Case Report

Raising awareness of immune-related side effects in oncological patients under palliative care: a report of two cases

Anne Strunk[1,2], Yann-Nicolas Batzler[3]^, Mirjana Ziemer[4], Martin Neukirchen[3,5], Jacqueline Schwartz[3], Michael Sachse[6], Marlene Garzarolli[1,2], Cristin Strasser[1,2], Lydia Reinhardt[1,2], Martin Kaatz[7], Ulrich Schuler[8], Friedegund Meier[1,2]

[1]Department of Dermatology, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; [2]Skin Cancer Center at the University Cancer Center Dresden and National Center for Tumor Diseases, Dresden, Germany; [3]Interdisciplinary Center for Palliative Care, University Hospital, Heinrich Heine University, Düsseldorf, Germany; [4]Department of Dermatology, University Hospital Leipzig, University of Leipzig, Leipzig, Germany; [5]Department of Anesthesiology, University Hospital, Heinrich Heine University, Düsseldorf, Germany; [6]Department of Dermatology, Klinikum Bremerhaven-Reinkenheide gGmbH, Bremerhaven, Germany; [7]Department of Dermatology, SRH Wald-Klinikum Gera, Gera, Germany; [8]University Palliative Center, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany

Contributions: (I) Conception and design: M Sachse, U Schuler, F Meier; (II) Administrative support: A Strunk, YN Batzler, C Strasser, L Reinhardt, F Meier; (III) Provision of study materials or patients: A Strunk, YN Batzler, M Ziemer, M Neukirchen, J Schwartz, M Garzarolli, M Kaatz, U Schuler, F Meier; (IV) Collection and assembly of data: A Strunk, YN Batzler, M Ziemer, F Meier; (V) Data analysis and interpretation: A Strunk, YN Batzler, M Ziemer, F Meier; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. med. Yann-Nicolas Batzler. Interdisciplinary Center for Palliative Care, University Hospital, Heinrich Heine University, Moorenstraße 5, 40225 Düsseldorf, Germany. Email: yann-nicolas.batzler@med.uni-duesseldorf.de.

Background: Immune checkpoint inhibitors (ICI) have emerged as a successful treatment option for diverse cancer entities. However, ICI therapy can be associated with immune-related adverse events (irAE) that can affect any organ system. These side effects can be severe, irreversible and sometimes even fatal. Due to the presentation as diverse and often unspecific clinical patterns, end-of-life care concepts may be pursued hastily suspecting disease progression in oncological patients receiving palliative care (PC).

Case Description: This report describes two cancer patients whose symptom burden was caused by such irAEs: One patient with metastatic cutaneous squamous cell carcinoma (SCC) presenting with disorientation and urinary incontinence, another patient with metastatic melanoma presenting with a sudden and unspecific deterioration of the overall condition. After imaging and blood sampling, an encephalitis and an immune-mediated diabetes mellitus were diagnosed. After treatment with corticosteroids and hydration alongside insulin substitution both patients experienced a complete symptom relief.

Conclusions: We aim to emphasize the importance of continued collaboration between primary care givers and PC teams as well as raise awareness among PC providers of severe immune-related side effects in cancer patients receiving ICI. Especially within this patient cohort, PC teams play a crucial part in detecting possible irAEs, which resolve in the majority of cases when receiving early guideline-adapted treatment.

Keywords: Palliative care (PC); immunotherapy; adverse events (AEs); systemic corticosteroids; case report

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^ ORCID: 0000-0002-4436-6448.

Introduction

Immune checkpoint inhibitors (ICI) have revolutionized oncology in recent years. For example, the anti-programmed-death-1 (anti-PD-1) antibody nivolumab combined with the anti-cytotoxic-T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody ipilimumab achieves longer survival rates for almost 60% of patients with metastatic melanoma (melanoma-specific survival rate of 56% at 6.5 years) (1). In 2015, the successive expansion of approval to additional tumor entities started with head and neck squamous cell carcinoma (SCC), followed by non-small cell lung cancer, classical Hodgkin's lymphoma, and urothelial carcinoma (2).

