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Case Report

Occurrence of Fatal Tubulopathy in an Old, Fit Patient Receiving Nivolumab and Ipilimumab for Metastatic Melanoma: A Case Report

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Keywords

Case report · Melanoma · Immune checkpoint inhibitors · Fanconi syndrome · Elderly

Abstract

Introduction: The use of immune checkpoint inhibitors has revolutionized cancer treatment, and their application to older people is considered safe by the scientific community. However, immune-related adverse events (irAEs) remain common, and their management poses significant challenges, especially in this population. ***Case Presentation:*** We report the case of a fit 82-year-old woman who developed immune-mediated colitis and Fanconi syndrome during treatment with ipilimumab and nivolumab for metastatic melanoma. Treatment consisted of discontinuation of immunotherapy, use of systemic corticosteroids, and second-line immunosuppressants. Despite well-managed treatment, the patient did not recover and died from a gastrointestinal infection. ***Conclusion:*** Although studies have shown identical efficacy and safety in younger patients compared to older patients, the consequences of irAEs can potentially be more serious in the older population. The fatal outcome despite well-managed treatment highlights the need to identify predictive factors of immunotherapy-related adverse events in the older population.

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Introduction

As the population ages, the prevalence of cancer is increasing worldwide and is becoming an important healthcare topic. Meanwhile, immune checkpoint inhibitors (ICPIs) have revolutionized cancer treatment, with significant survival benefits in the early and advanced stages of melanoma [1]. ICPI activates the immune system to target cancer cells and prevent them from escaping immune recognition. However, ICPI has been associated with the occurrence of immune-related adverse events (irAEs) [2]. Previous clinical trials did not show a higher risk of irAEs in the older population, but older people are often underrepresented in these trials [1, 3]. In this report, we describe the occurrence of a fatal tubulopathy (Fanconi syndrome) in an old, fit patient treated for metastatic melanoma. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535553).

Case Report

A 79-year-old woman with no known comorbidities, no underlying autoimmune disease, or chronic treatment was diagnosed with a left pretibial lentigo maligna melanoma in December 2018. Breslow thickness was 3.7 mm with 10 mitosis/mm^2 without ulceration, and there was no evidence of metastasis (pT3aNx). The disease was classified as stage IIA. The melanoma was NRAS-mutated and BRAF-wild-type. The patient had a well-preserved performance status (ECOG of 0) and a low frailty index of 17, according to the G8 screening score. She received standard treatment with a surgical excision and negative resection margins.

In November 2021, at the age of 82 years, the patient presented with a subcutaneous induration on the pretibial scar. The PET/CT showed a locoregional recurrence with suspicion of inguinal lymph node involvement (Fig. 1). A complete blood workup revealed a LDH level of 200 UI/L (baseline unknown), and the disease was classified as stage IV. The G8 assessment score remained normal at 16, and the patient received standard treatment with nivolumab monotherapy (240 mg every 2 weeks for 14 cycles). Unfortunately, the disease progressed 6 months later, and the PET/CT revealed inguinal lymph node progression and a new pretibial lesion. She received ipilimumab (3 mg/kg) in addition to nivolumab (1 mg/kg).

After two cycles of combined nivolumab and ipilimumab treatment, she was admitted to the emergency department with extreme fatigue and grade 3 diarrhea. The blood test findings showed hypokalemia of 2 mmol/L with a decreased bicarbonate level of 16 mmol/L, a decreased phosphate level of 0.48 mmol/L, an elevated creatinine level of 2.7 mg/dL corresponding to acute kidney injury stage III according to the AKIN classification (baseline 0.88 mg/dL), and an inflammatory syndrome with a CRP level of 114 mg/dL (Table 1). Urine spots revealed urinary potassium wasting (K 79 mmol/g creatinine), acidification default (pH of 7.1), glucosuria, and tubular proteinuria. An abdominal CT scan, stool analysis, and colonoscopy confirmed the presence of diverticulitis associated with nonspecific colitis. The biopsy confirmed grade 3 aspecific colitis. The nonspecific chronic colitis and acute kidney injury grade 3, with severe electrolyte imbalance, were all attributed to the ICPI. Initial management included discontinuation of nivolumab and ipilimumab, intravenous (IV) hydration, oral and IV potassium supplements up to 300 meq/day, and systemic corticosteroids (prednisolone 2 mg/kg/day) according to the ESMO (European Society for Medical Oncology) guidelines for immune-related ICPI toxicity. Kidney function normalized after IV fluid loading, but electrolyte imbalances persisted, necessitating a high dose of IV

