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CASE BASED REVIEW

Anti-programmed death-1 inhibitor nivolumab-induced immune-related adverse events: hepatitis, renal insufficiency, myositis, vitiligo, and hypothyroidism: a case-based review

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Abstract

Nivolumab (NIVO) is a monoclonal antibody used to treat renal cell cancer. It is an anti-programmed death-1 (anti-PD-1) inhibitor, enhancing the tumor-targeted immune response of T lymphocytes, resulting in immune-mediated adverse events (AEs). We present five immunological AEs in a single patient treated with NIVO. A 68-year-old male patient with metastatic renal cell carcinoma and right-sided nephrectomy received NIVO after pazopanib and sunitinib treatment. Two and a half months after starting NIVO, hepatocellular enzymes and creatinine were elevated. Concomitantly, the patient noticed hypopigmentation of the hand skin and a change in voice and speech. Due to hepatitis, he has been treated with dexamethasone 16 mg daily for 22 days, after which hypothyroidism and increased creatine kinase were found without muscle pain and functional impairment. Dexamethasone was continued, and a rapid decline in all parameters except thyroid-stimulating hormone (TSH) and vitiligo was observed. Myositis was initially considered a part of hypothyroidism and elevated renal parameters due to hypohydration. The rapid regression on glucocorticoid treatment and a longer time for creatinine normalization than expected with hydration were noticed. Nivolumab likely induced those side effects as assessed by Naranjo Adverse Drug Reaction Probability Scale. The literature review shows that the consequences of PD-1 inhibition are not uniform. Side effects of checkpoint inhibitors should be monitored carefully in the early and later treatment schedules evaluating subclinical manifestations like myositis and worsening of kidney parameters. Early administered higher doses of glucocorticoids can stop drug toxicity and reverse-induced tissue damage.

Keywords PD-L1 Inhibitors · Hepatitis · Toxic · Thyroid gland · Myositis · Renal Insufficiency · Chronic · Vitiligo

Introduction

Programmed death-1 (PD-1) and its ligands (PD-1 ligands, PD-Ls) pathway have been widely studied in rheumatic diseases. Most rheumatic diseases are systemic, and so far, we do not know all the pathways involved in developing and treating systemic manifestations [1]. The PD-1/PD-L pathway represents a complex network of interactions in tumor immunology and autoimmune disorders. The EULAR recommendations recognize the rheumatic adverse events of checkpoint inhibitors. Adequate reporting of different organ manifestations related to PD-1 treatment could help define the immunologic phenotype of PD-1/PD-L1 blockade. Nivolumab (NIVO) is a monoclonal antibody (a fully human IgG4 PD-1 immune checkpoint inhibitor antibody) used to treat renal cell cancer (RCC) and other solid and hematological malignancies [2, 3]. It enhances the tumor-targeted immune response of T lymphocytes, resulting in

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immune-mediated side effects. Nivolumab can induce a positive cancer response 5–8 weeks after initial treatment. The positive impact can last more than two years in some patients. Most immunologic-related adverse events ((ir) AEs) occur within the first few months of treatment and do not increase with time. Brahmer described the most severe irAEs: pneumonitis, colitis, hepatitis, vitiligo, hypophysitis, and thyroiditis in up to 41% of patients [4]. Based on reported cases worldwide, up to three AEs occur in one patient. In the retrospective study, including 47 patients with metastatic RCC (mRCC), in patients who experienced irAEs grade 3 that requires cessation of NIVO, no multiple AEs were described [5]. Benfaremo et al. analyzed different immune checkpoint inhibitors (ICI), including NIVO, across various tumors in case reports and observational studies showing detailed symptoms and final rheumatic diagnosis and outcome [6]. To the best of our knowledge and up to date, no patients with mRCC who experienced five AEs simultaneously have been described.

