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Pembrolizumab-Associated CD8$^+$ Vasculitic Mononeuritis Multiplex in a Patient With Mesothelioma

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Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer treatment and achieves unexpectedly durable tumor remission. However, therapeutic efficacy comes along at the cost of a wide spectrum of immune-related adverse events (irAEs). Immune checkpoints, such as the programmed cell death 1 (PD-1) receptor, PD-1 ligand (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4),[1,2] inhibit T-cell activation and are used by tumor cells to escape the immune surveillance.[3]

Physiologically, immune checkpoints are important for maintaining self-tolerance during T and B-cell maturation. Thus, their inhibition can trigger de novo or preexisting autoimmune and paraneoplastic disorders.[2,3] The most common ICI-associated irAEs involve the skin, the gut, and the endocrine organs.[1] Neurologic side effects and ICI-associated vasculitis are rare,[3] the latter affecting mostly large and medium vessels.[2] ICI-associated vasculitic peripheral neuropathy (VPN) and ICI-associatedperinuclear antineutrophil cytoplasmatic antibody (p-ANCA)-positive mononeuritis multiplex[4] have only been reported once, but without histologic verification. We report an ICI-associated, ANCA-negative mononeuritis multiplex diagnosed by neuromuscular ultrasound and histology.

Case Description

A 61-year-old woman suffering from a pleural mesothelioma (cT3cN0cM0) was initially treated with carboplatin/pemetrexed followed by maintenance therapy with the anti-PD-1 inhibitor pembrolizumab (timeline shown in figure, A). After 1 year, pembrolizumab was ceased because of suspected but not confirmed ICI-related colitis. After first progression (rib metastasis), pembrolizumab was readministered (3-weekly, 15 cycles) until multiple cutaneous petechiae developed. A skin biopsy demonstrated perivascular lymphocyte infiltrates, suggesting a late-stage small vessel vasculitis (not shown). Suspecting a pembrolizumab-associated cutaneous irAE, treatment was stopped. After 2 weeks, she presented with a bilateral foot drop syndrome and paresis in the distribution of the right ulnar nerve. Clinical examination additionally revealed concomitant hypoesthesia/allodynia of the feet, the right hand, and the left thumb.

Motor nerve conduction studies (NCS) demonstrated severe axonal damage (reduced amplitudes, preserved distal latencies, and velocities) in the right median and ulnar nerves as well as both peroneal and tibial nerves. Sensory NCS of the sural and peroneal superficial nerves were absent, and axonal sensory impairment of the right ulnar and the radial superficial nerve was also shown (reduced amplitudes and preserved velocities). EMG (of the right dorsal interosseous muscle and right tibial anterior muscle) demonstrated acute axonal damage. Nerve ultrasound revealed multifocal fascicular nerve swelling (in both sural and ulnar nerves), raising suspicion of a vasculitic neuropathy (figure,