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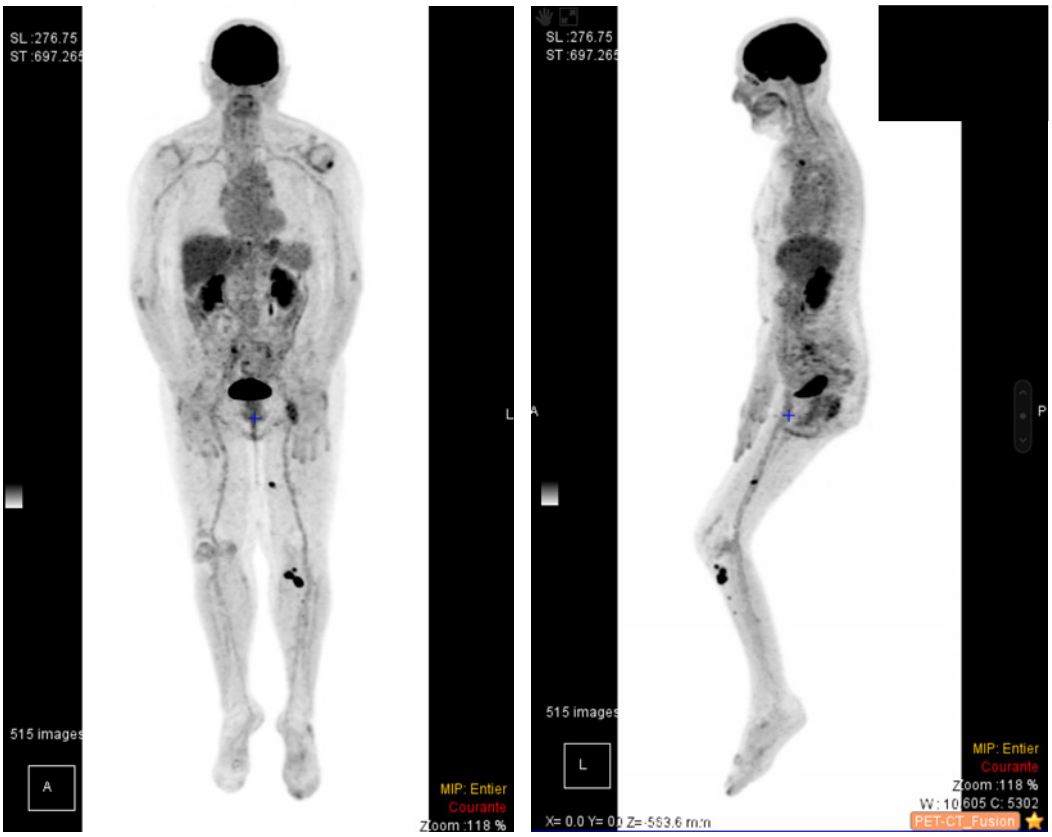

Fig. 1. PET/CT showing a locoregional recurrence of the left pretibial with suspicion of inguinal lymph node involvement.

potassium to control hypokalemia. No renal biopsy was performed at this stage, as colitis-related symptomatology was in the foreground. Following 2 weeks of high-dose steroids, the patient received infliximab (5 mg/kg) as there was no improvement in diarrhea and hypokalemia. Three injections over a period of approximately 2 months were administered without recovery. The patient was mainly managed in the hospital as oral supplementation proved insufficient to control potassium levels. Given refractory colitis with persistent gastrointestinal symptoms, the patient was administered vedolizumab (a monoclonal antibody to anti-integrin α4β7) in compassionate use after three cycles of infliximab. Although diarrhea finally decreased, high-potassium supplements were still required. PET/CT demonstrated an excellent partial metabolic response but persistent colic inflammation. Nearly 3 months after her admission, the patient was finally able to leave the hospital with oral potassium supplementation in addition to potassium-sparing diuretics (spironolactone 25 mg/d).

