of contrast medium from the lymphatics into the adjacent tissues. A, Left side. B, Right side.

intermittent albumin infusions. He remains in complete remission from his melanoma based on his most recent positron emission tomography and oncological evaluations.

DISCUSSION

Capillary leak syndrome is a rare disease process characterized by loss of protein-rich fluid from intravascular to interstitial space with associated generalized edema, hemoconcentration, and hypoalbuminemia in the absence of albuminuria.[1] The disease process was first reported as idiopathic CLS in 1960.[2] Unlike primary CLS, secondary CLS is associated with other disease, treatment, and medications. In the hematology/oncology field, anticancer agents and therapy including granulocyte colony-stimulating factor, IL-2, gemcitabine, and immunotherapy have been associated with secondary CLS.[3] Although substantially improved outcomes of metastatic melanomas have been reported with immune checkpoint inhibitors,[4,5] their ability to increase the activity of the immune system has been associated with immune-related adverse events that manifest in various organs.[6] Several hypotheses about these immune-related adverse events have been suggested. One is increased cross-reactivity between T cells directed against tumor and T cells directed against a related antigen in normal tissue,[7] as seen in patients with melanoma who have development of vitiligo from a possible autoimmune attack on melanocytes, which occurred in our patient. To our knowledge, there is only one case reported in the literature of secondary CLS associated with malignancy. It was reported in a 50-year-old woman who had development of CLS after receiving 12 cycles of nivolumab as second-line treatment for advanced lung adenocarcinoma. She had no notable response to high-dose intravenous corticosteroids, as seen in our patient, which led to her death.[8] In our case, CLS was confirmed after extensive unremarkable work-up for a cardiac, nephrological, and gastrointestinal tract etiology. Angiographic imaging (lymphangiography and lymphoscintigraphy) confirmed our suspicion.

Although the mechanism of CLS is not clearly understood, hypotheses based on case reports and case series have implicated inflammatory factors. It was proposed that inflammatory factors cause profound vascular endothelial dysfunction, as seen in secondary CLS in one patient with psoriasis,[9] in addition to leakage of plasma and proteins into the interstitial compartment. Thus, a patient typically presents with intravascular hypovolemia, generalized edema, and the diagnostic triad (severe hypotension, hypoalbuminemia, and hemoconcentration). Other manifestations of CLS include anasarca (generalized edema), ascites, bilateral pleural effusions, pericardial effusions, cerebral edema, and encephalopathy. It is less common to see chylothorax as occurred in our case, which may be related to lymphatic leakage. Although our patient's partial right inguinal lymphadenectomy may have caused lymphatic capillary dysfunction in his right leg, it would be unusual to have bilateral lymphatic dysfunction, along with chylothorax and chylous ascites. Thus, we suspect that our patient had systemic CLS and lymphatic capillary dysfunction from pembrolizumab.

As to the treatment of CLS, multiple case reports suggested the use of anti-VEGF antibody (bevacizumab, 5 mg/kg/d for 5 days)[10] or terbutaline and theophylline before the era of IVIG.[11] Although one cohort study reported no survival benefit of IVIG in patients requiring intensive care unit admission,[12] multiple studies have suggested the use of

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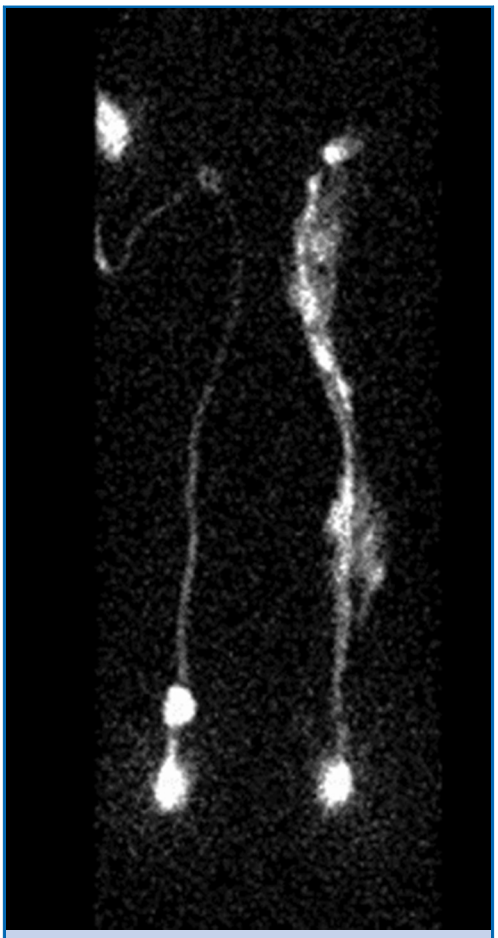

FIGURE 2. Lymphoscintigram showing prompt transit of radiotracer through the lymphatic system of the bilateral lower extremities.

high-dose IVIG followed by monthly infusions.[13,14] Thus, with failure of corticosteroids in the acute phase of our patient's illness and the need to avoid further immunosuppression with remission of his malignancy, we devised a strategy to inhibit VEGF receptors, thereby blocking the angiogenesis that has also been implicated in the invasiveness and resistance of various tumors.[15] Bevacizumab was discontinued in our patient, and axitinib was initiated because of the development of venous thromboembolism. Our patient's condition quickly stabilized after 5 days of IVIG treatment along with axitinib, supporting the use of IVIG in secondary CLS. Octreotide was introduced when he was found to have portal vein thrombosis to reduce splanchnic blood flow and chylous ascitic fluid output. We attempted balancing his need for intravascular volume expansion and diuresis of excess extracellular fluid volume with amiloride, which is an epithelial sodium channel blocker with fewer antihypertensive effects. There is also increasing evidence of the role of epithelial sodium channel blockers in the activation of antigen-presenting cells leading to T-cell activation and inflammatory cytokines, endothelial function, and vasculature.[16] With these conservative measures, our patient can maintain a quality of life with improvement of his symptoms, and he remains cancer free.

CONCLUSION

Pembrolizumab-induced CLS is rare. To our knowledge, we report the first verified case of pembrolizumab-induced secondary CLS with successful treatment. Because of the complexity of CLS, our treatment experience suggests a potential need for combination therapy to achieve a good outcome.

Abbreviations and Acronyms: **CLS** = capillary leak syndrome; **IL** = interleukin; **IVIG** = intravenous immunoglobulin; **VEGF** = vascular endothelial growth factor

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Correspondence: Address to Svetomir N. Markovic, MD, PhD, Division of Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

ORCID

Haixia Qin: https://orcid.org/0000-0002-9908-8940; Svetomir N. Markovic: https://orcid.org/0000-0002-9238-4325

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