However, this progress is associated with a previously unknown spectrum of side effects that differs fundamentally from those of other anticancer agents. Instead of pancytopenia and polyneuropathy, uncommon immune-mediated, complex clinical patterns are observed and require special attention (3,4). These immune-related adverse events (irAEs) classified by the Common Terminology Criteria for Adverse Events (CTCAE v5.0) (5) can affect any organ system and result from the activation of the immune system and the loss of immunological self-tolerance, which usually identifies the organism's own antigens and prevents autoaggression. IrAEs can present as exanthema, thyroiditis, hypophysitis, diabetes, enterocolitis, hepatitis, pneumonitis, nephritis, arthritis, myositis, myocarditis, and neurologic adverse events (AEs), just to name a few (6). Most commonly, they manifest within the first six weeks after initiation of therapy but may occur even several months after its completion (7,8). The most common irAEs include thyroiditis, colitis, hepatitis, and pneumonitis, whereas the most fatal irAEs include myocarditis, myositis, and adrenalitis (9,10). Severe CTCAE grade 3 or 4 AEs occur in about 20% of cases with anti-PD1 monotherapy, and often result in an impaired general condition and require hospitalization (5,11). Under combined therapy with anti-PD-1 and anti-CTLA-4 antibodies, almost every patient experiences at least one mild AE and the rate of severe grade 3 or 4 AEs is as high as 59% (12).

Often, irAEs include non-specific symptoms such as an impaired general condition, clouding of consciousness, headache, and visual disturbance (13,14). For example, patients receiving ICI may develop symptoms consistent with SARS-CoV-2 infection such as fever, cough, and dyspnea (ir pneumonitis), elevated troponin or heart failure (ir myocarditis), and elevated liver function tests (ir hepatitis). This results in an increased risk of misdiagnosis, especially in patients with tumor entities commonly associated with a poor prognosis. Disease progression or even end-stage disease may be suspected, potentially leading to end-of-life care without any further diagnostic assessments. However, when detected as such, irAEs are effectively treatable and in most cases are reversible. However, if not treated timely and efficiently, can lead to irreversible damage and even death (9,10).

We present two cases of patients: One with metastatic cutaneous SCC and one with metastatic melanoma. In both cases, due to the final stages of the disease alongside a high symptom burden, a referral to the palliative care (PC) unit was considered. In this context, it is of high importance to raise awareness about diagnostic and therapeutic steps in the management of irAEs emphasizing on interdisciplinary collaboration to improve early diagnosis. We present this article in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1077/rc).

Highlight box

Key findings

- Ongoing collaboration between primary caregivers and palliative care teams is essential for the early detection of immune-related adverse events in palliative patients receiving immunotherapy.

What is known and what is new?

- Immune-related adverse events present as non-specific symptoms, which makes detecting them difficult, even more in patients under palliative care where disease progression may be suspected.
- Palliative care teams play an important role in the detection of immune-related adverse events and their timely treatment.

What is the implication, and what should change now?

- Awareness of immune-related adverse events should be risen through cross-clinic and cross-setting education.

Case presentation

The first case we report is a 77-year-old male patient receiving immunotherapy with a PD-1 antibody for metastatic cutaneous SCC. One month after therapy initiation the patient was admitted to the hospital presenting with pyrexia and reduced vigilance. Based on the information available and the symptoms presented, the emergency department's medical staff intended to transfer the patient to the PC unit without further diagnostic

assessments. Severe infection and brain metastases were suspected, and the case was assessed as an overall best supportive care situation. However, a consultation with the treating dermato-oncologist took place and transfer to the treating skin cancer center was agreed.

There the patient presented with pyrexia, disorientation, reduced memory, urinary incontinence, was unable to follow complex sequences of actions and suffered a bilateral convulsive seizure. Laboratory findings included a discrete leukocytosis and a minimally elevated C-reactive protein (CRP). The cerebrospinal fluid (CSF) showed a 2-fold increase in protein content without evidence of malignancy or infection. An electroencephalogram (EEG) demonstrated severe diffuse brain dysfunction with a postictal state, and cranial magnetic resonance imaging (MRI) confirmed the suspected diagnosis of leptomeningitis with concomitant encephalitis. Systemic therapy with intravenous methylprednisolone 2 mg/kg body weight and anticonvulsive therapy with levetiracetam was initiated immediately and the neurological symptoms regressed. PD-1 antibody therapy was not resumed in view of the severe side effect. However, three years after discontinuation of ICI therapy, the patient has experienced a complete remission of both the SCC and the neurological side effects.

We further report the case of a 62-year-old female melanoma patient with lung and brain metastases. She received whole-brain radiotherapy and systemic treatment with a PD-1 antibody, which was well tolerated except for an immune-mediated thyroiditis. The lung and brain metastases regressed, and the final follow-up showed a complete remission. One week after the last visit to the clinic, the attending family physician contacted the treating oncologist and reported a rapid deterioration of the overall condition. The patient was perceived as in her final phase of life and transferred to a hospice sought as soon as possible.

