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Autoimmune Pancerebellitis as an Immune-Related Adverse Event: An Illustrative Case

D. Valančius
I. Zagorskienė
A. Klimašauskienė

Center of Neurology,
Vilnius University

Summary. Immune checkpoint inhibitors have already proved their effectiveness in the treatment of various forms of cancer, and every day their use is becoming more and more prevalent. Unfortunately, every effective treatment has its side effects, and immunotherapy is no exception. In this article, the authors present an illustrative and rare clinical case of a patient who developed autoimmune pancerebellitis during therapy with immune checkpoint inhibitors.

Keywords: immune checkpoint inhibitors, autoimmune encephalitis, autoimmune pancerebellitis.

INTRODUCTION

Immune checkpoint inhibitors are a class of immunotherapy drugs that represent a relatively novel way of approaching cancer therapy. They affect immune system cells, such as T cells, and in doing so, release a natural "brake" on the immune response. This is accomplished by inhibiting specific molecules, called "immune checkpoints", which are expressed on the surface of T cells. An example of this type of immunotherapy drug is pembrolizumab, which inhibits a checkpoint molecule called PD-1, or programmed death-1. Because of that, the otherwise suppressed immune response against cancer is unleashed. This kind of treatment has already been proved effective in several multicenter randomized controlled trials and has been approved for use in various types of cancer [1, 2]. Unfortunately, such striking results are accompanied by relatively common and potentially life-threatening complications called immune-related adverse events. One of the most dangerous are central nervous system (CNS) complications as they are associated with a high death rate: encephalitis 6.3–19%, meningitis 7.4–8.3%. Fortunately, CNS complications are relatively rare, occurring in only 0.46% of all patients treated with immune checkpoint inhibitors [3, 4]. Because of the rareness and clinical heterogeneity of these complications, we wanted to present a case of pembrolizumab-associated immune-related pancerebellitis.

CASE REPORT

A 72-year-old Caucasian man in December 2019 noticed a new skin lesion 5 centimetres in diameter on the posterior of his left calf. This skin abnormality started to bleed spontaneously or with minimal trauma and rapidly increased in size. The following February, the lesion was surgically removed, however, the tissue sample was not sent for histological evaluation. In April 2020, the patient was referred to the surgeon again, but this time due to an insidiously growing lesion in the groin area. Ultrasonography of the lesion area revealed lymphadenopathy with cystic inclusions, suspicious for malignancy, so the patient was referred to a hematologist. Only a few routine blood tests were performed, none of them showed any abnormalities. Although the lesion grew ominously, the punch biopsy was done only 5 months later, in July. The diagnostic delay was mainly due to the extreme healthcare system conditions in Lithuania during the COVID-19 pandemic. Histological results confirmed melanoma and its metastasis in the left groin tissue. In addition, positron emission tomography/computer tomography (PET/CT) revealed the

Address:
Domantas Valančius
Clinic of Neurology and Neurosurgery, Vilnius University
Santariškių St. 2, LT-08410 Vilnius, Lithuania
E-mail: domantas.valancius@mf.vu.lt

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spread of melanoma in the calf surgical scar tissue and lymphadenopathy in the groin and pelvis. Systemic conservative therapy was the only treatment choice as no surgical strategy could ensure complete tumor removal. No mutations suitable for targeted cancer therapy were identified, so immunotherapy using immune checkpoint inhibitors was the best option. Finally, on 4 August 2020, the patient received the first dose of pembrolizumab (200 mg intravenously). The second and third doses were given every three weeks. Meanwhile, the treatment seemed to be effective, the lymph nodes regressed, the number of small subcutaneous metastases was noticeably less.

On September 23, just one week after the third dose of pembrolizumab, the patient was admitted to Vilnius University Hospital Santaros Klinikos due to subacute progressive coordination impairment. Some subtle coordination difficulties were already presented three weeks ago, but they worsened in the last days before hospitalization. When the patient arrived at the emergency room, he was unable to walk independently and complained of constant diplopia. The patient's vital signs were stable and physical examination, except for the skin lesions mentioned, was unremarkable. He was alert, attentive and oriented. Further thorough neurological examination revealed left-beating horizontal nystagmus on left gaze, left hemiataxia and right leg ataxia consisting of left-sided dysmetria, intention tremor on finger-to-nose, finger-to-finger, heel-to-shin tests in the affected limbs, and prominent gait ataxia. This incoordination remained with eyes either open or closed. When standing and trying to walk, the patient displayed a wide-based ataxic stance and gait. The strength in all the limbs was intact, as was the sense of position and vibration, touch, temperature, and pain sensations. No obvious asymmetry in deep tendon reflexes was observed and no pyramidal tract lesion signs were elicited. Urgent brain CT did not show any acute pathological findings. The patient was hospitalized to the neurological ward for further evaluation and treatment.

In the following few days after admission, the patient was quickly getting worse: his speech became scanning and slurred, ataxia progressed further – he was unable to stand even when leaning on nearby objects, horizontal nystagmus was now present in all directions of gaze, the patient complained of severe diplopia, nausea, and dizziness. The patient underwent an extensive workup for his signs and symptoms. No epileptiform activity was recorded by electroencephalography. Brain MRI with contrast did not show any abnormalities: metastases, signs of encephalitis, and other structural changes were excluded. A lumbar puncture and cerebrospinal fluid (CSF) analysis were performed. CSF glucose concentration was normal (3.28 mmol/L), protein concentration was elevated (0.883 g/L), and microscopy revealed mononuclear pleocytosis consisting predominantly of macrophages and plasma cells (21 WBC/ l). To rule out an infectious cause of encephalitis, molecular analysis of cytomegalovirus and Epstein-Barr virus was performed, which was negative. We also analyzed the serum for antineuronal antibodies, but no antibodies (which we could have performed in our laboratory) were detected.

