Longitudinally extensive transverse myelitis after pembrolizumab and lenvatinib therapy for a rare subtype of renal cell carcinoma: A case report

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Abstract. Immune checkpoint inhibitors (ICIs) have revolutionized oncology, shifting the approach from directly targeting tumor cells to enhancing the immune response of the host towards tumor cells by blocking inhibitory receptors or ligands. The present report describes the case of a 26-year-old female patient diagnosed with a rare subtype of renal cell carcinoma (RCC), transcription factor E3-rearranged (t)RCC, who presented with progressing motor weakness of the lower extremities, along with urinary and fecal incontinence, which had begun 3 days prior to admission. A diagnosis of longitudinally extensive transverse myelitis (LETM) was made, resulting in the administration of methylprednisolone and intravenous immunoglobulin. Subsequently, the condition of the patient markedly improved. LETM, a rare and potentially life-threatening condition, manifests through symptoms such as pain, sensory deficits, motor impairments and disturbances in bladder and rectal function. The positive neurological outcome in the patient in the present case underscores the significance of timely intervention. Whilst the synergistic impact of combining radiotherapy and immunotherapy in cancer treatment is widely emphasized, their influence on the spectrum and severity of toxicities remains underexplored. The present case, documenting LETM after treatment of tRCC with pembrolizumab, sheds light on a rare neurological adverse effect of ICIs. It underlines the need for prompt action in the effective management of immune-related adverse effects. Furthermore, the present case serves as a noteworthy contribution to the evolving understanding of the intricate dynamics between immune modulation and treatment-related complications in the context of innovative cancer therapies.

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Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies used for cancer treatment that augment host immune responses toward tumor cells by blocking signaling pathways responsible for T cell inhibition [such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1)]. Despite their notable oncological efficacy, ICIs can potentially elicit undesired immune responses, such as dermatitis, pneumonitis, joint and muscle pain, colitis, hypothyroidism or other endocrinopathies (1,2). In a systematic review of neurological adverse events associated with ICIs, Cuzzubbo *et al* reported that the incidence of severe neurological immune-related adverse events (irAEs) was <1%. Although rare, they have the potential to cause severe disability or life-threatening consequences (3). Thus, early identification and effective management of these irAEs is imperative; albeit, further research is warranted to establish optimal clinical guidelines. Longitudinally extensive transverse myelitis (LETM) is one of the most fatal and rapidly progressive neurological syndromes, most commonly associated with neuromyelitis optica spectrum disorder (NMOSD). Other causes include spinal cord infarction, parainfectious myelopathy, or, as in the present case, a complication of treatment with ICIs (4). The symptoms usually include motor weakness, para- or tetraparesis, sensory deficits, bowel/bladder disturbances, and in severe cases, respiratory failure. Radiologic imaging, usually MRI of the spinal cord, can reveal a variety of lesions, although the extent of abnormalities may not always be associated with clinical findings (5). Risk factors for LETM vary, depending on the etiology and underlying disease. The present paper reports a comprehensive case elucidating the efficacious treatment and eventual resolution of LETM as an irAE.

Case report

The oncological history of the patient in the present report, a 26-year-old woman, began in December 2020 with a sudden onset of hematuria. The patient admitted themselves to the Emergency Department, Kazimierz Hołoga Hospital (Nowy Tomyśl, Poland). CT imaging revealed a 95x76 mm nodular mass in the right kidney (data not shown), which led to the performance of a right-sided nephrectomy, without any post-operative complications. Pathological and immunohistochemical examination, performed in accordance with widely recognized standards for diagnosing renal cell carcinoma (RCC) variants (6), revealed a rare subtype of RCC-a TFE3-rearranged (t)RCC (data not shown). The patient started receiving 400 mg intravenous (i.v.) pembrolizumab every 6 weeks and 20 mg lenvatinib orally in May 2021 as the first-line therapy. A total of 2 months later, the patient underwent a simultaneous integrated boost-intensity-modulated radiotherapy aimed at multiple metastatic sites in 10 courses of treatment for 2 weeks: A total dose of 30 Gy for the thoracic spine at the Th8-Th10 level and a total dose of 48.5 Gy for several locations, such as the liver and lungs. Other interventions included a right-sided adrenalectomy and oral L-thyroxine supplementation titrated according to fluctuating TSH levels. The diagnosis and treatment timeline of the patient is presented in Table I.

