JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2021, VOL. 11, NO. 3, 388–392
https://doi.org/10.1080/20009666.2021.1903133

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CASE REPORT

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Pembrolizumab related Guillain barre syndrome, a rare presentation in a patient with a history of lupus and bladder cancer

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ABSTRACT

Immune checkpoint inhibitor-related neurotoxicity causing Guillain Barre Syndrome is relatively uncommon. We discussed an 80-year-old patient with known systemic lupus erythematosus who presented with lower extremity weakness, areflexia and then progressed to respiratory muscle and upper extremity weakness after receiving immunotherapy with checkpoint inhibitors for metastatic bladder cancer. With the increasing use of immunotherapy for the management of cancer, awareness of neurological autoimmune side effects is essential. Immune checkpoint inhibitor-mediated GBS can be severe and fatal if not diagnosed promptly. The hospitalists, neurologists, and oncologists should be aware of neurotoxicity related to immune checkpoint inhibitor therapy requiring a multidisciplinary approach to patient care. Prompt initiation of immunosuppressive therapy is required for the management of immune checkpoint inhibitor-related neurotoxicity.

ARTICLE HISTORY
Received 31 July 2020
Accepted 10 March 2021

KEYWORDS
Keytruda; pembrolizumab; Guillain barre syndrome; immune checkpoint inhibitor; neurological complications; PD 1 antibody

1. Introduction

Pembrolizumab is an anti-PD-1 IgG monoclonal antibody that was first approved by Food and Drug Administration (FDA) in September 2014 in advanced melanoma who progressed following treatment with ipilimumab and a BRAF inhibitor in patients with BRAF mutation [1]. Since then it has been approved as the first line, second line and third line management either alone or in combination with chemotherapeutic agents for multiple cancers. Pembrolizumab blocks the PD1 receptor, also known as an immune checkpoint on lymphocytes, and allows the immune system to destroy cancer cells. Due to its action, it is also called the Immune checkpoint inhibitor (ICI) [2]. Immunotherapy is being increasingly used in clinical practice and is better tolerated than chemotherapy with common side effects of pruritus, fatigue, rash, nausea, diarrhea, decreased appetite, and asthenia apart from autoimmune side effects. We need to monitor for autoimmune side effects, as the activated immune system carefully can attack any organ, with thyroid being the most affected organ [2–4]. Sporadic cases of Guillain-Barré syndrome (GBS) have been mentioned with the use of ICI [5]. We are presenting a rare case of GBS, which developed secondary to the use of pembrolizumab used to treat bladder cancer in our patient.

2. Case report

An 80-year-old gentleman with recently diagnosed metastatic bladder cancer to bones and retroperitoneal lymph nodes was started on pembrolizumab. Patient was not considered for cisplatin-based therapy given decreased performance status and chronic renal impairment. Patient did have a history of lupus treated with mycophenolate and hydroxychloroquine. Given his clinical condition and comorbidities, his oncologist considered pembrolizumab is a better option for the patient as his lupus is well controlled. He presented to the emergency room with worsening weakness and inability to walk after receiving his first

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Abbreviations
:PD-1 = programmed death receptor-1 PDL-1=programmed death ligand 1 GBS=Guillain Barre Syndrome ICI = Immune checkpoint inhibitor FDA=Food and Drug Administration Ig G = Immunoglobulin G PAD= Peripheral arterial disease. BPH =Benign prostatic hyperplasia COPD= chronic obstructive pulmonary disease PO = per oral IVIG= Intravenous immunoglobulin EMG= Electromyography NCS = Nerve Conduction study CPK= creatine phosphokinase

cycle of pembrolizumab. He has been deconditioned over the past few weeks but was able to walk with a walker and perform daily activities at baseline. However, he was unable to get up from the bed and was extremely weak in bilateral lower extremities after receiving immunotherapy and hence sought medical attention.

He reported extensive past medical and surgical history that includes hypertension, hyperlipidemia, hypothyroidism, lupus, peripheral arterial disease status post stent placement in right mid popliteal artery, coronary artery disease status post percutaneous intervention, tachy brady syndrome status post pacemaker placement, congestive heart failure with ejection fraction of 40%, chronic obstructive pulmonary disease, squamous cell carcinoma of supra-glottis status post radiation therapy in remission, chronic back pain, and benign prostatic hypertrophy.

