Case Reports in Oncology

Case Rep Oncol 2023;16:722–727
DOI: 10.1159/000532100
Received: March 20, 2023
Accepted: July 11, 2023
Published online: August 25, 2023

Case Report

Pembrolizumab-Induced Rhabdomyolysis in a Clear Cell Renal Cell Carcinoma Patient: A Case Report

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Keywords
Pembrolizumab · Rhabdomyolysis · Renal cell carcinoma · Oncology

Abstract
Pembrolizumab is one of the approved treatments for many types of cancer including clear cell renal cell carcinoma (ccRCC). It has improved the prognosis of renal cell carcinoma, yet has many possible immune-related side effects. We discuss a rare case of rhabdomyolysis in an ccRCC patient treated with pembrolizumab. The case was complicated with acute kidney injury and severe hypothyroidism, which can be attributed to pembrolizumab.

Introduction

Renal cell carcinomas (RCCs) that arise within the renal cortex constitute around 80% of all primary renal tumors [1]. The incidence of RCC varies, with about 400,000 new cases globally each year and approximately 170,000 deaths [2]. RCC originates from the proximal tube and typically has 3p chromosome deletion [3], with an association between high nuclear grade and poor prognosis [4]. Curative surgery has resulted in case fatality rate improvement, and due to early detection at smaller sizes of kidney tumors, the 5-year survival rate has increased over the last 60 years to reach around 75% in 2015 [5, 6]. In non-metastatic cases, radical nephrotomy is the standard care, and it is curative especially in early stages [7].

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Pembrolizumab is an immune checkpoint inhibitor (ICPI) that was approved as an adjuvant treatment for patients who underwent nephrectomy due to clear cell renal cell carcinoma (ccRCC) [8]. Musculoskeletal pain, fatigue, rash, diarrhea, pruritus, and hypothyroidism are the most common immune-related adverse events (irAEs), occurring in around 20% of patients on pembrolizumab [9].

ICPIs can cause some rare or very rare irAEs including cardiotoxicities, hematological toxicities, infection reactivations, and neurologic toxicities [10–13]. Rhabdomyolysis is an unusual adverse reaction with only a few cases of pembrolizumab-induced rhabdomyolysis reported in the literature up to our knowledge. There is insufficient evidence to determine the specific pathophysiology of this unusual occurrence. We discuss a case of pembrolizumab-induced rhabdomyolysis in a patient diagnosed with ccRCC.

Case Presentation

A 53-year-old gentleman presented with a medical history significant for type 2 diabetes mellitus and hypertension on oral hypoglycemic agents and amlodipine with bisoprolol. The patient was diagnosed with stage 3 ccRCC of the right kidney in December 2021 and had undergone a right radical nephrectomy in the same month. After surgery and recovery, the patient was referred to the oncology clinic and was started on pembrolizumab 200 mg every 3 weeks in February 2022. His baseline laboratories before starting pembrolizumab were remarkable for creatinine level of 140 umol/L and estimated glomerular filtration rate of 48. His baseline thyroid function test showed normal T4 and normal thyroid-stimulating hormone of 4.52 mIU/L. The patient was kept under close follow-up with the oncology team and nephrology team. In May 2022, follow-up laboratories showed deterioration in renal function as creatinine level slowly reached 170 umol/L (Fig. 1). Renal work-up showed negative proteinuria and negative immunological screen. Ultrasound showed normal echogenicity of the left kidney and no signs of obstructive uropathy.

In July 2022, after finishing 9 cycles of pembrolizumab, the patient presented to our emergency department with symptoms of generalized fatigue and progressive lower limb edema with facial puffiness. On physical exam, mild lower limb swelling was noted; otherwise, the physical examination was unremarkable. Laboratories showed elevated creatinine levels from 170 to 200 mmol/L. The patient was assessed by the nephrology team and had the work-up for acute kidney injury (Table 1), as his creatinine kinase and myoglobin were quite high. Also, we found that his thyroid-stimulating hormone was highly elevated (81 mIU/L) with low T4 (0.7 pmol/L), along with a deranged liver function test.