However, 5 days later, the patient was readmitted to the hospital due to the recurrence of severe symptomatic hypokalemia (2.3 mmol/L) and a low bicarbonate level (14 mmol/L). Given the persistence of severe hypokalemia with urinary potassium loss and acidosis, a multidisciplinary consultation was organized with the nephrology team. The diagnosis of Fanconi syndrome (proximal tubular dysfunction) was posed, and the differential diagnosis of acquired Fanconi syndrome was negative as there was no evidence for an underlying hematological or immunological disorder or exposure to toxic agents, and there was no other identifiable medication that could have led to the diagnosis. A kidney biopsy was performed at

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Table 1. Laboratory findings on the 1st admission to the hospital

	First admission	Reference range	
Hemoglobin	10.5	12–16	g/L
Erythrocytes	3.39	3.80–5.00	× 10^6/L
Hematocrit	29.3	35.0–47.0	%
MCV	86	80–100	fL
Platelets	265	150–440	× 10^3/L
WBC	9.91	3.5–11.0	× 10^3/L
ANC	6.80	1.50–6.70	× 10^3/L
Lymphocytes	1.73	1.20–3.50	× 10^3/L
Monocytes	1.09	0.10–1.00	× 10^3/L
Eosinophils	0.24	0.10–0.50	× 10^3/L
Basophils	0.05	<0.10	× 10^3/L
CRP	114	<5.0	mg/L
Natrium	138	136–145	mmol/L
Potassium	2.0	3.4–4.4	mmol/L
Bicarbonate	16	23–29	mmol/L
Calcium	2.16	2.20–2.55	mmol/L
Phosphorus	0.48	0.75–1.39	mmol/L
Urea	86	17–48	mmol/L
Creatinine	2.70	0.50–0.90	mg/dL
eGF	89	>60	mL/min/1.7 m^2
AST	22	<32	UI/L
ALT	19	<33	UI/L
GGT	45.6	6–42	UI/L
ALP	71	35–104	UI/L
LDH	226	135–214	UI/L
Bilirubin	0.4	<1.2	mg/dL
Lipase	217	40–49	UI/L
Albumin	41		g/L
Glucose	95		mmol/L

MCV, mean corpuscular volume; WBC, white blood cell count; ANC, absolute neutrophil count; CRP, C-reactive protein; eGF, estimated glomerular filtration; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase.

this stage, showing severe tubulitis with tubule destruction and acute tubular necrosis (Fig. 2). Immunohistochemical detection of T cells with anti-CD8 and anti-CD4 antibodies showed labeling for CD8 T cells but not for CD4 T cells. PD-L1 expression was present in the biopsy samples (Fig. 3). Despite second-line immunosuppressive treatment, the patient still required high-dose potassium supplements. Eventually, she developed a diverticulitis associated with a peradiverticular abscess. Despite broad-spectrum antibiotic therapy, the patient developed a septic shock. According to her wishes, no therapeutic escalation was performed, and the patient died in comfort care.

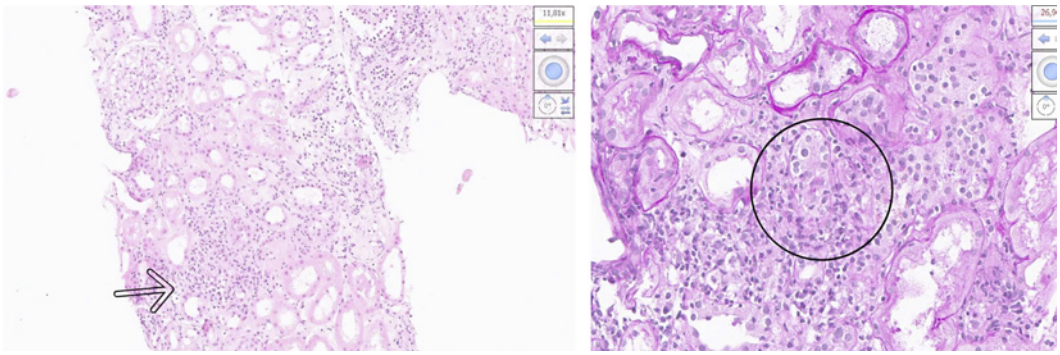

Fig. 2. Kidney biopsy showing severe tubulitis with tubule destruction and acute tubular necrosis.

