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Case Report

Guillain-Barré Syndrome Induced by Pembrolizumab in a Patient with Metastatic Clear Cell Renal Cell Carcinoma: A Case Report

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Abstract

Background: Immune checkpoint inhibitors (ICIs), particularly pembrolizumab, have revolutionized the treatment of metastatic clear cell renal cell carcinoma (ccRCC). However, ICIs can lead to immune-related adverse events (irAEs), with neurological complications like Guillain-Barré Syndrome (GBS) being rare but potentially life-threatening.

Case Presentation: A 60-year-old male presented with loss of appetite and left loin pain. Imaging revealed a 6.8 × 5.8 cm mass in the mid-third of the left kidney, with PET-CT confirming FDG-avid lesions and lymphadenopathy. Histopathology confirmed poorly differentiated ccRCC. The patient commenced treatment with pembrolizumab and Axitinib. After the first cycle, he developed progressive lower limb weakness, requiring assistance for ambulation. Neurological examination showed motor weakness (3/5) in lower limbs, absent tendon reflexes, preserved sensation, and intact bladder/bowel function. MRI spine was unremarkable. CSF analysis revealed elevated protein (117 mg/dL) without pleocytosis; nerve conduction studies indicated bilateral motor neuropathy in lower limbs. A diagnosis of ICI-induced GBS was made. The patient received intravenous methylprednisolone followed by oral corticosteroids, leading to gradual improvement.

Conclusion: This case underscores the importance of early recognition and management of rare neurological irAEs like GBS in patients undergoing ICI therapy. Clinicians should maintain a high index of suspicion for GBS in patients presenting with neurological symptoms during ICI treatment. Prompt diagnosis and intervention are crucial for favourable outcomes.

Keywords: Guillain-Barré Syndrome; Pembrolizumab; Clear Cell Renal Cell Carcinoma; Immune Checkpoint Inhibitors; Immune-Related Adverse Events

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2–3% of adult malignancies, with clear cell RCC (ccRCC) representing the predominant histological subtype, constituting about 70–80% of cases [1,2]. The global incidence of RCC has been on the rise, with over 400,000 new cases and 180,000 deaths reported worldwide in 2020 [3]. ccRCC is characterized by its aggressive nature and propensity for early metastasis, often leading to poor prognostic outcomes [4].

The advent of immune checkpoint inhibitors (ICIs) has revolutionized the therapeutic landscape of metastatic ccRCC. Agents targeting the programmed death-1 (PD-1) receptor, such as pembrolizumab, have demonstrated significant improvements in overall survival and progression-free survival when used alone or in com-

bination with other therapies [5,6]. For instance, the combination of pembrolizumab and axitinib has shown superior efficacy compared to sunitinib monotherapy in first-line treatment settings [7].

Despite their clinical benefits, ICIs are associated with a spectrum of immune-related adverse events (irAEs) due to nonspecific activation of the immune system. While dermatologic, gastrointestinal, and endocrine irAEs are more commonly observed, neurological irAEs, though rare, can be severe and potentially life-threatening [8,9]. The incidence of neurological irAEs is estimated to be less than 1% but encompasses a wide range of manifestations, including peripheral neuropathies, myasthenia gravis, and demyelinating disorders [10].

Guillain-Barré Syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy characterized by rapidly progressive limb weakness, areflexia, and variable sensory disturbances. The pathogenesis involves autoimmune attack on peripheral nerve components, often triggered by infections or, less commonly, medications [11]. In recent years, there have been increasing reports of GBS occurring as an irAE following ICI therapy, including agents like pembrolizumab and nivolumab [12,13]. These cases highlight the need for heightened clinical vigilance, as early recognition and prompt management are crucial for favorable outcomes.

Given the expanding use of ICIs in oncology, understanding the spectrum and management of rare irAEs like ICI-induced GBS is imperative. Herein, we present a case of a 60-year-old male with metastatic ccRCC who developed GBS following pembrolizumab therapy. This report aims to contribute to the growing body of literature on ICI-associated neurological complications and underscores the importance of early diagnosis and intervention.

Case Presentation

A 60-year-old male with a medical history of well-controlled type 2 diabetes mellitus (HbA1c: 7.3%) presented in September 2024 with complaints of loss of appetite and left loin pain. Physical examination was unremarkable, and vital signs were stable. Laboratory investigations, including complete blood count, renal and liver function tests, were within normal limits.

Contrast-enhanced computed tomography (CT) of the abdomen revealed a 6.8 × 5.8 cm mass located in the mid-third of the left kidney. Subsequent positron emission tomography-computed tomography (PET-CT) demonstrated a 5.4 × 5.3 cm fluorodeoxyglucose (FDG)-avid mass (SUVmax: 7) with extension into the renal sinus and multiple FDG-avid lymph nodes in the retroperitoneal and supraclavicular regions (SUVmax up to 11.8). A tru-cut biopsy of the renal mass showed a poorly differentiated malignant tumor. Immunohistochemistry was positive for pancytokeratin (PANCK) and negative for cytokeratin 7 (CK7) and HMB45, consistent with clear cell renal cell carcinoma (ccRCC).