He is a former smoker, quits smoking 10 years ago, drinks alcohol occasionally, and reports no illicit drug use. There is no significant family history. Medication list includes apixaban, clopidogrel, levothyroxine, mycophenolate, atorvastatin, hydroxychloroquine, tamsulosin, finasteride, and omeprazole. On initial examination, his vitals are stable. Physical examination was significant for the patient in distress from back pain radiating to bilateral lower extremities associated with weakness. Also noted chronic macular darkening of leg. Neurological examination was significant for weakness in the lower extremities with a strength of 3 out of 5 bilaterally. There was no sensory loss. The patient did have a normal rectal tone. The rest of the physical examination was unremarkable. Patient's urinalysis was negative. Portable chest x-ray revealed emphysema, no other acute findings. Patient's admission labs are summarized in Table 1.

Hospital course: Due to lower back pain and weakness in the lower extremities, he underwent computed tomography (CT) of the cervical, thoracic and lumbar spine which revealed multiple bony sclerotic lesions consistent with metastasis and multifocal lymphadenopathy. The patient received 10 mg of dexamethasone initially. Magnetic resonance imaging (MRI) was not done due to pacemaker placement 2 months ago. Neurosurgery recommended no indication for surgical decompression. With a history of Peripheral arterial disease and associated chronic skin discoloration in lower extremities, arterial ultrasound was ordered, which showed occlusion of left distal superficial femoral and left dorsalis pedis arteries with extensive plaque formation bilaterally. Vascular surgery was consulted who reviewed the ankle-brachial pressure index (ABPI), which is more specific for lower extremity ischemia, which was negative. They concluded that the weakness is unrelated to arterial insufficiency.

Oncology team presumed that it could be lupus flare related to immunotherapy and recommended checking antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), complement levels. The results came back as ANA positive confirming lupus however had negative complement levels and undetectable ds DNA negating acute flare. Neurology was consulted due to worsening weakness, after the pacemaker representative was contacted MRI of cervical thoracic and lumbar spine was obtained which revealed multilevel stenosis, small C3 sclerotic lesion, no definitive fractures, or metastasis. The imaging studies are summarized in Table 2. The thyroid-stimulating hormone, 25-hydroxy vitamin D, vitamin B12, and folate levels were all within the normal range. Creatinine phosphokinase (CPK) was checked due to suspicion of medication-induced neuromuscular weakness associated with the use of hydroxychloroquine, which was reported as normal. Additional laboratory findings are summarized in Table 3.

Due to persistent, progressive weakness both in lower and upper extremities, as well as worsening shortness of breath. A more detailed neurological

Table 1. Admission labs.

Laboratory Findings	Result (Normal)
White blood cell count	6.04 (4–10 x10^3/μL)
Hemoglobin	10.7 (13.7–17.5 gm/dl)
Platelet	241 (163–369x10^3/μL)
Sodium	135 (135–144 meq/l)
Potassium	4.3 (3.5–5.0 meq/L)
Bicarbonate	26 (20–30 meq/l)
Blood urea nitrogen	13 (8–26 mg/dl)
Creatinine	0.9 (0.7–1.25 mg/dl)
Aspartate Aminotransferase	30 (5–42 units/L)
Alanine transaminase	12 (5–49 units/L)
Alkaline phosphatase	171 high (35–141units/L)
C – Reactive protein	6.1 high (0.02–0.5 mg/dl)
Lactic acid	1.1 (0.5–2.2 mmol/L)
Magnesium	1.9 (1.6–2.6 mg/dl)
B- type natriuretic peptide	979 high (0–99 pg/ml)
Folate	12.4 (5.9–20 ng/ml)
Hemoglobin A1C	5.3 (4.2–5.9%)

(mg/dl = milligram per deciliter; ng = nanogram; pg = picogram; gm = gram; L = liter; μg = microgram; mmol = millimoles; meq = milliequivalent; % = percentage).

Table 2. Summary of imaging studies.

Imaging	Report
CT cervical- thoracic – lumbar w/o contrast	Sclerotic lesions involving the C3 vertebral body, sternum, right iliac bone concerning for metastasis Multiple spiculated nodules in the lungs
MRI Cervical w/wo Contrast	Sclerosis within the C3 vertebral body
MRI Thoracic w/wo Contrast	No abnormal enhancing mass lesions seen.
MRI Lumbar w/wo Contrast	Degenerative changes. No convincing evidence of osseous metastases
Arterial ultrasound of the lower extremities	Occlusion of the left distal Superficial femoral artery and left dorsalis pedis arteries.
Right shoulder x ray	Osteopenia, long standing rotator cuff injury with atrophy of rotator cuff.

(MRI = Magnetic Resonance Imaging; CT – computed tomography; w/wo = with/without; C3 = third cervical vertebra).

Table 3. Summary of additional laboratory findings.

