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Severe complications of nivolumab monotherapy in an adolescent with malignant melanoma

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Abstract

This study presents a case of a 17-year-old female patient who had previously undergone surgical resection of melanoma in the right periscapular area. She was administered adjuvant treatment with the PD-1 inhibitor nivolumab as monotherapy. The mechanism of action of this drug is based on increased stimulation of the immune system. The patient developed a series of complications including capillary leak syndrome and hypothyroidism after the fifth cycle of therapy, as a result of dysregulation of immunity. Nivolumab treatment had to be discontinued and glucocorticosteroids were administered as a salvage therapy. After several months, two relapses developed in the subcutaneous tissue – first in the left and then in the right iliac region, confirmed as distant metastases of malignant melanoma, treated with resections of the lesions and intensity-modulated radiation therapy. Follow-up imaging studies and clinical examinations showed no metastases or pathologically enlarged lymph nodes.

Key words: *melanoma, hypothyroidism, nivolumab, capillary leak syndrome.*

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Introduction

Malignant melanoma is considered to be one of the most aggressive skin cancers and its incidence is increasing, particularly amongst Caucasians [1-3]. Despite significant development of immunotherapy and targeted therapy in the treatment of skin melanomas, possible side effects of therapy remain a constant challenge for physicians. The results of published clinical trials show an improvement in survival rate in cases where PD-1 (programmed death-1) immune checkpoint inhibitors, such as nivolumab, were administered after surgical resection [4]. Therapy with this drug is associated with increased stimulation of the immune system, which is manifested in a large percentage of patients with fatigue, diarrhea, rash or itching of the skin [5, 6]. In order to treat these side effects, immunomodulatory therapy, predominantly with glucocorticoids, is used [6]. There is a hypothesis that the use of immunomodulatory therapy to treat toxicity has no effect on the response to anticancer treatment [7].

We present a case of a 17-year-old female patient with malignant melanoma who developed capillary leak syndrome (CLS) and hypothyroidism as a complication of adjuvant treatment with nivolumab.

Previous diagnostics

A 17-year-old female patient was found to have a suspicious pigmented nevus located in the right periscapular area. The lesion was resected under local anesthesia in January 2020. In the histopathological examination of the specimen, a malignant melanoma of the nodular type with a 5 mm infiltration according to Breslow with ulceration was diagnosed. In the pTNM classification the tumor was assessed as T4bN2M0 stage, i.e. stage IIIc, Clark's grade IV. Mitotic activity was determined by Ki67, which was found in 40% of cell nuclei. Immunophenotyping was performed and the markers S100+, Melan A+, HMB45+, and Vim+ were found. CK proved to be negative. The molecular assay revealed the presence of mutations in codon V600 of the BRAF gene in the available histopathological material.

After the resection, the patient was hospitalized twice at the Department of Pediatric Surgery, at the beginning

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and at the end of April 2020, respectively. During the first hospitalization, lymphoscintigraphy was performed, followed by the procedure of widening the scar excision margin and excision of the sentinel node located near the right armpit, the pathological results of which were negative. Bone scintigraphy showed an increase in uptake in the shaft of the left femur, so the diagnostics was extended to X-ray of the femur, in which no lesions were visible. Chest computed tomography (CT) showed a 4 mm subpleural nodule in the 5L segment and small fibrous lesions at the base in the 10L segment. During the second hospitalization, brain magnetic resonance imaging (MRI) was performed, which was normal.

Treatment with nivolumab

In May 2020, the patient was referred to the Department of Pediatric Oncology for further diagnosis and possible treatment. On admission, the patient was in good general condition, with no signs of infection. Laboratory tests were performed, which showed only a decrease in vitamin D3 concentration and the lactate dehydrogenase (LDH) activity was normal. The positron emission tomography-computed tomography (PET-CT) scan showed however increased metabolism of 18-FDG in the lymph node of the right armpit. For this reason, the patient underwent right axillary lymphadenectomy. The histopathological examination confirmed the presence of neoplastic metastases in 2 out of 11 examined nodes.