Case report

A 68-year-old Caucasian who suffered from chronic kidney disease (eGFR 50.3 mL/min/1.73 m^2) was diagnosed with right-sided mRCC, histologically described as a clear cell with sarcomatoid differentiation, and metastases to the lungs, lymph nodes, and left adrenal gland. A right-sided nephrectomy was performed. The first line of treatment was pazopanib 800 mg for only five months due to poor tolerance, increased liver enzymes, and diarrhea. The patient continued standard treatment with sunitinib 50 mg. Nine months after starting sunitinib treatment, a progression in the number and size of metastases was found. Hence, NIVO was started (3 mg/ kg every two weeks, 240 mg). The patient received five cycles of NIVO monotherapy. Two and a half months after the first dose, he developed hypopigmentation of the hand skin (Fig. 1). Simultaneously, elevated hepatocellular enzymes, aspartate aminotransferase (AST) 86 unit per liter, U/L (referent value, RV < 37), alanine aminotransferase (ALT) 50 U/L (RV < 36), total bilirubin (TBIL) 7 µmol/L (RV < 27), and creatinine 160 umol/L (RV < 99) were detected. Four days later, the oncologist started the dexamethasone (DEX) treatment scheduled as 8 + 8 mg daily oral administration and noticed a further increase in liver enzymes accompanied by increased creatine kinase, CK 5073 U/L (RV < 155). Differential diagnoses included polymyositis, and the patient was referred to a rheumatologist. The patient received glucocorticoids (GC) for 22 days before the rheumatological examination. Inflammatory parameters, sedimentation rate (ESR), and C-reactive protein (CRP) were within referent intervals. The patient felt well, without muscle pain and muscle impairment. The arms and legs electromyoneurography (EMNG) and abdominal and thyroid ultrasound results were normal. The patient had a good clinical presentation, and a muscle biopsy was not indicated. Elevation of thyroid-stimulating hormone (TSH) 36.5 mIU/L (RV 0.45–5) showed hypothyroidism. Urine sediment was normal with negative urine myoglobin. Immunological specific antibodies, antinuclear antibody (ANA), extractable nuclear antigen (ENA) panel, and anti-double-stranded DNA (anti-dsDNA) were within the normal range. The serology tests ruled out hepatitis B and C viruses. Glucocorticoids were further reduced to DEX 4 + 4 mg daily. In addition to GC, saline infusions for two weeks were administrated, aiming to treat elevated creatinine. A rapid decline in transaminases and CK were observed in 7 days during hospitalization (AST 230 to 67, ALT 157 to 65, CK 5073 to 473 U/L, creatinine 179 to 141 (eGFR 43 mL/min/1.73 m^2). The patient recovered all laboratory findings. Initial values of creatinine were obtained after four months. Hypothyroidism and hand vitiligo remained. The timeline of NIVO administration and GC treatment, the occurrence of AEs, and their regression are shown in Table 1 and Fig. 2.

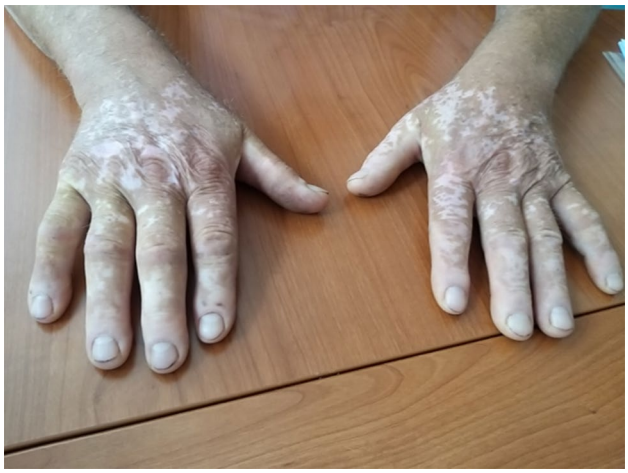

Fig. 1 Vitiligo

Observed AEs belong to G1 and G2 (mild-medium) degrees of immune-mediated adverse drug reactions of NIVO. Cancer treatment with NIVO has been continued, and the progression of the disease has not been observed for nine months since the first NIVO was administered. After NIVO, the patient was treated with vinblastine and thereafter with everolimus. Up to October 2022, the patient has been treated for four years.