Additional Laboratory Findings	Result (Normal Range)
ESR	39 high (0–20 mm/hr)
Vitamin B12	814 (213–1041 pg/ml)
Vitamin D 25 OH	33.1 (20–60 ng/ml)
TSH	2.62 (0.33–4.94 µU/l)
ANA profile	>8.0 high (0.2-.0.9 AU/ml)
Anti SS – A Ig G	
Anti SS – B	<0.2 (0.2-.0.9 AU/ml)
SM Ig G	<0.2 (0.2-.0.9 AU/ml)
RNP Ig G	0.5 (0.2-.0.9 AU/ml)
SCL – 70 Ig G	0.2 (0.2-.0.9 AU/ml)
JO – 1 antibody	<0.2 (0.2-.0.9 AU/ml)
Ds DNA	1.0 (1.0–4.0 IU/ml)
Centromere Ig G	<0.2 (0.2-.0.9 AU/ml)
Chromatin Ig G	<0.2 (0.2-.0.9 AU/ml)
Ribosomal P Ig G	<0.2 (0.2-.0.9 AU/ml)
Sm – RNP Ig G	<0.2 (0.2-.0.9 AU/ml)
Rheumatoid Factor (RF)	<20 (0–30 IU/ml)
Anti – CCP	<0.5 (0.2-.0.9 AU/ml)
Complement C3	96 (82–193 mg/dl)
Complement C4	27 (15–57 mg/dl)
aldolase	6.3 (< 7.7 units/lt)
CPK	139 (43–312 U/lt)

(ESR = Erythrocyte sedimentation rate; TSH = Thyroid stimulating hormone; SS = Sjogren's syndrome, Ig = Immunoglobulin, RNP - = Ribonucleoprotein, SM – smooth muscle SCL = Scleroderma; Ds DNA + double stranded DNA, AU = astronomical unit ml = milliliter, IU = international units, CCP – citrullinated protein; ANA = Anti-Nuclear antibody, CPK = Creatinine phosphokinase).

examination was done that showed absence of deep tendon reflexes in lower extremities, downswing plantar reflexes, decreased power in bilateral lower extremities 2/5, decreased handgrip 2/5, and absent vibration sense below the knees. Lumbar puncture was done after holding apixaban for 48 hours and cerebrospinal fluid studies revealed normal cell count, cytology with no evidence of infection. It did show increased protein with increased albumin cytological dissociation confirming Guillain Barre syndrome, which could be related to pembrolizumab. The lumbar puncture findings are summarized in Table 4. The patient's forced vital capacity dropped to 14 mls/kg due to respiratory muscle weakness. The patient was then started on intravenous immunoglobulin daily for 5 days with close monitoring of forced vital capacity. Patient's forced vital capacity increased to 21mls/kg at the time of discharge. Neurology recommended outpatient electromyography/nerve conduction studies. Oncology determined that he was not a candidate for chemotherapy given his poor functional status and recommended hospice. The patient's weakness started to improve and was recommended to transfer to a rehabilitation home for continued physical therapy. The patient and his family want to pursue hospice after discharge from the rehabilitation home.

Table 4. Lumbar puncture findings.

CSF Results	Result (normal range)
Color	Colorless
Turbidity	Clear
White blood cell	0
Red blood cell	19
Glucose	118 high (40–70 mg/dl)
Protein	212.2 high (15–45 mg/dl)
Cytology	Negative
Gram stain	Negative
Culture	Negative
Indian ink	No encapsulated yeast like organisms seen in Indian ink
AFB	Negative
VDRL	Negative

(CSF = cerebrospinal fluid; AFB = Acid fast bacilli; VDRL = venereal disease research laboratory).

3. Discussion

This patient has baseline deconditioning and extensive medical and surgical history making the differential broad. We discussed the differential diagnosis taking into account the presenting symptoms, clinical signs on examination, laboratory, and radiological findings along with multiple comorbidities. We also discussed the side effects related to ICI therapy below.

Lupus flare secondary to Immunotherapy: Certain musculoskeletal and neuropathies are involved in SLE. Owing to acute worsening of weakness, one would think lupus flare is a high possibility. However, anti ds-DNA, complement levels turned out to be negative. Empiric steroids started on admission did not show any response as to the improvement of weakness.

Myopathy secondary to medication: Our patient has been on more than one medicine that can cause myopathy. These include atorvastatin, hydroxychloroquine, finasteride, and omeprazole. Although the diagnosis is generally supported with MRI finding of edema, histopathology shows acid-phosphatase–positive autophagic vacuoles, and other labs include elevated creatinine kinase [6]. The best way to confirm is electromyography (EMG) and Nerve conduction studies (NCS). Several cases have shown that discontinuation of the drug caused the marked improvement, confirming drug-induced neuromuscular weakness [7]. In this case, his medications were stopped on admission with no improvement in weakness. CPK and Aldolase were within the normal range.