The patient was then admitted to the Department of Genitourinary Oncology of the Maria Skłodowska-Curie National Research Institute of Oncology (Warsaw, Poland) in March 2022 due to progressing hyposthenia of the lower extremities and urinary retention. The onset of symptoms occurred 3 days before the patient reported to the hospital. Initially, the patient experienced muscle weakness in the right lower limb, and then developed weakness in the other leg, leading to disability and the need for a wheelchair. Apart from the weakness of the lower limbs, there was a concurrent report of pain localized to the left gluteal region. The patient also experienced urinary and fecal incontinence 1 day prior to admission. Upon arrival at the Emergency Department, the performance status of the patient was assessed and classified as Eastern Cooperative Oncology Group (ECOG) 4 (7). A total of 2 mg/kg i.v. methylprednisolone was administered on the day of admission. Moreover, until an infectious background could be ruled out, the patient was administered 3x1,000 mg i.v. meropenem. MRI of the spinal cord and a CT scan of the thorax, abdomen and small pelvis were performed. MRI revealed a new nodular lesion in the piriformis muscle area, alongside an irregular enhancement of the contrast at the level of Th9-Th10 of the spinal cord, indicative of an autoimmune or inflammatory origin. Additionally, oedema of the spinal cord ranging from the Th2 to the conus medullaris was revealed (Fig. 1). CT imaging demonstrated extensive nodular infiltration propagating through the obturator foramen into the soft tissues of the left buttock, possibly involving the gluteal muscles (data not shown). Subsequently, an ultrasound-guided biopsy of the lesion was performed, revealing oedema, mixed inflammatory infiltrates and fibrinous exudate (data not shown). To exclude infectious transverse myelitis, the more common cause of myelitis (namely, viral: herpes zoster and Cytomegalovirus; bacterial: Lyme disease and tuberculosis; and fungal) (8), a comprehensive assessment was performed, including a complete blood count with inflammatory markers, as well as cerebrospinal fluid (CSF) analysis and flow cytometry which revealed a lack of neoplastic cells and pleocytosis (data not shown), indicating an underlying inflammatory process (9,10). As none of these investigations indicated an

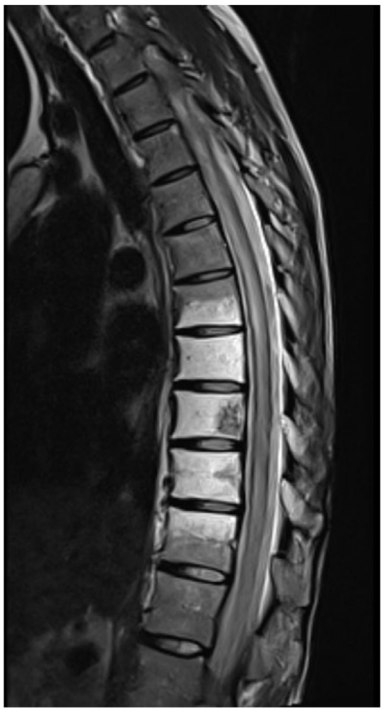

Figure 1. MRI image presenting oedema of the spinal cord ranging from the Th2 to the conus medullaris.