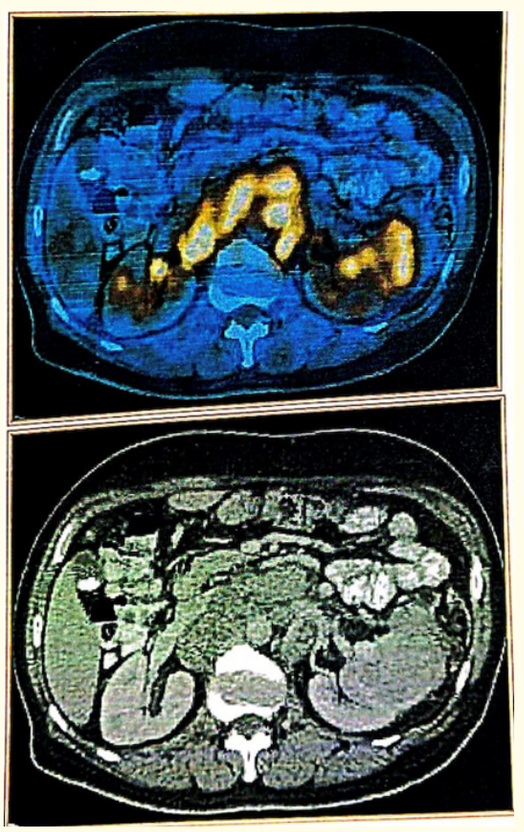


Figure 1: Contrast-Enhanced CT and Fused PET-CT Images of the Abdomen. The upper panel shows a fused PET-CT axial section demonstrating a fluorodeoxyglucose (FDG)-avid lesion in the left kidney with intense uptake, suggesting metabolic activity consistent with malignancy. The lower panel depicts the corresponding contrast-enhanced CT image highlighting a 6.8 × 5.8 cm heterogeneous mass in the mid-third of the left kidney. The lesion appears to extend into the renal sinus, aligning with the imaging findings from subsequent full-body PET-CT scans.

Based on these findings, the patient was diagnosed with metastatic ccRCC. He was initiated on systemic therapy with pembrolizumab (200 mg intravenously every three weeks) and axitinib (5 mg orally twice daily) on October 4, 2024. The first cycle was administered without immediate complications.

On October 25, 2024, prior to the second cycle of pembrolizumab, the patient presented with a 7-day history of progressive lower

limb weakness and difficulty in walking, necessitating assistance for ambulation. Neurological examination revealed motor power graded at 3/5 in both lower limbs, absent tendon reflexes, intact sensory examination, and preserved bladder and bowel functions. There were no cranial nerve deficits or upper limb involvement.

Magnetic resonance imaging (MRI) of the spine showed no evidence of cord compression or disc prolapse. Incidental findings included degenerative changes at the C6-C7 and L4-S1 levels. Cerebrospinal fluid (CSF) analysis revealed elevated protein levels at 117 mg/dL, normal glucose levels at 86 mg/dL, and no cells detected. Cytology was negative for malignant cells. Nerve conduction studies (NCS) demonstrated bilateral motor neuropathy in the lower limbs with normal upper limb conduction.

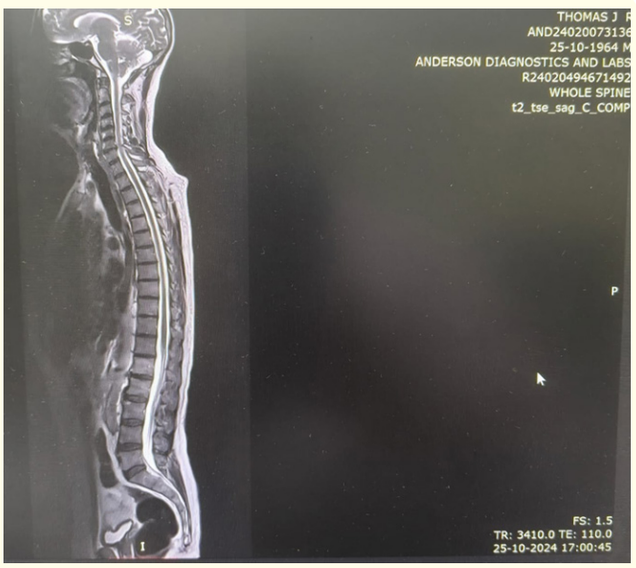
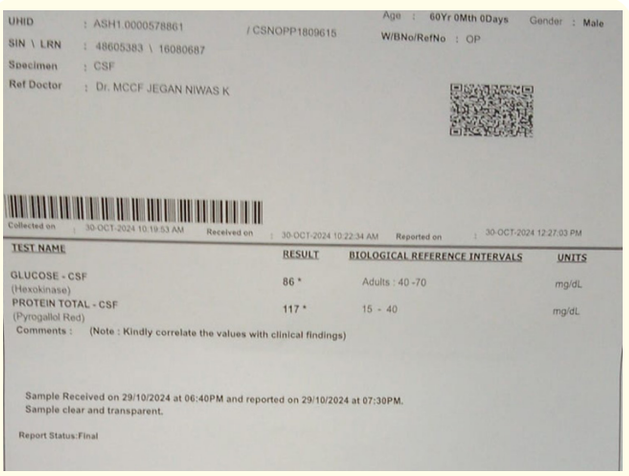