The patient was started on IV fluids with an improvement of kidney function over 2 days. Before discharge, his creatinine improved to 170 umol/L. In addition, he was started on levothyroxine 125 μg. The impression is that the patient's presentation and his laboratory findings of rhabdomyolysis, new severe hypothyroidism, high aspartate transferase and alanine transferase, and progressive increase in serum creatinine, were all contributed to pembrolizumab. Patient was discharged after significant improvement and was asked to follow up as an outpatient.

Discussion

Pembrolizumab has been used as an adjuvant treatment in many types of malignancies, and it has been well tolerated, yet with various irAEs. Regarding nephrotoxicity, increased creatinine is common, AKI is less frequent, and nephritis has a rare occurrence [14, 15]. The

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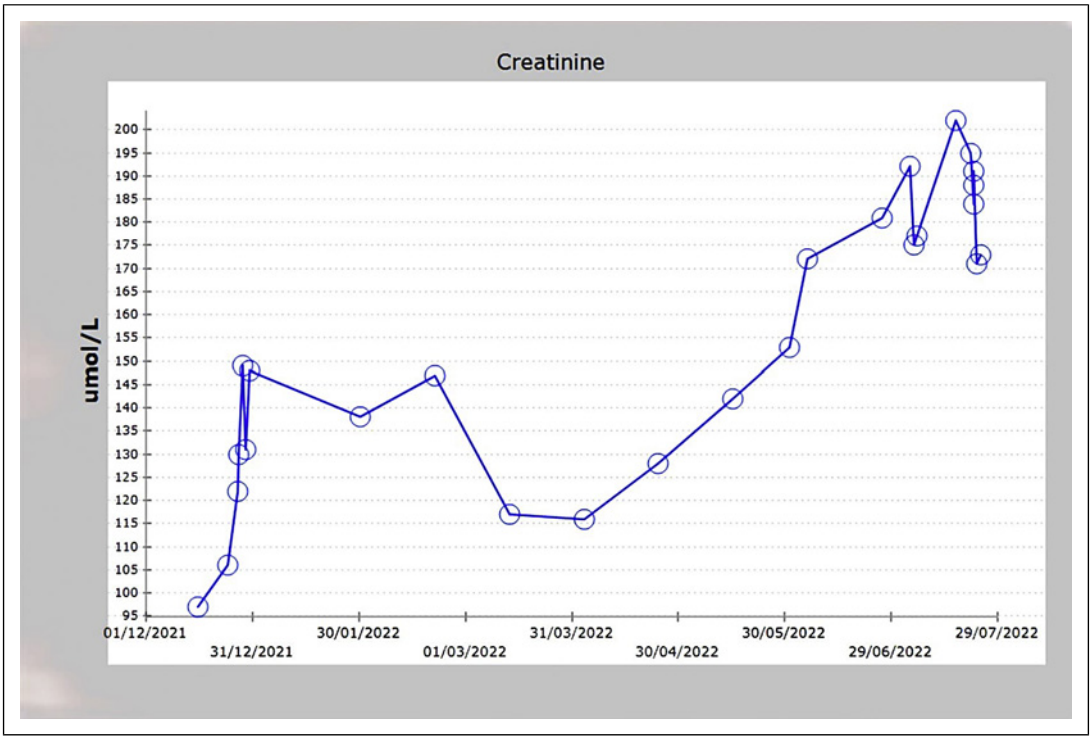

Fig. 1. Trend of serum creatinine over the course of 8 months.

mechanism is considered to be immunological and non-dose-related [15]. The onset varies, and it was reported that increased creatinine occurs from 12 to 48 weeks after first dose [16, 17]. Our patient developed a high creatinine level after around 24 weeks of treatment initiation, which we believe is a result of rhabdomyolysis.