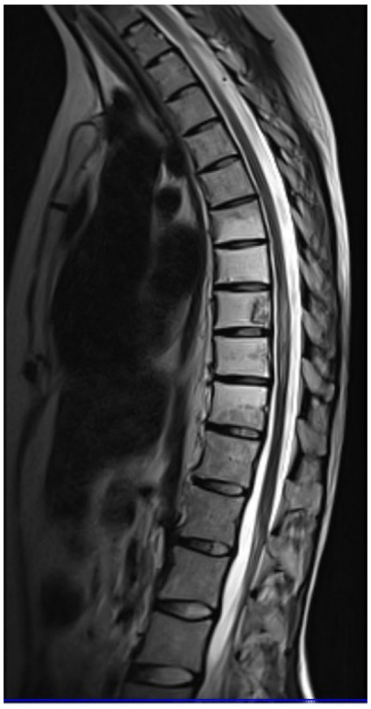

Figure 2. MRI image presenting the decreased oedema of the spinal cord and a contrast enhancement of an area with an elevated signal intensity at the level of Th9-Th10.

Table I. Timeline of diagnosis and treatment details of the patient in the present study.

Timeline	Diagnosis and treatment
December 2020	Diagnosis of transcription factor E3-rearranged renal cell carcinoma
May 2021	Implementation of pembrolizumab and lenvatinib therapy
July 2021	Simultaneous integrated boost-intensity-modulated radiotherapy for Th8-Th10, total dose of 30 Gy
March 2022	Onset of symptoms Gradual loss of muscular strength of the lower extremities and urinary and fecal incontinence
	Paraparesis and urinary retention-admission to the Department of Genitourinary Oncology, Maria Skłodowska-Curie National Research Institute of Oncology (Warsaw, Poland)
April 2022	MRI revealed a diffused spinal cord lesion at the Th9-Th10 level, with a possible autoimmune or inflammatory origin
	Diagnosis of longitudinally extensive transverse myelitis and implementation of methylprednisolone and intravenous immunoglobulin
	Patient was gradually regaining muscular strength, with control of urination and superficial feel
	Discharge from hospital, pembrolizumab discontinued and lenvatinib upheld

infectious etiology, meropenem was discontinued. Based on the radiological findings and the neurological examination, a diagnosis of LETM was established in April 2022. Thus, the patient began receiving 1,000 mg i.v. methylprednisolone daily for 3 days and 2 mg/kg intravenous immunoglobulin for 4 days. Over the course of 11 days, the patient gradually regained muscular strength and superficial sensation (exteroceptive sensation). The ability to perform certain daily tasks, as well as the control of urination, was also regained, and the performance score of the patient improved from ECOG 4 to 3. Therefore, the urinary catheter was removed. Furthermore, the patient regained the ability to walk using a walker. Pembrolizumab was discontinued, due to G4 toxicity, with lenvatinib upheld. A total of 11 days after the patient was diagnosed with LETM, they were discharged from the hospital. Due to the long half-time life of ICIs, it was crucial to provide the patient with long-term treatment with oral prednisone, with tapered dosage, to decrease the possibility of reoccurrence.

MRI after 5 months was performed as a follow-up. The oedema of the spinal cord had markedly decreased, and the contrast enhancement of an area with an elevated signal intensity at the level of Th9-Th10 was more pronounced than in the previous scan (Fig. 2). At follow-up, the patient was still walking with the aid of a walker and had not experienced any other irAEs.

Discussion

tRCC is a rare RCC subtype harboring TFE3 translocations. It is typically diagnosed in younger patients than clear cell RCC, and when diagnosed, it is often already at a metastatic stage due to its typically aggressive clinical behavior (11). Most patients are usually at stage III or IV of the disease upon diagnosis. Certain studies (12,13) estimate that tRCC accounts for ~5% of all RCCs in adults and between 23-50% of all RCCs in children. However, these numbers are likely to be higher in reality. To identify tRCC, fluorescence *in situ* hybridization is required. Immunohistochemical staining targeted at TFE3 can be insufficient due to possible false-positive results. tRCC also has many overlapping pathological characteristics with other types of RCC (14). Therefore, it is usually diagnosed at an advanced stage, and it may remain undiagnosed in many patients. It is presumed that a history of chemotherapy could be a risk factor for developing tRCC; however, there are no other established risk factors (15).