The patient was referred for adjuvant treatment with anti-PD-1 monoclonal antibody for a period of 12 months and at the beginning of July 2020 received the first infusion of nivolumab at a dose of 6 mg/kg body weight (1 infusion every 4 weeks). LDH levels were above the upper limit of normal on the day of the first dose.

Response to treatment and side effects

The patient experienced moderate diarrhea during treatment classified as level I/II in Common Terminology Criteria for Adverse Events (CTCAE). Microbiological tests revealed the presence of *Clostridium difficile* toxin in the stool, so metronidazole therapy was initiated. In the absence of improvement, short-term steroid therapy was used, which brought a satisfactory effect.

After the third dose of nivolumab, a follow-up PET-CT scan was performed, which showed a complete metabolic response to the treatment (the study was compared to the one performed previously in May 2020).

In November 2020, slowly progressive peripheral edema and ascites appeared after the 5th cycle of therapy. Laboratory tests showed a slightly increased activity of LDH, indicators of the state inflammation (CRP), and elevated creatinine levels (1.4 mg/dl) (Table 1). The patient reported a feeling of breathlessness which increased in the supine position (she reported that she had been sleeping in a sitting position for several days). During hospitalization, scanty diuresis and an increase in edema (peripheral as well as in body cavities) were observed. Due to the patient's condition, diuresis was initially forced with infusions of furosemide, and then 20% of albumin, theophylline plus furosemide plus mannitol mixture and spironolactone. The diagnosis was CTCAE III CLS. Methylprednisolone therapy (2 mg/kg/d i.v.) was initiated, resulting in a gradual improvement in the patient's condition and normalization of laboratory tests. Due to significant toxicity and remission of the underlying disease, it was decided to discontinue nivolumab treatment (Table 2).

During the follow-up visit in the course of the dosage reduction of methylprednisolone (December 2020), the patient had persistent eyelid edema, despite the reduction in body weight (almost complete disappearance of peripheral edema and fluid in the body cavities). In the laboratory tests performed at that time, attention was drawn to the significantly increased TSH concentration (100 μIU/ml), with very reduced fT4 < 0.42 ng/dl and fT3 < 0.95 pg/ml, high anti-thyroglobulin levels of 130 IU/ml and absent anti-thyroid-peroxidase antibodies. Ultrasonography (USG) examination of the thyroid gland revealed a small, echogenically heterogeneous thyroid, without focal changes, and with increased vascular flow. Hypothyroidism was diagnosed and treatment with L-thyroxine was started in increasing doses.

In the PET-CT study as of December 23, 2020, the appearance of moderately active upper bilateral and lower left cervical lymph nodes, as well as ambiguous left pre-vascular and axillary lymph nodes, was described. Moreover, the examination showed the presence of fluid in the body cavities and diffuse, moderately increased FDG metabolism in the spleen, which were found to be a result of treatment. In other parts of the body there were no foci of increased FDG metabolism. Parallel ultrasound revealed the reactive nature of the described lymph nodes.

By February 2021, a total of two CLS relapses were observed, each CTCAE grade III. During episodes II and III, the girl was initially treated with pulses of methylprednisolone (20 mg/kg in total), and then in gradually reduced doses. Unfortunately, after episodes I and II, after discontinuation of glucocorticosteroids, a rapid increase in the patient's body weight was observed after about a week (about 3-4 kg in 1-2 days). It was decided to extend the oral administration of methylprednisolone at the target dose (lowest effective) of 4 mg every other day (the patient weighs about 55 kg).

In September 2021 PET-CT examination showed an isolated change in the subcutaneous tissue in the left iliac region, 3 cm from the iliac crest, measuring about 3 cm. No features of metastasis were found in the performed examination.