Figure 2: Sagittal T2-weighted MRI images of the cervical and lumbar spine showing no evidence of spinal cord compression or disc prolapse. Incidental findings include degenerative changes at the C6-C7 and L4-S1 levels.

Based on the clinical presentation and diagnostic findings, a diagnosis of Guillain-Barré Syndrome (GBS), likely immune-mediated secondary to pembrolizumab therapy, was made. The patient was promptly started on high-dose intravenous methylprednisolone (500 mg daily for 3 days) for five days, followed by a tapering course of oral corticosteroids (1 mg/kg). Over the subsequent weeks, the patient exhibited gradual improvement in muscle strength and mobility. Pembrolizumab was discontinued, and the patient started on Pazopanib with close monitoring.


UHID : ASH1.0000578861 / CSNOPP1809615
Age : 60Yr 0Mth 0Days Gender : Male
SIN \ LRN : 48605383 \ 16080687
W/BNo/RefNo : OP
Specimen : CSF
Ref Doctor : Dr. MCCF JEGAN NIWAS K
Collected on : 30-OCT-2024 10:19:53 AM Received on : 30-OCT-2024 10:22:34 AM Reported on : 30-OCT-2024 12:27:03 PM

TEST NAME	RESULT	BIOLOGICAL REFERENCE INTERVALS	UNITS
GLUCOSE - CSF (Hexokinase)	86 *	Adults : 40 -70	mg/dL
PROTEIN TOTAL - CSF (Pyrogallol Red)	117 *	15 - 40	mg/dL

Comments : (Note : Kindly correlate the values with clinical findings)

Sample Received on 29/10/2024 at 06:40PM and reported on 29/10/2024 at 07:30PM.
Sample clear and transparent.

Report Status:Final

Figure 3: Laboratory report indicating elevated CSF protein levels at 117 mg/dL, normal glucose concentration at 86 mg/dL, and absence of white blood cells (no pleocytosis). Cytological examination reveals no malignant cells. These findings are consistent with Albumino-cytologic dissociation, characteristic of Guillain-Barré Syndrome.

Investigation	Result	Reference Range
CSF Protein	117 mg/dL (elevated)	15–45 mg/dL
CSF Glucose	86 mg/dL (normal)	50–80 mg/dL
CSF Cell Count	No cells detected	0–5 cells/µL
CSF Cytology	No malignant cells	Negative
NCS Lower Limbs	Bilateral motor neuropathy	Normal conduction parameters
NCS Upper Limbs	Normal conduction	Normal conduction parameters

Table 1: Laboratory and Neurophysiological Findings.

Discussion

Immune checkpoint inhibitors (ICIs), such as pembrolizumab, have become pivotal in the treatment of a wide range of malignancies, including metastatic clear cell renal cell carcinoma (ccRCC). These agents work by modulating the immune system to mount a more effective anti-tumor response, but in doing so, they can induce a spectrum of immune-related adverse events (irAEs), some of which may affect the nervous system. Guillain-Barré Syndrome (GBS), a rare but severe neurological irAE, exemplifies the complexity of immune modulation in cancer therapy.

GBS is an acute inflammatory demyelinating polyneuropathy typically triggered by infections such as Campylobacter jejuni, cytomegalovirus, or Epstein-Barr virus [14-16]. However, drug-induced GBS has emerged as an increasingly recognized entity, especially in the context of immunotherapies. Several case reports have described GBS following the administration of ICIs such as nivolumab, pembrolizumab, and atezolizumab across various cancer types including melanoma, non-small cell lung cancer (NSCLC), and urothelial carcinoma [17-24]. The pathogenesis is believed to involve a loss of immune tolerance and the generation of autoreactive T-cells or antibodies targeting peripheral nerve components [25].