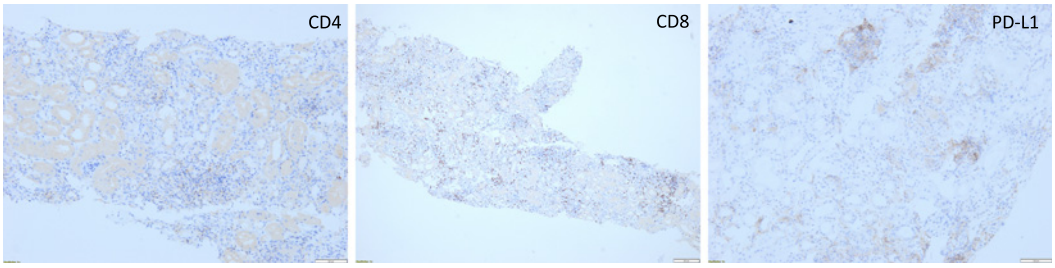

Fig. 3. Immunohistochemical detection of T cells with anti-CD4 and anti-CD8 antibodies and PD-L1 expression.

Discussion

We report the case of an older but fit patient with metastatic melanoma who died from unusually severe and refractory irAE on nivolumab-ipilimumab bitherapy. The incidence of melanoma has been steadily increasing over the past few years and is correlated with higher mortality. Melanoma occurring in older patients is associated with unfavorable prognostic factors such as a thicker Breslow, ulcerations, and a higher mitotic rate of the tumor [1]. Performance status (PS) and LDH levels are additional prognostic factors for melanoma.

For patients with metastatic melanoma, ICPI has emerged as an integral part of treatment by prolonging long-term survival [1]. ICPIs are monoclonal antibodies that inhibit immune checkpoints, a receptor-ligand system that mediates the negative regulation of T cells and self-tolerance. They include anti-cytotoxic T lymphocyte antigen 4 (anti-CTLA-4), anti-programmed death 1 (anti-PD-1), or anti-programmed death 1 ligand (anti-PD-L1) antibodies. ICPIs play a key role in the treatment of different cancer types but have been associated with the occurrence of irAEs [2]. IrAEs are frequently observed, especially with double immunotherapy (59–85%), affecting virtually all organs, with the skin, gastrointestinal tract, and liver being the most commonly affected organs across all studies. Risk factors associated with ICPI are age under 60 years, high body mass index, anti-CTLA4 for women or anti-PD-1/PD-L1 for men, and chronic smokers [4]. The risk is amplified with combination therapy, and for metastatic melanoma, the association of anti-CTLA-4 and PD1/PD-L1 leads to irAEs in 95% of the patients, of which 55% are severe irAEs (grade 3 or higher) [5]. Kidney toxicity directly related to ICPI (excluding prerenal causes, chemotherapy toxicity, contrast-induced nephropathy, or obstructive uropathy) is uncommon and affects between 2.2% and 5% of the patients. The underlying mechanism of kidney toxicity remains unclear. Potential risk factors identified for

ICPI-associated acute kidney injury (ICPI-AKI) include the concomitant use of classical medications known to induce acute interstitial nephritis (such as proton pump inhibitors, non-steroidal anti-inflammatory drugs, and antibiotics) and the combination of ICPI. Patients who experienced ICPI-AKI were found to have a higher probability of pre-existing renal dysfunction, while the type of malignancy or age do not seem to be predictive factors [4]. Interestingly, retrospective data reports that ICPI-AKI developed in patients with concomitant or prior extrarenal iRAEs such as skin rash, colitis, or thyroiditis, as observed in this case [6].