The histopathological examination of the lesion resected at the beginning of October confirmed distant metasta-

Table 1. Laboratory results observed during treatment

Date	TSH [μIU/ml] norm: 0.58-3.59	fT3 [pg/ml] norm: 2.31-3.71	fT4 [ng/dl] norm: 0.89-1.37	LDH [U/l] norm: 0-248	Hematocrit [%] norm: 37-47	Leukocytes [10^3/μl] norm: 4-10	Platelets [10^3/μl] norm: 140-440	Creatinine [mg/dl] norm: 0.3-1	Total protein [g/dl] norm: 5.7-8	CRP [mg/l] norm: 0-5
13.05.2020	n/d	n/d	n/d	178	44.2	5.65	238	0.88	7.8	0.41
31.07.2020	n/d	n/d	n/d	**344**	40.4	4.72	213	0.71	7.2	1.72
31.08.2020	n/d	n/d	n/d	**303**	42.6	9.65	319	**1.07**	7.5	0.41
28.09.2020	n/d	n/d	n/d	**335**	43.9	6.18	288	**1.09**	n/d	1.11
26.10.2020	n/d	n/d	n/d	**323**	38	8.65	198	0.99	n/d	**16.78**
07.11.2020	n/d	n/d	n/d	**564**	**48.3**	8.96	224	**1.41**	6.9	**10.69**
20.11.2020	n/d	n/d	n/d	200	**36.4**	8.37	229	0.74	7.1	0.4
08.12.2020	**94.22**	**0.95**	**0.42**	**278**	38.5	**3.6**	162	**1.11**	6.9	0.65
15.12.2020	**99.006**	**1.04**	**0.42**	**267**	37.8	**3.76**	231	0.97	6.7	0.56
23.12.2020	**95.387**	**1.12**	**0.56**	**273**	40.4	5.08	198	0.97	6.6	1.1
29.12.2020	n/d	n/d	n/d	**271**	40.1	**10.57**	273	0.86	7.6	0.24
05.01.2021	**45.672**	n/d	1.05	**263**	43.1	**13.36**	286	0.89	7.4	0.28
12.01.2021	**25.767**	n/d	1.22	239	43.3	9.44	252	0.84	7.2	n/d
22.01.2021	**23.35**	n/d	1.31	208	43.3	6.95	266	0.85	7.3	0.4
02.02.2021	n/d	n/d	n/d	n/d	39.9	6.32	309	0.8	6.6	0.48
12.02.2021	**10.065**	3.09	1.13	189	41.2	6.38	358	0.76	6.5	0.33
13.02.2021	n/d	n/d	n/d	n/d	**36.4**	**13.6**	365	n/d	6.1	n/d
14.02.2021	n/d	n/d	n/d	n/d	**34.5**	**21.05**	370	n/d	6.2	n/d
15.02.2021	0.78	**1.9**	1.08	210	**34.4**	**19.32**	357	0.72	5.9	0.2
16.02.2021	n/d	n/d	n/d	n/d	37.8	**10.39**	327	n/d	n/d	0.17
19.02.2021	n/d	n/d	n/d	211	41.3	**15.04**	419	0.67	n/d	<0.4
04.03.2021	n/d	n/d	n/d	208	40.7	**12.24**	344	0.69	7.1	0.2
18.03.2021	n/d	n/d	n/d	n/d	42.6	**10.49**	358	0.82	n/d	0.26
15.04.2021	n/d	2.67	1.22	n/d	40.4	**13.1**	379	n/d	n/d	n/d
28.04.2021	n/d	n/d	n/d	241	40	**13.05**	427	0.82	7.1	0.88
27.05.2021	n/d	n/d	n/d	195	**26.7**	**15.52**	**674**	0.85	6.9	0.27
01.06.2021	n/d	n/d	n/d	184	**24.9**	9.86	**608**	0.83	n/d	n/d
09.06.2021	n/d	n/d	n/d	230	**29.9**	**11.15**	**793**	0.77	6.7	0.3
24.06.2021	1.501	2.82	1.16	173	39.3	**14.54**	**530**	0.79	7.8	n/d
15.07.2021	n/d	n/d	n/d	n/d	40.6	**15.41**	421	n/d	n/d	n/d
26.08.2021	1.038	n/d	n/d	185	39.3	**10.37**	342	0.71	n/d	0.57
05.10.2021	n/d	n/d	n/d	231	41	8.46	398	0.73	n/d	0.74