Surgical treatment is usually performed in localized tRCC as long as there is a possibility for a radical procedure. ICIs are also one of the possible treatment options in the advanced stage of the disease. ICIs have been gaining popularity in recent years when it comes to their efficacy in several cancer types. However, due to their mechanism of action, irAEs such as dermatitis and colitis can arise during the therapy. Moreover, irAEs of any kind can affect ≤40% of patients during ICI treatment (16). One of the possible systems that can be affected is the central nervous system, although this occurs relatively infrequently compared with other irAEs. Furthermore, LETM is a rare but potentially life-threatening condition that can present with pain, sensory deficits, motor deficits, or bladder and rectal sphincter dysfunction (17). Apart from MRI, it is vital to exclude infectious causes, perform CSF analysis, and assess for paraneoplastic antibodies.

NMOSD is one of the most common causes of LETM and should be taken into consideration in differential diagnosis (4). To confirm the diagnosis of NMOSD, testing for the presence of NMOSD-specific antibodies such as anti-aquaporin 4 and anti-myelin oligodendrocyte should be performed (18). However, the Maria Skłodowska-Curie National Research Institute of Oncology could not assess these parameters and the nearest neurological clinic could not provide them quickly enough, as it would significantly postpone the treatment. Therefore, in the present case, the therapy was implemented without assessing the presence of the antibodies.

There are reports of LETM as an adverse effect of both radiotherapy near the spinal cord and ICI treatment (19,20). In cases such as in the present report, where both risk factors appear, it was challenging to establish the main trigger of LETM. Nonetheless in this particular case, it seemed that this adverse effect occurred as a complication of immunotherapy

with pembrolizumab, rather than the radiation therapy itself. The patient in the present case had also been receiving lenvatinib (a vascular endothelial growth factor receptor tyrosine kinase inhibitor) together with pembrolizumab. However, it is highly unlikely that lenvatinib caused LETM in the patient, as this drug is not associated with causing myelitis.

irAEs can occur at any time during immunotherapy treatment (21). The time interval for developing myelitis from the initiation of ICI differs throughout the literature, ranging from several days to >40 weeks (15). The patient in the present report developed LETM 9 months after pembrolizumab was initiated, and 3 weeks after its last infusion. The changes in the spinal cord were described as inflammatory or of an autoimmune origin, hinting at the underlying cause, whilst CSF analysis suggested an inflammatory process: Pleocytosis and borderline protein level. Moreover, the biopsy of the piriformis muscle revealed an inflammatory infiltrate and fibrous exudation. Such co-occurrence of auto-aggressive incidents implies that pembrolizumab was the trigger for LETM.

The National Comprehensive Cancer Network (NCCN) guidelines for the management of immunotherapy-related toxicities state that patients with suspicion of LETM should be treated with methylprednisolone boluses with dosing of 1 g per day for 3-5 days and strongly suggest considering intravenous immunoglobulin or plasmapheresis (22). Additionally, the NCCN recommends discontinuing treatment with ICIs. Therefore, upon admission to Department of Genitourinary Oncology at Maria Skłodowska-Curie National Research Institute of Oncology, pembrolizumab was discontinued and lenvatinib was upheld. Apart from the aforementioned recommended treatment, there are reports of treatment of LETMs with cyclophosphamide or infliximab, a monoclonal antibody targeting tumor necrosis factor, with outcomes varying depending on the condition of the patient (23,24).

The spinal cord has a high sensitivity to radiation and is susceptible to damage by irradiation. However, such effects are dose-related and a safe dose for spinal radiotherapy has been established. The probability of myelitis is 0.03 and 0.2% for 45 and 50 Gy, respectively (25), whilst the median tolerance dose for myelopathy has been estimated at 69.4 Gy (26). The patient in the present report received a total of 30 Gy in 10 fractions at the region of Th8-Th10. This dose is well below the safe dose for the spine, therefore it seems unlikely that radiation could be the cause of LETM. Moreover, the occurrence of lesions revealed during MRI performed on the day of the admission (Th9-Th10) corresponded to the irradiated location (Th8-Th10). However, these lesions were already visible in previous MRI scans, a few months before the LETM developed. Furthermore, the radiologist evaluating the MRI scan assessed these changes as mostly of an autoimmune or inflammatory origin.