The Adverse Drug Reaction (ADR) Probability Scale developed by Naranjo in 1991 is simple and still widely used [7]. Definite drug reaction is considered if the score is nine or higher, probable 5- 8, possible 1- 4, and doubtful if 0 or less. In this case, the total score was judged as 7; the adverse events (AEs) are probable due to NIVO treatment.

Table 1 Timeline of nivolumab and glucocorticoid treatment and occurrence of adverse events

Date	1.3	29.4	17.5		21.5	5.6	12.6		14.6	16.6		19.6	22.6	24.6		26.7		28.8	25.9
Treatment	First NIVO		DEX 8+8 mg				DEX 4+4mg			MP 16 mg				MP 8 mg		NIVO continued			
Creatinine [umol/L]	124	150	160		151	174	179		162	170		141	154			137		125	126
AST [U/L]	31	32	86		164	98	230		207	75		67	54			28		24	
ALT [U/L]	28	30	50		67	88	157		156	107		84	65			29		21	
CK /[U/L]							5073		3927	1126		473						80	
TSH/mIU/L							36		Tpo+									15.9	2785
CRP/mg/dl							1,1			5,2		4,8						3,2	
	Hydration iv, 1 and 2 l saline daily																		
	Levotyroxine 25µg ……50µg……75µg……100µg……																		
	11 weeks liver and creatinine, 14 weeks hypothyreosis and vitiligo, the exact time can not be determined for myositis (CK) and TSH																		

NIVO nivolumab, *DEX* dexamethasone, *MP* methylprednisolone, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CK* creatinine kinase, *TSH* thyroid-stimulating hormone, *CRP* C-reactive protein

Methods

We searched literature databases to investigate cases of NIVO toxicity reported worldwide and to discuss the results of this search compared to our topic. The search strategy included seven main search term concepts: (1) "nivolumab"; (2) "renal cell cancer; (3) "hypothyroidism," (4) "vitiligo," (5) "myositis," (6) "hepatotoxicity," and (7) "kidney." In addition, we did a hand search from the reference list of selected articles. We searched a Medline database (via PubMed) over the last ten years and Web of Science (WoS) with no time limit ending with November 6, 2022. Articles that were not in English were excluded. The PRISMA flow chart is shown in Fig. 3. Included studies based on the search strategy are shown in Table 2. This case-based review is written according to recommendations for narrative biomedical review [8]. A written informed consent has been obtained.

Discussion

We presented a patient treated with NIVO 5 doses who developed a multitude of irAEs. The hepatotoxicity and hypothyroidism, usually easily addressed, were accompanied by myositis, renal impairment, and vitiligo. For some medicines, a genetic predisposition that led to increased toxicity has been found. Considering NIVO, specific genetic mutations related to drug efficacy are well-known (ALK, CD274, EGFR). Still, no specific genetic mutation linked to increased susceptibility to adverse drug reactions (ADRs) has yet been demonstrated and incorporated into guidelines [9]. Only the TT genotype in the PDCD1 rs2227981 polymorphism was proposed to be related to decreased NIVO toxicity [10]. The patient received DEX 16 mg, which is much more potent (equivalent to methylprednisolone (MP) 85.3 mg) and poses a more extended (72 h) anti-inflammatory effect, so the patient had a higher cumulative dose during the day. European Society for Medical Oncology (ESMO) guidelines recommend MP 1 mg/kg body weight for hepatitis grade 2: AST and ALT 3–5 times higher and discontinuation of the precipitated drug [11]. The dose given to the patient was appropriate to treat both increased CK and creatinine. The guidelines suggest an MP dosage of 1–2 mg/kg/day for moderate myositis and elevated CK, also found in EULAR recommendation No.8 [12]. In this case, we cannot say when the CK elevation started and what was the maximum level. Creatine kinase was measured for the first time when the patient was already treated with DEX. Muscle biopsy after 22 days of DEX treatment may give some information about myositis, though it is not essential to decide on GC treatment. Also, glucocorticoids mask inflammation, and it is difficult to interpret the pathohistological