Cervical myelopathy or spinal cord compression secondary to metastases: Our patient had metastatic bladder cancer with reported metastases in the cervical, thoracic, lumbar region on an initial CT scan. MRI did not reveal any definitive multiple bone metastasis other than sclerotic lesions in the C3 area. Neurosurgery was evaluated and found no clinical evidence of cord compression.

Pembrolizumab related polyneuropathy: Pembrolizumab can cause demyelination and subsequent neuropathy; however, it takes weeks to develop and would not be in an acute setting after receiving Pembrolizumab. This can also be confirmed based on MRI finding, EMG/NCS [8].

Multifocal motor neuropathy: This is an uncommon neuropathy with a predilection to the upper extremity. It is a slowly progressive weakness and can improve with IV immunoglobulin (IVIG). NCS is critical in the diagnosis [9].

Hypothyroidism is associated with myopathies: In this case, TSH was normal, and the current patient dose seems to be appropriate.

Peripheral arterial disease: Based on the absence of rest pain, intact pulses on exam, and negative ABPI, vascular surgery opined etiology of his weakness was non-ischemic in nature.

For stage IV bladder cancer, cisplatin-based chemotherapy is the current standard of care. ICIs are currently approved for the treatment of metastatic urothelial cancer as second-line treatment. As per FDA there five checkpoint inhibitors for the treatment of metastatic bladder cancer [pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab]. The use of ICI as first-line agents is only for patients who are ineligible for cisplatin-based treatments which happens in about 50% of the patients due to advanced age, comorbidities, renal function. Even though immunotherapy is better tolerated than chemotherapy. It can cause common side effects such as fatigue, pruritus, nausea, diarrhea, decreased appetite, and asthenia. However, we need to be watchful of autoimmune side effects due to the activated immune system attacking any organ in the body, most commonly involving thyroid and those affecting the nervous system include encephalitis, aseptic meningitis, transverse myelitis, posterior leukoencephalopathy syndrome, peripheral motor and sensory neuropathy, myasthenia gravis and GBS [4].

Neurological complications of ICI therapy occurred in approximately 1–5% of treated patients. As per the report, the incidence of GBS secondary to ICI amounted to 0.25% and chronic polyneuropathies and mononeuropathies of 0.05% and 0.09%, respectively. GBS is less reported with anti-PD 1/PD L1 compared with anti-CTLA-4 monotherapy and more frequently associated with combination ICI therapy. There are increasing levels of ganglioside-directed T-cell lymphocytes as per studies in GBS [10]. Therefore, it was suggested that T-lymphocyte activation and proliferation due to checkpoint inhibitors such as PD-1 antibodies might explain the pathogenesis of pembrolizumab-induced GBS. Another possible explanation could be a blockade of PD-1 on peripheral lymphocytes that are refractory to regulatory T cells inhibitory effects [11].

The management of ICI-related neurological toxicity even for grade 1 severity is to withhold the therapy. If the patient has progressive symptoms, corticosteroids are recommended as the first line of therapy either with prednisone or methylprednisolone, even in patients with GBS. If the symptoms do not improve with corticosteroids, then other options include intravenous immunoglobulin as administered in our patient and plasmapheresis. There have been anecdotal reports for the use of additional immunomodulators, including infliximab, cyclosporine, mycophenolate, and natalizumab [12].

Patients with autoimmune disorders receiving ICI therapy can result in significant exacerbation of the underlying autoimmune disorder. As per National comprehensive cancer network recommendations, ICI therapy can be considered in patients with non-life-threatening autoimmune diseases with reasonable disease control with low levels of immunosuppressive therapy or no immunosuppression [13]. Generally, these patients require a multidisciplinary team approach involving autoimmune disease specialists and oncologists before initiating therapy [13]. In patients with severe uncontrolled life-threatening autoimmune disease, pre-existing autoimmune neurological, or neuromuscular disease one should consider avoiding the use of ICI and consider alternative options [13].

4. Conclusion

We discussed a rare presentation of GBS developed after receiving pembrolizumab in a patient with metastatic bladder cancer with a known history of systemic lupus erythematosus. This case emphasizes the importance of detailed neurological examination, which in our case led to suspicion of Guillain Barre syndrome. ICI-related GBS can be severe and fatal if not diagnosed promptly. The hospitalists, neurologists, and oncologists should be aware of neurotoxicity related to ICI therapy requiring a multidisciplinary approach to patient care. Prompt initiation of immunosuppressive therapy is required for the management of ICI-related neurotoxicity. With the increasing use of immunotherapy for the management of cancer, awareness of neurological autoimmune side effects is essential.

Disclosure statement

No potential conflict of interest was reported by the authors.

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