Table 2. Side effects of nivolumab

Nivolumab immune-related adverse effects (irAEs)		
Common side effect ≥ 1/10	**Likely side effect ≥ 1/100**	**Possible side effect ≥ 1/1000**
– lymphocytopenia, anemia, leukopenia, neutropenia, thrombocytopenia – upper respiratory tract infection – decreased appetite, hyperglycemia, hypoglycemia – headaches – shortness of breath, cough – diarrhea, vomiting, nausea, abdominal pain, constipation – rash, itching – musculoskeletal pain, arthralgia – tiredness, fever, swelling	– eosinophilia – pneumonia, bronchitis – infusion related reaction, hypersensitivity (including anaphylactic reaction) – hypothyroidism, hyperthyroidism, thyroiditis – dehydration, weight loss – peripheral neuropathy, dizziness – blurred vision, dry eye syndrome – tachycardia, atrial fibrillation – hypertension – pleural effusion – colitis, stomatitis, dry mouth – vitiligo, dry skin, erythema, alopecia, urticaria – arthritis – kidney failure – chest pain	– hemophagocytic lymphohistiocytosis – sarcoidosis – adrenal insufficiency, hypopituitarism, hypophysitis, diabetes – metabolic acidosis – polyneuropathy, neuropathy of autoimmune origin – uveitis – myocarditis, pericardial disorders, arrhythmia – infiltrates in the lungs – pancreatitis, gastritis – psoriasis, rosacea, erythema multiforme – rheumatic polymyalgia
Other irAEs (fewer than 1/1000):		
aseptic meningitis, histiocytic necrotizing lymphadenitis, hemophagocytic lymphohistiocytosis, rejection of a transplanted solid organ, ketoacidosis, hypoparathyroidism, tumor lysis syndrome, Guillain-Barré syndrome, demyelination, muscular weakness syndrome, encephalitis, Vogt-Koyanagi-Harada syndrome, vasculitis, duodenal ulcer, toxic epidermal necrolysis, Stevens-Johnson syndrome, lichen sclerosus, other lichen-like disorders, Sjogren's syndrome, myopathy, myositis, rhabdomyolysis, tubulointerstitial nephritis, non-infectious cystitis		

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sis of malignant melanoma to the soft tissues of the left hip resected in the healthy tissue margin R1. CT examination of the head, thorax, abdominal cavity and pelvis did not reveal any metastatic changes. The staging was changed to T4bN2bM1a s.c. IV, BRAF+.

By the decision of the council doctors on November 2021, the patient was qualified for radiotherapy treatment of the area after the lesion with the intensity-modulated radiation therapy (IMRT) technique every 2 days for 10 days with a dose from D.f. = 6 Gy to D.c. = 30 Gy/5 fr. She was excluded from immunotherapy treatment due to the previous toxicity of nivolumab. The patient underwent scheduled radiotherapy, the only complication of which was the appearance of radiation erythema.

At the clinical follow-up visit in March 2022, a subcutaneous lesion about 8 mm in diameter was detected in the area of the right superior iliac spine, with no changes in the lymph nodes. A week later, R0 resections of the lesion were performed and histopathological examination confirmed another metastasis of malignant melanoma to the subcutaneous fat, which was removed with a margin of healthy tissues. Imaging studies showed no metastasis or pathologically enlarged lymph nodes.

As part of the post-treatment follow-up, it was decided to perform PET-CT and USG checks every 3 months. In the event of recurrence due to the presence of BRAF mutations, administration of BRAF and MEK inhibitors may be considered.

Discussion

For many years, the gold standard of malignant melanoma treatment has been surgery [8, 9]. However, it is not sufficient in patients in advanced stages of the disease, especially in those with lymph node metastases or distant metastases [10]. For this reason, in recent decades, there has been an intense search for alternative chemotherapy regimens with the lowest possible toxicity.

A recently used method of treatment that raises high hopes in the treatment of malignant neoplasms is the blockade of the immune checkpoint PD-1 and its PD-L1 ligand, which leads to regression and stabilization of the disease [11, 12]. In the chemotherapy of malignant neoplasms, a widely used drug is nivolumab, a monoclonal antibody to PD-1.