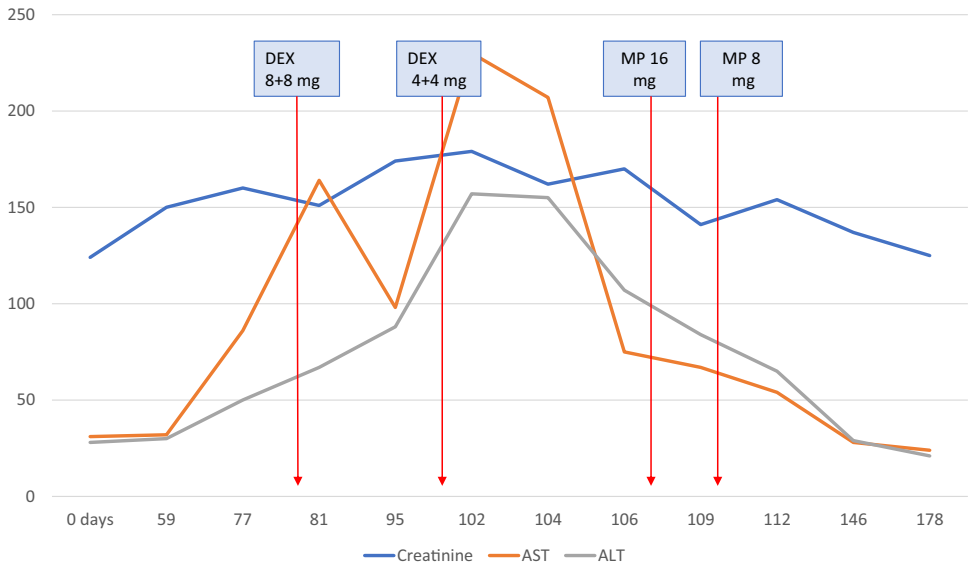

Fig. 2 Timeline of creatinine, AST, ALT elevation. *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *DEX* dexamethasone, *MP* methylprednisolone