The patient presented in the emergency department with abdominal pain, nausea, vomiting and hyperventilation. An immune-mediated diabetes mellitus was diagnosed with significantly increased blood sugar (44 mmol/L), hyperkalemia (6.64 mmol/L), dehydration, and consecutive prerenal kidney failure. The patient was transferred to the intensive care unit. With hydration and insulin substitution, a normalization of the electrolytes and blood glucose levels was achieved. Immunotherapy was not resumed due to the radiological complete remission.

Table 1 provides an overview of five further oncological patients who developed irAEs under immunotherapy.

All procedures performed in this study were in accordance with the ethical standards of the institution and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Awareness of irAEs has improved significantly in recent years with the increasing number of therapeutic targets for ICIs. However, fatal side effects continue to be reported (>600 in Vigilyze) (5,15). IrAEs may occur very early after therapy initiation and with marked differences between ICI regimens (8,9). An early diagnosis is often challenging, as irAEs may involve different organs, present as diverse, previously unknown clinical patterns, and often with non-specific symptoms (4,9). IrAEs can thus mimic tumor progression, an infection or autoimmune disease, for example, and symptoms can easily be misinterpreted. Disease progression or even end-stage disease may be suspected, potentially leading to end-of-life care without any further diagnostic assessments.

It is a challenge for physicians to determine if patients in palliative situations should receive life prolonging therapies when the symptom burden is high. However, palliative is not equivalent to the best supportive care.

Referral to PC in an early stage of the disease is preferable (16). This, however, is still not the usual practice and often PC is integrated only when patients present with poor performance status, increasing frailty, and high symptom burden (17-19). These factors all contribute to the onset of severe and life threatening irAEs (6,17). The patients' symptom burden might be aggravated due to renal, cardiac, or pulmonary comorbidities, which themselves are risk factors for the development of organ specific irAEs (6). Adding up, patients in PC often present with sarcopenia, which is another risk factor for irAEs (17). Since palliative treatment regimens are increasingly implemented nowadays, palliative patients are at high risk of developing late onset high grade irAEs more than six months after starting ICI treatment and need continuous follow-up care (8,20,21). Involving PC early on leads to better symptom control (22), timely end of life discussions and a reduction in readmissions to hospital which ameliorates the patients' overall quality of life (16-18,23).

If a patient presents with the above-mentioned symptoms

Table 1 Further oncological patient cases with irAEs associated with immunotherapy, presenting symptoms, diagnostic steps performed and irAE treatment

Case number	Presentation of oncological disease	Immunotherapy	Symptoms	irAE	Diagnostic procedures and treatment*
1	MUP with cerebral and pulmonary metastasis	Ipilimumab + nivolumab, followed by nivolumab monotherapy	Acute deterioration of general condition, anuria, disorientation, confinement to bed	Acute renal failure stage 3 in ir nephritis, ir encephalitis, ir arthralgia and ir myalgia	D: Biopsy (with proven interstitial nephritis) T: Methylprednisolone 2 mg/kg body weight in decreasing doses; melperone for disorientation; rehydration; antibiotics; termination of drug therapy for tumors; dialysis was refused
2	Metastatic melanoma	Pembrolizumab	Weight loss of 20 kg in 4 months, weakness, right calf muscle pain, hypercalcemia, appetite loss, nausea	ir hypophysitis and ir adrenalitis	D: MRI pituitary; exclusion of peripheral artery disease, deep vein thrombosis, herniated disc T: High-dose methylprednisolone therapy followed by corticosteroid replacement with hydrocortisone
3	Renal cell carcinoma	Nivolumab	Cloudiness, muscle twitching, anemia, acute renal failure with hyperkalemia	ir nephritis	D: 5-fold elevated creatinine, reduced hemoglobin and GFR (the staging CT showed a significant reduction of the carcinoma) T: Diuretics and glucose-insulin infusion (after dialysis refused)†
4	Metastatic renal cell carcinoma	Pembrolizumab + axitinib	Tachypnea, dyspnea	ir pneumonitis	D: CT thorax T: High-dose intravenous prednisolone therapy (1 mg/kg/day) for a total of seven days, oral after day 7 and reduced by 10 mg every seven days; morphine for symptom control
5	Metastatic urothelial carcinoma of the urinary bladder	Pembrolizumab	Diarrhea	ir colitis	D: Microbiology (without detection of the pathogen, clinical diagnosis); strict laboratory chemical controls of the electrolytes T: High-dose intravenous prednisolone therapy (1 mg/kg/day) for a total of seven days, oral after day 7 and reduced by 10 mg every seven days

*, the diagnostic and therapeutic procedures in this table were carried out in accordance with the current ASCO guidelines (9). †, in this case, the ASCO guidelines recommend the application of prednisolone 1–2 mg/kg body weight (9). irAE, immune-related adverse event; MUP, melanoma of unknown primary; ir, immune-related; MRI, magnetic resonance imaging; CT, computed tomography; GFR, glomerular filtration rate; ASCO, American Society of Clinical Oncology.

after receiving immunotherapy all involved clinicians, from oncologists to PC teams, should be aware that these might be reversible with little effort (24-26).