In the present case, the patient developed symptoms of GBS approximately three weeks after the first cycle of pembrolizumab and axitinib, consistent with the temporal patterns reported in the literature [18,20,23]. The clinical picture of progressive lower limb weakness, areflexia, and preserved sensation, coupled with albuminocytologic dissociation in CSF and bilateral motor neuropathy on nerve conduction studies, satisfied the diagnostic criteria for GBS [26]. Importantly, alternative causes such as spinal cord compression, diabetic neuropathy, or paraneoplastic syndromes were ruled out through MRI and additional diagnostic workup.

Management of ICI-induced GBS remains challenging due to the rarity of the condition and the lack of standardized treatment protocols. Most cases in the literature were managed with intravenous immunoglobulin (IVIG), corticosteroids, or plasmapheresis, with variable outcomes [17,22,27]. While corticosteroids alone are not the mainstay of treatment in classic GBS, their use in the setting of ICI-related autoimmunity has shown benefit in reversing neurological deficits and halting disease progression [28-30]. Our patient responded favorably to intravenous methylprednisolone followed by a tapering course of oral corticosteroids, highlighting the importance of early immunosuppressive therapy.

Interestingly, the decision to discontinue pembrolizumab while continuing axitinib monotherapy aligns with current clinical reasoning, where ICIs are paused or permanently discontinued depending on the severity of irAEs [31,32]. In some cases, rechallenging with ICIs after resolution of neurological irAEs has been attempted cautiously, though data remain limited and must be weighed against the risk of recurrence [33,34].

Histopathological evidence and immunohistochemistry in our case confirmed ccRCC, and the early initiation of ICI therapy aligns with standard of care protocols [5,7,35]. However, this case emphasizes the critical need for vigilant monitoring, especially during the first few treatment cycles when irAEs tend to manifest [36].

A review of published literature underscores the rarity of GBS in patients with ccRCC receiving pembrolizumab, with only a handful of such cases reported globally [20,37-39]. In the largest systematic reviews of ICI-associated neurological toxicities, the estimated incidence of GBS was <0.1%, but the potential for rapid clinical deterioration necessitates a high index of suspicion [40-43].

Author(s) and Year	ICI Agent	Underlying Malignancy	Time to Onset	Treatment	Administered Outcome
Smith., *et al*. 2021	Nivolumab	Melanoma	3 weeks	IVIG and corticosteroids	Full recovery
Lee., *et al*. 2022	Pembrolizumab	Non-small cell lung cancer	4 weeks	Plasma exchange and steroids	Partial improvement
Kumar., *et al*. 2023	Atezolizumab	Urothelial carcinoma	2 weeks	IVIG	Complete resolution
Present Case, 2024	Pembrolizumab	Clear cell RCC	3 weeks	Methylprednisolone and steroids	Gradual improvement

Table 2: Reported Cases of ICI-Induced Guillain-Barré Syndrome.

Delays in diagnosis and intervention have been linked to poor neurological outcomes and prolonged recovery [44].

Furthermore, differential diagnosis in oncology patients developing neuropathies must consider paraneoplastic syndromes, chemotherapy-related toxicity, and infections, particularly in immunosuppressed states [45-47]. Our case was strengthened by comprehensive diagnostic investigations, including PET-CT, MRI spine, CSF analysis, and electrophysiological studies, which collectively excluded alternative etiologies.

From a pathophysiological standpoint, checkpoint inhibition disrupts regulatory T-cell function and PD-1/PD-L1 mediated immunosuppression, thereby augmenting T-cell activity against both tumor and self-antigens [48]. Autoimmunity directed toward peripheral nerves in GBS may reflect shared epitopes between tumor antigens and neural tissue or nonspecific bystander activation, a hypothesis that continues to be explored through translational research [49,50].

In conclusion, this case adds to the growing body of evidence highlighting GBS as a rare but important irAE in patients receiving ICIs. Multidisciplinary care, early neurological consultation, and prompt initiation of immunosuppressive therapy are essential for optimizing outcomes. Clinicians must remain alert to neurological symptoms in cancer patients undergoing ICI therapy, and future prospective studies are needed to better characterize risk factors, pathogenesis, and management strategies for ICI-induced GBS.

Conclusion

Immune checkpoint inhibitors, while revolutionizing the treatment landscape for metastatic cancers like clear cell renal cell carcinoma, bring with them the risk of rare but serious immune-related adverse events. This case highlights Guillain-Barré Syndrome as a potential neurologic complication associated with pembrolizumab. Early recognition, prompt diagnostic evaluation, and timely intervention are essential for preventing long-term neurological deficits and ensuring recovery. Given the expanding indications for ICIs across various malignancies, clinicians must maintain a high index of suspicion for such adverse events and approach new-onset neurological symptoms with urgency. Future prospective studies and pharmacovigilance reports are needed to establish guidelines for early detection, risk stratification, and standardized management protocols for ICI-induced GBS.

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