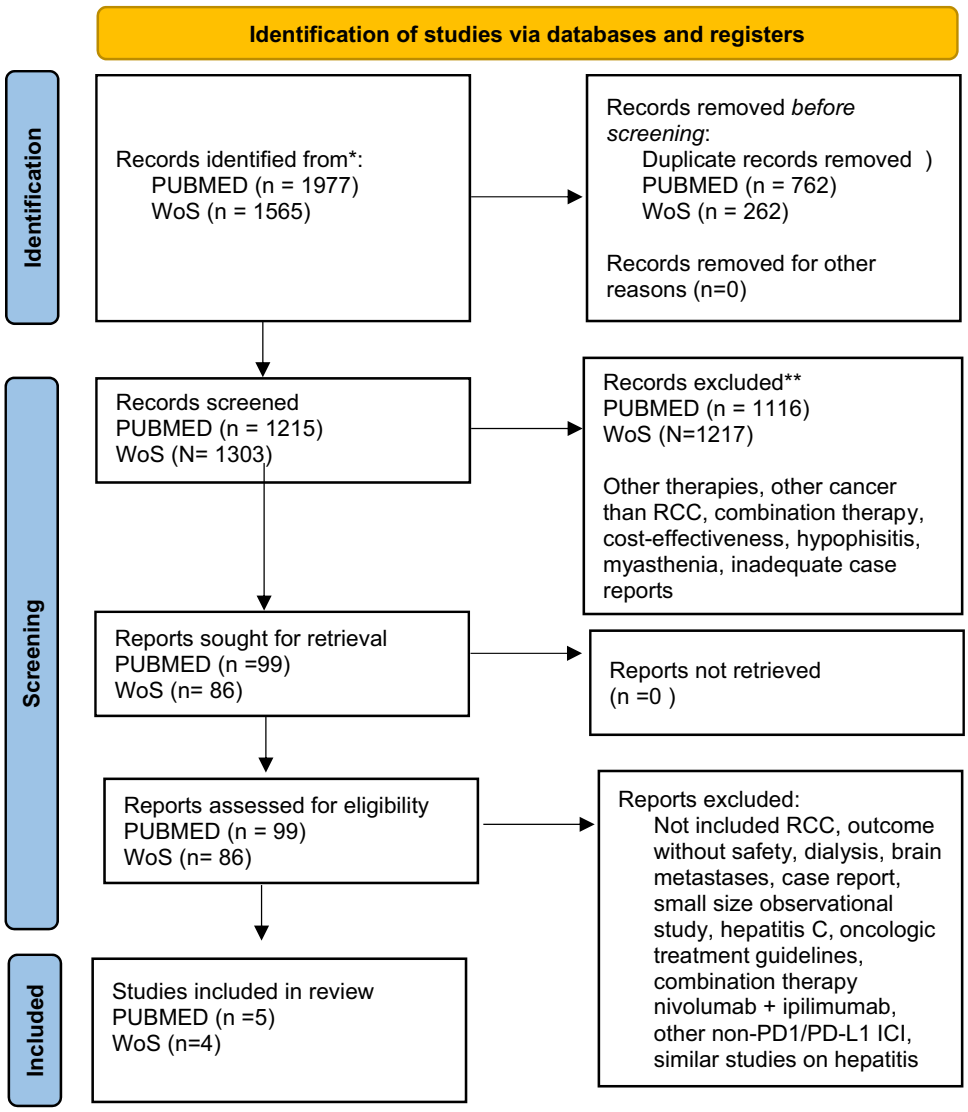

Fig. 3 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 2 Included studies based on the search strategy

Included studies	Type	No. Pt	Conclusion
Ishihara [5]	Retrospective observational	47	No significant differences in the risk of elevated blood indicators of hepatotoxicity comparing PD-1/PD-L1 inhibitor monotherapy, PD-1/PD-L1 inhibitor plus chemotherapy, or chemotherapy alone were described
Brahmer [4]	Review		It seems that the safety profile of nivolumab compared to standard cytotoxic chemotherapy regimens and with ipilimumab is more tolerable. Although nivolumab-related AEs are generally manageable, many clinicians are unfamiliar with them
Zarrabi [20]	Meta-analysis (27 clinical trials)	5287	Nivolumab significantly increased the RR of all-grade AST/ALT elevations (RR 1.58, 95% CI 1.1–2.2; RR 1.62, 95% CI 1.2–2.3). Tumor type and addition of ipilimumab ($p < 0.001$) may contribute to the effect estimates of AST or ALT elevation, based on subgroup analysis
Gamulin [17]	Retrospective chart review	30	This study's incidences of immune-related adverse events were similar to those already described in the literature. Nivolumab appears to be an excellent second-line therapy option
Ugo de Giorgi [16]	Prospective observational	398	The safety and efficacy demonstrated in this study were comparable with those reported in the Checkmate 025 trial. Nivolumab seems to have a favorable profile in particular subgroups of patients: non-clear-cell mRCC who were elderly, pretreated with everolimus, and had bone and brain metastases
Belum [18]	Meta-analysis (clinical trials)	4244	Nivolumab had a higher RR of developing all-grade vitiligo than chemotherapy or pembrolizumab
Badovinac [22]	Case report	1	Nivolumab-induced myositis (biopsy proven) and hypothyroidism occurred simultaneously
Baxi [21]	Meta-analysis (13 clinical trials)	6676	PD-1 inhibitors increased rates of hypothyroidism (OR 7.56, 95% CI 4.53 to − 2.61), pneumonitis (5.37, 2.73 to 10.56), colitis (2.88, 1.30 to 6.37), and hypophysitis (3.38, 1.02 to 11.08). There was a higher incidence of rash. Reporting of musculoskeletal irAES highly varied
Costa [19]	Meta-analysis (9 clinical trials)	5353	PD-1 inhibitors, NIVO and PEM, are associated with a relatively low risk of irAEs, hyperthyroidism (RR of 3.44 (95% CI 1.98–5.99), and hypothyroidism [RR of 6.79 (95% CI 3.10–14.84; $P < 0.001$)