Looking at the efficacy and safety profile, one can find a randomized study based on patients with untreated melanoma comparing the use of nivolumab with ipilimumab both in monotherapy and in combination. The analysis of the results showed that the use of nivolumab alone or a combination of the two drugs is more effective than the use of ipilimumab alone, which leads to longer progression-free survival (PFS). Combining these two drugs proved beneficial, especially for people with PD-1 negative tumors. The obtained benefit in the case of nivolumab monotherapy is a much smaller percentage of patients who developed 3 and 4 grade symptoms of treatment tox-

icity (16.3%) compared to ipilimumab alone (27.3%) or the combination of nivolumab plus ipilimumab (55%). Only in 7.7% of patients treated with nivolumab was it necessary to discontinue the treatment due to adverse events [5].

Nivolumab is a well-tolerated drug in most patients with effective antitumor activity [12]. The most common side effects are fatigue, diarrhea, pruritus, nausea, and decreased appetite [5, 6]. The toxicity of nivolumab occurs in a small percentage of patients and appears almost exclusively within the first 6 months of treatment [13, 14].

In the present case, the use of nivolumab treatment in monotherapy resulted in severe toxicity in the form of CLS, characterized by leakage of plasma through capillaries into tissues, organs or body cavities. T cell infiltration in organs and increased cytokine concentration, which translates into impaired functioning of normal cells, are caused by impaired function of the immune system while using PD-1 inhibitors [15]. In cases of drug-induced CLS immediate therapy with corticosteroids is vital [16-18]. Diuretics should also be administered in order to reduce swelling [16]. The administration of methylprednisolone to our patient resulted in regression of side effects of the therapy, but it was decided to discontinue the nivolumab therapy.

Thyroid dysfunction is an endocrinopathy observed during nivolumab treatment [19-21]. Studies show that this adverse event can be predicted before PD-1 inhibitor therapy with FDG-PET [22]. It has been reported that thyroid dysfunction was not the cause of discontinuation of treatment and it develops in about 22.5% of patients [23, 24]. Hypothyroidism is about three times more common than hyperthyroidism and the etiology of autoimmune processes in the thyroid gland induced with anti-PD-1 antibodies is not yet well understood [25]. The relationship between the occurrence of this disorder and gender and age of patients has not been described so far. It is believed that the development of thyroid dysfunction may be affected by the number of nivolumab doses administered [21].

In cases of hyperthyroidism, glucocorticoid therapy is used (for example prednisone 1 mg/kg), and in the case of hypothyroidism, L-thyroxine is administered (starting with a dose of 25-50 μg) [25]. Routine monitoring of thyroid parameters is recommended prior to the initiation of nivolumab therapy and after each subsequent dose in order to quickly detect abnormalities and initiate adequate treatment [21, 26]. In addition, it is worth checking patients for the development of type 1 diabetes, pituitary function or hypogonadism [20].

Studies show that melanoma patients are more prone to develop secondary melanoma or other skin tumors, which occur in about eight percent within two years from the initial diagnosis [27]. Therefore, in the present case it is necessary to regularly evaluate the disease status, because the patient could not continue the anticancer treatment with nivolumab. If recurrence of the disease is detected once again, the patient still has a chance to be treated with BRAF and MEK inhibitors, but the toxicity that will result from this therapy is unpredictable.

The progress of new technologies allows the development of new drugs with a better profile of action and safety. The purpose of publishing this clinical case is to draw clinicians' attention to the side effects of drugs that modulate the immune system response. Immunotherapy progresses over time and dealing with its possible side effects can be a concern not only for oncologists, but also for general practitioners and other clinicians. Together, we strive to expand knowledge about oncological treatment of both pediatric and adult patients in order to optimize treatment and make it as comfortable as possible.

Due to the fact that oncological diseases are much more common in adults than in children [28], a much larger body of data is available in the literature regarding therapeutic options and how to effectively manage side effects in adult patients. The present case shows what to pay special attention to when treating pediatric patients with immunotherapy and how to deal with its side effects.

The authors declare no conflict of interest.

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