The patient in the present report received radiotherapy in July 2021, whilst the neurological symptoms began in March 2022, so there were almost nine months in between. Such a delayed onset of LETM is possible, as radiation myelopathy has two different manifestations: i) Early delayed or transient myelopathy, which occurs usually between 6 weeks to 6 months after irradiation and presents with Lhermitte's sign. This is usually benign and self-limiting; and ii) Delayed or progressive myelopathy, which is a more malignant manifestation, that develops usually >6 months after radiotherapy (most commonly between 9-15 months after) and can consist of a wide range of clinical manifestations, such as minor motor and sensory deficits, Brown-Séquard syndrome, transverse myelopathy, and bladder and bowel sphincters dysfunctions (27). The precise mechanism by which radiation causes myelitis is still unknown, but oligodendrocytes and endothelial cells of the blood vessels of the spinal cord have been reported to be especially susceptible to radiation. Both tissues, however, differ in the usual latency in which the potential damage manifests itself. Endothelial cells are more sensitive to radiation and the damaging effects have a longer latency period in contrast to the glial cells, which are less sensitive and have a shorter latency of the onset of the symptoms. Therefore, the early transient form of myelopathy is associated more with the damage of the neuroglia, whilst more persistent and delayed damage is linked to the damage of the small vessels and small areas of ischemia within the spinal cord (28). Radio-sensitizing chemotherapeutics are a risk factor for developing radiation myelopathy. Khan *et al* (28) reported that the incidence of radiation myelitis was higher in patients with previous or concurrent chemotherapy treatment. This finding is also consistent with reports by Seddon *et al* (29), Rubin (30) and Chao *et al* (31).

A previous study suggested that apart from having a collaborative effect on cancer treatment, combining radiotherapy and immunotherapy also has an effect on the incidence of adverse effects (32). Radiotherapy increases the immunogenic death of tumor and host cells, and it is possible that this mechanism underlies an 'abscopal effect' of radiotherapy, in which non-irradiated metastases regress after irradiation of another neoplastic lesions. Radiotherapy stimulates the release of tumor cell antigens, antigens of non-malignant, healthy tissues, as well as damage-associated molecular patterns which activate antigen-presenting cells (APCs), and thus results in increased antigen presentation to T-cells (33). APCs that have taken up the antigens of tumor cells migrate to the draining lymph nodes where priming and activation of naive T-cells occurs. Radiotherapy increases the repertoire of circulating T-cell receptors of the circulating T lymphocytes and induces the release of inflammatory chemokines and cytokines, which can in turn recruit and promote migration of the immune cells to the tumor microenvironment, promoting antitumor responses. However, it also promotes auto-aggressive events. Additionally, anti-PD-L1 antibodies decrease T-cell exhaustion. Their synergistic mechanism of action in terms of immunologic response might also affect the spectrum and severity of treatment-related toxicities (34).

In conclusion, the initial diagnosis of LETM is often difficult. The differential diagnosis should include NMOSD, infectious causes, paraneoplastic myelitis, multiple sclerosis or other autoimmunological conditions (35). The patient in the present report was diagnosed with LETM and treated adequately rather quickly: Symptoms began in March and the treatment was implemented in April. The patient eventually regained the ability to walk and their quality of life improved significantly. However, permanent neurological deficits are a common complication of LETM, and death is also a possible outcome. To the best of our knowledge, the present case report is the first to describe LETM that occurred during the

treatment of tRCC. As ICIs gain more indications for oncological treatment, it is important to emphasize that such therapy can result in serious or even life-threatening adverse effects, which should be diagnosed and treated as quickly as possible.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MP and BK wrote and revised the manuscript. JK, TD, AH, PD and JJ initiated and designed the project. MP, BK, JK, TD, PD, JJ and AH collected and organized all data. All authors reviewed and edited the manuscript, and read and approved the final version of the manuscript. MP and JK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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