muscle findings. Creatinine was monitored regularly, but the initial elevation of creatinine was not associated with drug toxicity. The creatinine elevation is significant when elevated at 0,3 mg/dl (26,53 µmol/L) or 1,5–2 times above initial values. [13]. In our case, the increase was 55 µmol/L and did not improve with hydration but with GC treatment. The acutization of chronic kidney disease is the rarest irAEs, up to 1%, mild and often develops in 3 weeks to 6 months after NIVO treatment. The most often cause is acute tubulointerstitial nephritis. In a review by Wanchoo et al., NIVO-induced elevated renal parameters were described in up to 2–3% of patients. Additionally, acute kidney injury developed late during the treatment (6–12 months), and 75% of renal parameters normalized with GC therapy [14].

In the open-label phase III randomized controlled trial (RCT), CheckMate 025, NIVO was compared to everolimus in 803 RCC patients. Of 406 NIVO-treated participants, 71% discontinued treatment primarily due to disease progression and 9.6% due to AEs. The incidence of NIVO-related AEs was 80.5% (grade 3–4, 21.4%). The most common AEs were fatigue (34.7%), pruritus and nausea (15.5% and 15%), and diarrhea (13.8%). Immune-related AEs of any grade mainly affected skin (27.8%, grade 3 or 4 1.2%) and gastrointestinal (GI) system (GI 14.0%, grade 3 or 4 2.2%), followed by endocrine (11.1%, grade 3 or 4 1.0%) and hepatic (11.3%, grade 3 or 4 3.0%). Renal and pulmonary AEs occurred in 6.9% of participants (grade 3 or 4, 1.0%); and 5.2% (grade 3 or 4, 1.5%) [15]. A real-life prospective Italian study that compared a cohort of 397 mRCC patients to the CheckMate 025 described a lower incidence of grade 3–4 AEs in Italian participants (7–19%). It was attributed to underreporting of ADRs in local hospitals [16]. A retrospective chart review of 30 mRCC patients treated with NIVO described fatigue, anemia, colitis, hepatitis, and endocrinopathy. A maximum of four AEs in a single patient was reported, and three AEs in four. Patients were mostly treated with different GC doses [17]. In a meta-analysis investigating dermatologic events related to PD-1 treatment, pembrolizumab (PEM), and NIVO in patients with melanoma, both drugs were associated with low-grade rash, pruritus, and vitiligo. The incidence of NIVO-related vitiligo was 7.5%. Patients exposed to NIVO have a 15 times higher risk of developing vitiligo (RR = 14.6, 95% CI 0.9 to 235.0; $P = 0.058$) than controls treated with other chemotherapy [18]. Vitiligo occurs more often in patients with metastatic melanoma (RR 4.92; 95%CI 2.07–11.69; $P < 0.001$) [19]. A meta-analysis included 27