The timing of ICPI-AKI onset varies from 12 to 14 weeks after the initiation of the treatment but could be even less in the case of a combination of ICPI. The most common histopathological findings in patients developing ICPI-AKI included acute interstitial nephritis and acute tubular necrosis and, less commonly, glomerular disorders such as minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis, renal vasculitis, and C3 glomerulopathy [6]. Renal tubular acidosis is a very uncommon complication and is rarely reported [7]. Charmetan et al. [8] described distal renal tubular acidosis in patients treated with ICPI without the development of acute kidney failure. This might have been caused by an autoimmune response against type A intercalated cell receptors or pumps (H+-ATPase or Cl/HCO3). Fanconi syndrome, due to proximal tubular dysfunction, is rarely reported. Only 2 case reports have been published reporting on the occurrence of Fanconi syndrome after ICPI use for non-small cell lung carcinoma and hepatocellular carcinoma [9, 10]. Clinicians must be aware that combined electrolyte disorders may be due to an underlying renal tubular acidosis, and diagnosis should not be missed as early management is of utmost importance. The concomitant occurrence of several irAEs further complicates diagnosis, as illustrated in our clinical case.

Immune-mediated colitis is a frequent adverse event and occurs in up to 25% of patients. One-third of the patients are resistant to corticosteroids, and second-line immunosuppression must be introduced to treat immune-mediated colitis. Off-label use of infliximab and vedolizumab has been associated with good clinical responses. This patient reported not having a good response to Infliximab, but vedolizumab seemed effective on gastrointestinal symptoms [11].

Several studies have demonstrated the efficacy and safety of ICPI in older patients with cancer, including those with melanoma [1, 3]. Nevertheless, older people are underrepresented in clinical studies, and most of the recommendations come from age subgroup analyses. The main difference lies in the impact and management of side effects, which can be more challenging for older patients [12]. Studies with older and vulnerable patients have shown that patients with irAEs tend to stop treatment earlier and have a higher requirement for immune-modulating medications [3, 12]. Specific tools, such as the G8 screening tool or the comprehensive geriatric assessment, when necessary, enable the identification of frail patients at risk of developing more severe side effects [13]. In addition to geriatric assessment, an extensive blood analysis and a baseline renal function profile (sediment, proteinuria, albuminuria, and biochemical analysis) are essential prior to immunotherapy to promptly detect any changes from baseline and possible ICPI-induced renal toxicities [6].

This patient had a normal G8 screening score and showed no biological abnormalities before starting immunotherapy, but she developed fatal consequences. However, in the absence of robust clinical data, it is essential to balance the risks and benefits of the addition of a second immunotherapy medication in the treatment of older patients, as the risk of severe infections should not be minimized, as illustrated in our case.

Finally, additional studies are needed to identify predictors of irAE. For example, C-reactive protein level has been proposed to be a predictive biomarker of irAE even before clinical symptoms [4, 6]. The research also focuses on easily available biomarkers that could be used in current clinical practice to early detect the occurrence of irAEs, such as absolute circulating blood cell counts, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, or monocyte-lymphocyte ratio [4]. Interest is also growing regarding the intestinal microbiota,

which could potentially play a role in the occurrence of irAE, as well as the role of human leukocyte antigen [14]. Moreover, a recent preclinical model research showed that anti-PD-1 therapy induced irAE-like multiorgan dysfunctions in tumor-bearing older mice, with ectopic expansion of T and B cells in injured organs, whereas not in young mice [15].

Conclusion

To our knowledge, this is the first case report of a fatal case of severe Fanconi syndrome and colitis in an older patient receiving combined immunotherapy for advanced melanoma. As demonstrated by this case report, renal Fanconi syndrome caused by ICPIs is a rare but potentially severe adverse event that should not be underestimated. Although studies have shown identical efficacy and safety in younger patients compared to older patients, the consequences of irAEs can potentially be more serious in the older population. Early identification of toxicities and management by a multidisciplinary team are crucial. Physicians must be aware of potential treatment-resistant forms of irAEs. In addition, considering the decreased functional reserve associated with aging, careful evaluation of the benefits and risks of introducing second-line immunosuppression in older patients is crucial. Additional research is essential for identifying older patients at risk of irAEs.

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Statement of Ethics

Written informed consent for publication was obtained from the next of kin for the publication of this case report and the accompanying data. Ethics approval was not required for this case report in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.G. and A.R. drafted the initial manuscript, reviewed, and revised the manuscript. T.V., A.L.C., A.D., L.D.L., and H.R. reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. H.R. accepted responsibility for the finished work and controlled the decision to publish. H.R. is responsible for the overall content as the guarantor.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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