Rhabdomyolysis was reported to occur after only one dose of pembrolizumab [18], and myositis in general happened in around 1.5% of pembrolizumab-treated patients with average onset after 4.6 weeks of treatment beginning [19]. Myopathy due to ICPIs is not well studied, yet both increased CPK and rhabdomyolysis were reported [20].

Moreover, following 9 cycles of pembrolizumab, our patient was found to have hypothyroidism and rhabdomyolysis, which highlights the importance of not overlooking such side effects even after almost finishing the therapy plan, since irAEs can happen months after stopping the ICPIs [21]. Most hypothyroid individuals who suffer from rhabdomyolysis have a clear precipitating risk factor, such as statin usage or intense activity. None of these risk factors were present in our patient. Other endocrine irAEs include hyperthyroidism, adrenocortical insufficiency, and type 1 diabetes mellitus [22–24]. Our patient was found to have hypothyroidism which can be due to pembrolizumab treatment, and it requires a life-time replacement treatment [25, 26]. It is noteworthy that hypothyroidism can itself cause an increase in creatinine level [27], and in our patient, it was difficult to accurately identify whether the high creatinine is due to rhabdomyolysis alone, or hypothyroidism alone, or both.

Other noteworthy reported side effects are cardiovascular toxicity including acute myocardial infarction, myocarditis, and pericarditis [28]. Dermatological events were also reported and can be as severe as Stevens-Johnson syndrome [29] and toxic epidermal necrolysis [30]. These effects are non-dose-related, and their exact mechanism is not confirmed, yet it is believed to be immune-mediated [31].

Table 1. Laboratory blood tests

Laboratory test	Result	Normal value
White blood cell count	6.6 × 10^3/μL	(4–10) × 10^3/μL
Hemoglobulin	15.6 g/dL	(13–17) g/dL
Platelet	174 × 10^3/μL	(150–400) × 10^3/μL
Urea	4.8 mmol/L	(3.2–7.4) mmol/L
Creatinine	**202 μmol/L**	(64–110) μmol/L
ALT	**67 U/L**	(0–41) U/L
AST	**129 U/L**	(0–41) U/L
ALP	48 U/L	(40–129) U/L
Bilirubin	9 μmoL/L	(0–21) μmoL/L
Albumin	41 g/L	(35–50) g/L
HbA1C %	6.2	4.8–5.9
TSH	**81 mIU/L**	(0.3–4.2) mIU/L
Free T4	**0.7 pmol/L**	(11–23) pmol/L
Anti-thyroid peroxidase Ab	12 IU/mL	(0–34) IU/mL
Myoglobulin	**641 ng/mL**	(28–72) ng/mL
Creatinine kinase	**4,697 U/L**	(39–308) U/L
Urine 24 h protein	<0.27 g/24 h	(0–0.15) g/24 h

ALT, alanine transferase; AST, aspartate transferase; ALP, alkaline phosphatase; TSH, thyroid-stimulating hormone. The bold text indicates an abnormal result.

We emphasize this unique case in which the patient had two major adverse events of hypothyroidism and rhabdomyolysis. The later was unmasked by AKI which happened after a considerably long time from therapy initiation. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532100).

Conclusion

Pembrolizumab is one of the most promising agents in treating different types of malignancy, yet continuous follow-up should be offered for patients, even after completing the therapy plan to early identify any possible adverse effect, which can be as serious as rhabdomyolysis. Clinical and laboratory surveillance, especially for hypothyroidism and kidney injury, should also be considered.

Acknowledgments

The authors would like to thank the patient for allowing them to share his details with the medical community. Additionally, they acknowledge the Qatar National Library for funding the open access fees of this publication.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

M.A. and K.A.: conceptualization and writing – original draft; W.A., S.A., and K.A. participated in literature review and editing the manuscript; M.A. prepared the table and the graph; N.E.O.: reviewing the final manuscript; A.Z.: revision and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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