clinical trials with 5287 participants with different tumors and showed that treatment with NIVO poses a significantly higher risk of hepatotoxicity. The subgroup analysis found that hepatotoxicity was more common in ovarian cancer and advanced melanoma and less common in RCC [20]. It is speculated that prior nephrectomy and cytokine treatment affect the renal clearance of NIVO, but the real cause remains unclear. In most studies analyzing PD-1 toxicity across different malignancies, the survival rate was the primary endpoint. Although physicians must report AEs, a reporting bias can occur in many cases. Specifically, when more than one AE is present in a single patient, but only one AE has been reported, many AEs remained unrecognized. Another meta-analysis compared NIVO ($n=1534$), PEM ($n=1459$), and atezolizumab (ATEZ, $n=751$) to controls cetuximab ($n=2476$) or a biological agent ($n=397$). Most often, AEs with NIVO were hypothyroidism 4.7–7.2% and pneumonitis 1.5–3.1%. The reported incidence of musculoskeletal disorders differs for all drugs and often is not even reported. Across studies, in the PD-1 group, arthralgia occurred from 10 to 26%, back pain from 6 to 22%, musculoskeletal pain from 6 to 14%, and myalgia from 2 to 12%. [21]. The cut-off values between severe and mild grades of myositis are not numerically clearly defined in guidelines but according to the clinical presentation of muscle impairment. A similar case report described simultaneously elevated TSH and CK. Muscle biopsy showed immune-mediated damage to muscle fibers. Cell infiltration around muscle fibers mainly comprises CD4-positive lymphocytes and less CD8 and CD68. Inflammatory cells were also found within the muscle fibers [22]. The differences between ICI-induced myositis and classic polymyositis are notable. ICI-induced myositis appears to have a broad spectrum ranging from mild syndromes that do not require steroids to severe life-threatening presentations combined with myocarditis [23]. A retrospective, observational pharmacovigilance study described 1288 cases of rheumatic and musculoskeletal (RMS) irAEs. Myositis was described in 465 (36.1%; reporting-odds-ratios 4.9 (4.5–5.4)) patients. The onset of myositis was close to the beginning of the ICI treatment (median 31 days, interquartile range 19.2–57.8) and was more frequently associated with renal carcinoma than other RMS irAEs (11.8% vs. 1.2–8.3%, $p=0.02$). Data analyzed in this study originated from VigiBase from inception to January 2019 [24]. We found no muscle impairment or heart involvement in our patient.

Differential diagnosis included paraneoplastic syndrome, which was excluded based on the following facts: temporal relationship (time to event) with the new drug introduced (the patient had cancer for more than one year before, with normal clinical status, irAEs did not reappear with disease progression and new treatment) and by the Naranjo, objective pharmacologic scoring system.

Oncologists frequently treat patients with irAEs and quickly notice the most severe irAEs, while musculoskeletal disorders and worsening of chronic renal function may be underreported. Some institutions have a multidisciplinary approach to adequately diagnose irAES [25]. Initial treatment of irAEs consists of ICI-withholding. The use of higher doses of GC should not interfere with tumor treatment. There are concerns that it might bring an inferior outcome [26]. Analysis of studies with ICI and GC has shown different conclusions due to many confounders and biases on GC's effect (dose and timing of administration) on overall survival [27]. Our patient received a medium dose of GC for the resolution of G1 and G2 AEs. It resulted in the continuation of tumor treatment and nine months without disease progression, giving him a chance to continue other therapies.

Conclusion

The primary point of this case is the need for better reporting of adverse events. On the other hand, the literature review shows that the consequences of PD-1 inhibition are not uniform. The spectrum of irAEs depends on the personal characteristics of patients, the type of tumor, and the type of anti-PD-1 inhibitor. The irAEs of checkpoint inhibitors should be suspected early, and higher doses of GC should be started early to induce reversible changes. Subclinical manifestations should be carefully evaluated and reported in clinical trials. Since myositis is one of the fatal irAEs, regular screening of CK levels in the first months of treatment might help find high-risk patients. Adequate reporting of different organ manifestations related to PD-1 therapy is valuable and welcome for rheumatology practice.

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Data availability The datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval This narrative review is written in compliance with ethical standards.

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