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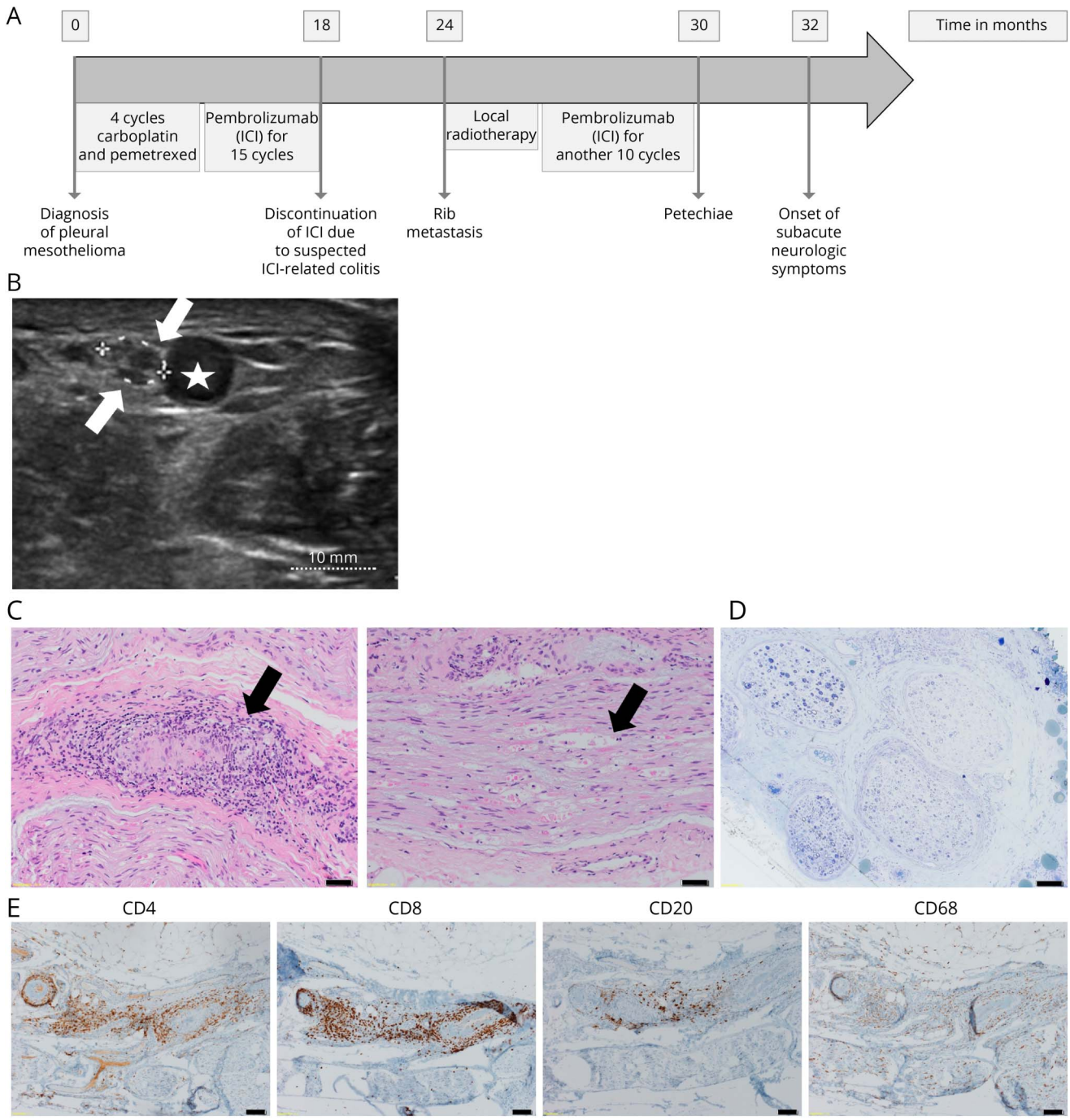
Figure Chronology of Patient's History, Sural Nerve Ultrasound and Histologic Findings



(A) Time course of the patient's history in months. (B) High-resolution nerve ultrasound (18 MHz, Philips Epiq Q5) of the right sural nerve showing fascicular swelling (arrows) and nerve enlargement (dotted circle, cross-sectional area 5 mm^2, norm <2 mm^2), vein (star). (C) Sural nerve biopsy revealed a small vessel vasculitis with fibroid necrotic changes (arrow) of the vessel wall and myelin sheath disintegration (arrow), hematoxylin and eosin staining. Scale bar; 50 µm. (D) Toluidine blue-stained semi-thin cross-sections of the epon-embedded nerve show signs of axonal degeneration and an inhomogeneous loss of nerve fibers among various nerve fascicles, the latter being a typical finding in vasculitic neuritis. Scale bar; 100 µm. (E) Immunohistochemistry (brown) for lymphocyte markers CD4, CD8, and CD20; CD68 (macrophages). Scale bar; 100 µm.