The extensive workup did not yield any significant findings, and based on this, in combination with the patient's treatment with pembrolizumab and knowledge of similar clinical presentations in the literature, the patient was diagnosed with an immune-related autoimmune pancerebellitis – an immune-related adverse event (irAE) [5]. The main differential diagnosis in our case was autoimmune pancerebellitis of a different origin, most likely a paraneoplastic syndrome. In either case, large dose corticosteroid therapy was indicated, so the patient was started on 1 g pulse of methylprednisolone for 5 days followed by oral therapy. Three days after the start of corticosteroid therapy, the patient's symptoms subsided slightly: the scanning speech became more understandable, diplopia was less noticeable, the patient could perform coordination maneuvers with more precision, and was also able to stand on his feet leaning on surrounding objects.

Considering there was only a marginal effect of steroid therapy, the patient was transferred to the oncology-chemotherapy ward for a plasma exchange course (plasmapheresis). Subsequently, 6 plasma exchanges were performed in addition to continued oral steroid therapy. After plasma exchanges, the patient was transferred to an inpatient rehabilitation ward since most of the symptoms did not resolve and only marginally improved. Nevertheless, the symptoms that persisted contributed to significant overall disability. After six weeks of active rehabilitation, there was considerable amelioration of symptoms, but complete regression of the disease was not achieved. The patient's balance, coordination of movement, and articulation improved substantially, the patient was able to sit or stand with minimal help, and could independently walk about 50 meters using an upright walker. Oral steroid therapy was continued during active rehabilitation period. When the patient was finally discharged from the hospital, the dose of methylprednisolone was 62 mg per day. The further treatment plan was to slowly reduce steroid dose to 20 mg per day, bearing in mind that the dose should be increased if symptoms worsen again.

DISCUSSION

In this case, after all the workup was done, the main differential diagnoses were a paraneoplastic autoimmune encephalitis (pancerebellitis) and an immune-related adverse event – pancerebellitis as a complication of treatment with pembrolizumab, an immune checkpoint inhibitor. Immune-related encephalitis is an exceedingly rare complication of immunotherapy, with only about 60 cases described in the literature. This patient is demographically similar to the population previously reported in that he is a male (58.3% were male) and of similar age as the median age reported in clinical cases (60 years). Hypothetically, if in this case paraneoplastic antibodies in our patient's serum were

positive, that would not have clinched the diagnosis of paraneoplastic syndrome, since 35% of cases of immune-related encephalitis had one or more paraneoplastic antibodies present in the serum or CSF [6]. In any case, the treatment is the same – immunosuppression with high dose steroid therapy. The response to steroid treatment differs, though, it is considerably worse in paraneoplastic syndromes, and in these cases, therapies directed against the cancer cells themselves are more effective [7]. On the contrary, in most of the reported cases of immune-related encephalitis (71.3%), the response to treatment was dramatic and resulted in either complete resolution or significant improvement of symptoms like in the case presented here [8]. According to the guidelines, most patients were treated with steroid therapy, but supplemental immunosuppression options differed. Some patients were treated with intravenous immunoglobulin, a few with plasma exchange, some with rituximab or other immunosuppressive drugs like azathioprine [6]. In our case, we chose the most easily available treatment in our institution – plasma exchange. Strict guidelines for the treatment of CNS irAE do not exist, as there is not enough evidence, although ESMO has presented some recommendations in various situations. They are based mainly on the treatment of autoimmune encephalitis in the general population [9]. However, some evidence already shows that at least in some conditions, such as immune-related Guillain-Barre syndrome, the optimal treatment strategy for irAE may differ from the corresponding disorders in the general population [10, 11]. Because immune-related encephalitis is considered a life-threatening complication of immune checkpoint inhibitor therapy, treatment has been withheld indefinitely. Even if immunotherapy seemed to be effective, it is not renewed for fear of recurrence of symptoms of immune-related encephalitis. Only one case has been reported in which the authors attempted to administer immune checkpoint inhibitors after such an event. Unfortunately, this attempt was unsuccessful, the patient's symptoms flared up again. In general, there is much unknown about the treatment and phenomenology of immune-related adverse events, and immune-related encephalitis in particular. More quality data is needed to improve our knowledge of how to avoid such dangerous complications and provide adequate treatment and care for these patients when they do occur.

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D. Valančius, I. Zagorskienė, A. Klimašauskienė

AUTOIMUNINIS PANCEREBELITAS KAIP SU IMUNOTERAPIJA SUSIJĘS NEPAGEIDAUJAMAS ĮVYKIS: KLINIKINIO ATVEJO APRAŠYMAS

Santrauka

Imuninės sistemos „kontrolės punktų" inhibitoriai įrodė savo veiksmingumą ir sukėlė proveržį įvairių vėžio formų gydyme ir, tikėtina, bus taikomi vis dažniau ir dažniau. Visgi kiekvienas efektyvus gydymas turi šalutinių reiškinių ar komplikacijų, ir imunoterapija nėra išimtis. Šiame straipsnyje autoriai pateikia iliustruojantį ir retą klinikinį atvejį, kai pacientui gydymo imuninės sistemos „kontrolės punktų" inhibitoriais metu išsivystė autoimuninis pancerebelitas.

Raktažodžiai: imuninės sistemos „kontrolės punktų" inhibitoriai, autoimuninis encefalitas, autoimuninis pancerebelitas.

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