With the sharp increase in the use of new immunotherapies in the field of oncology, the probability of such cases occurring is increasing. Due to the presentation as non-specific symptoms and/or diverse clinical patterns, irAEs may not be recognized or considered as such by colleagues in primary care settings. An end-of-life care concept may be pursued hastily in the presence of suspected disease progression, which emphasizes the important role PC teams play in detecting possible irAEs. In these cases, an ongoing collaboration between PC and primary caregivers is crucial to treat patients sufficiently.

An important general means with which to raise awareness of irAEs is repetitive, cross-clinic and cross-setting education, i.e., education of all who may be involved in the treatment of oncological patients. This includes targeted information for both patients and their families, who should be prepared for the potential occurrence of irAEs and informed about emergency management. Even so, regular lectures and training are essential to sensitize primary care providers, nursing staff and medical specialists. Detailed, up-to-date physician's letters shared with patients when they leave the clinic following an immunotherapy cycle may also be helpful. A patient passport or certificate with reference to ongoing or recent ICI therapy and relevant telephone contacts for the treating oncologist(s) could be stored in the patient's wallet for use in case of emergency (27).

If an irAE is suspected, prompt management is imperative. Various national and international guidelines provide orientation and support clinical management (9,28-30). Measures to be taken differ depending on the suspected diagnosis. For example, if a neurological side effect is suspected, a clinical neurological examination, CSF diagnostics, a brain MRI and an EEG should be performed (31,32). If cardiac involvement is suspected, cardiac enzymes, ECG, echocardiography, and cardiac MRI are required (10,33).

The way an irAE is managed depends on the severity, which can be classified into 5 grades according to the CTCAE (34). While low-grade toxicities may allow continued therapy, management of severe irAEs may require pausing ICI treatment and initiating glucocorticoid therapy, followed by a slow tapered reduction (35). Inpatient admission is often required in this setting. If an irAE is suspected or cannot be excluded, first-line therapy is the timely administration of corticosteroids (e.g., methylprednisolone 1–2 mg/kg/body weight) (20,29).

An exception is endocrine irAEs, which require not corticosteroid therapy but hormone replacement (36), as reported in our second case.

Recently, additive immunomodulators in the case of corticosteroid resistant side effects became of interest in the treatment of irAEs. These include CTLA-4 agonists such as abatacept, calcineurin inhibitors like tacrolimus or the IgG1 antibody infliximab (4,10,20,37). In late onset irAEs more than a year after initiation of ICI therapy up to a quarter of patients are in need of additional immunomodulators (8). Patients who experience rash and pruritus in dermatologic irAEs might benefit from gabapentinoids in addition to the above-mentioned therapies (4). Novel findings in detecting irAEs in a timely manner are targeted toward biomarkers. This is a field of ongoing research, however, circulating blood counts, TSH, T4 and certain genetic alterations associated with irAEs in melanoma patients (SMAD3, CD274, PRDM1 among others) (38) were identified and are a useful tool in diagnostics (6,38).

These two cases report is limited due to the inclusion of only patients with skin cancer receiving PD-1 antibodies. Additionally, we only described cases in which patients received ICI monotherapy, whereas in literature combination therapy of PD-1 and CTLA-4 antibodies distinctly increases the risk of severe irAEs (20). Moreover, apart from melanoma and SCC, other tumor entities are treated with different ICI such as PDL1-inhibitors (atezolizumab or avelumab) or LAG3-inhibitors (relatlimab). Furthermore, a longer follow-up period after the treatment of the described irAEs would be favorable.

Conclusions

Despite the high number of registered fatal events (15), the risk of fatal irAEs for individual patients with advanced cancer remains low and should not discourage the use of highly effective ICI (9). However, in oncological patients with an acute deterioration of their general condition, in addition to a possible tumor progression, an infection or other causes, consideration should always be given to ongoing or recent immunotherapy and potentially associated irAEs. Furthermore, patients benefit from close collaborations between PC teams and primary caregivers in detecting such irAEs (24-26).

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Footnote

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