B). The laboratory, CSF, and urine analyses were normal. The clinical phenotype, electrophysiology, and neurosonographic findings were suggestive of a nonsystemic vasculitic mononeuritis multiplex (NSVM) in which an accompanying chemotherapy-induced polyneuropathy may have contributed to the sensory impairment.

High-dose methylprednisolone with subsequent oral tapering was initiated, and an ultrasound-guided biopsy of the sural nerve was performed. Histology confirmed small vessel vasculitis (figure, C and D). The infiltrate showed a predominance of $CD8^+$ T cells over $CD4^+$ T and B lymphocytes (figure, E).

Because steroids failed to alleviate symptoms, immunosuppression was escalated with IV cyclophosphamide (6 cycles, every 4 weeks). However, severe allodynia persisted, and treatment with pregabaline, amitriptylin, and methadone showed only moderate efficacy.

Discussion

We are describing a case of histologically proven pembrolizumab-associated sensorimotor NSVM, occurring in a patient with malignant mesothelioma. The clinical hallmark was a painful mononeuritis multiplex preceded by a cutaneous vasculitis. Normal laboratory results (autoantibodies, CSF, and urine) without involvement of visceral organs made a systemic vasculitis with neurologic manifestation unlikely. Chemotherapy-induced polyneuropathy caused by platinum compounds is not inflammatory and mostly sensory because of dorsal root ganglion impairment, which may have contributed to the sensory deficit. A paraneoplastic origin was also unlikely due to the late onset of the neurologic symptoms in the absence of tumor progression, the concomitant irAE to the skin, and the general low incidence of paraneoplastic neurologic symptoms in malignant mesothelioma.

The characteristic composition of immune cell infiltrates in vasculitis is controversially discussed. No data exist so far on ICI-related vasculitis. In giant cell arteritis, inflammation consists mainly of $CD4^+$ helper T cells.[5] By contrast, $CD8^+$ cytotoxic T cells dominate in systemic vasculitis and in NSVM.[6] In our case, the $CD8^+$ T cells dominated the immune infiltrate, which was also reported in ICI-related myositis and myocarditis.[7]

Because of the rarity of the reported case, a comparison with the literature is not feasible, but some aspects might be noteworthy. irAEs often occur after 6–12 weeks of ICI treatment[3]; however, the interval varies with the immune checkpoint target, among other factors. The knowledge about side effects after reexposure to ICIs is very limited. In our case, irAEs evolved over ~30 weeks after reexposure, which is particularly long. Whether the preceding neurotoxic chemotherapy might have been a trigger for this neurologic irAE remains speculative.[3]

Optimal treatment in ICI-associated NSVM remains to be defined. ICI-associated Guillain-Barré–like syndrome (GBS) resembles the phenotype of classical cases, but steroids are the mainstay of treatment, in contrast to classical GBS. We also treated the patient with high-dose steroids and escalated with cyclophosphamide, which was reasonable according to the irAE treatment guidelines and treatment of NSVM. Careful evaluation and reporting of rare side effects broaden the knowledge and understanding of the complex immune network and the pathogenesis of neurologic ICI-related side effects.

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Markus Joerger, MD	Department of Hematology and Medical Oncology, Cantonal Hospital, St. Gallen, Switzerland	Oncologic treatment of patient
Lukas Flatz, MD	Department of Dermatology, Cantonal Hospital, St. Gallen, Switzerland	Dermatologic treatment of patient regarding skin vasculitis
Regulo Rodriguez, MD	Department of Pathology, Cantonal Hospital, St. Gallen, Switzerland	Histopathologic analysis of skin biopsy
Stephan Frank, MD	Department of Pathology, University Hospital, Basel, Switzerland	Histopathologic analysis of nerve biopsy
Ansgar Felbecker, MD	Department of Neurology, Cantonal Hospital, St. Gallen, Switzerland	Nerve ultrasound
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Thomas Hundsberger, MD	Department of Neurology and Department of Hematology and Oncology, Cantonal Hospital, St. Gallen, Switzerland	Neurologic and oncologic patient treatment, wrote article

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