Sneaky side effects and ineffectiveness of an immunotherapy with ipilimumab in a case of metastatic melanoma

Nathalie Kreck, Anna Zimmer, Bettina Friesenhahn-Ochs, Cornelia S. L. Müller, Thomas Vogt, and Claudia Pföhler

Department of Dermatology, Saarland University Medical School, Homburg/Saar, Germany; Department for Diagnostic and Interventional Neuroradiology, Saarland University Medical School, Homburg/Saar, Germany; Department of Internal Medicine II, Saarland University Medical School, Homburg/Saar, Germany

ABSTRACT
Ipilimumab is an anti-CTLA-4 antibody that is approved for the treatment of metastatic malignant melanoma. Side-effects are mostly immune-mediated and in many cases the lack of specific symptoms leads to delayed diagnosis and treatment of adverse events. We present the case of a female patient who experienced an uncommon combination of adverse reactions while undergoing therapy with ipilimumab and where the absence of specificity of the symptoms led to late diagnosis and treatment of side effects. Autoimmune disease was neither associated with tumor response nor with prolonged survival.

KEYWORDS
autoimmunity; ipilimumab; immunology; melanoma; orbital myositis; side effects; vitiligo

Introduction
Immune checkpoint inhibition with the anti-CTLA-4 antibody ipilimumab or the PD-1 antibodies pembrolizumab and nivolumab has become a valuable and effective treatment in metastatic melanoma. All substances have demonstrated significant and durable tumor responses with significant prolonged progression-free and overall survival. Side effects of a therapy with ipilimumab are mainly related to the mode of action of the drug resulting in activation of the immune system against autoantigens. Immune-mediated adverse events have been reported in 10-15% of the patients and primarily manifest as skin rash, diarrhea and colitis, hepatitis and endocrinopathies. However, side effects, particularly endocrinopathies are often difficult to diagnose in early stages because of their lack of specific symptoms.

Case report
We present the case of a 34-year old female patient with metastatic malignant melanoma undergoing treatment with the anti-CTLA-4 antibody ipilimumab. The clinical course of disease is shown in Table 1. Six days after the third infusion, the patient reported a persistent headache since 2 d. She interpreted this symptom as a symptom of premenstrual syndrome as she was waiting for her menstrual period and had already experienced similar headaches. There were no other symptoms such as nausea, impaired eyesight or fever. Laboratory testing was inconspicuous and showed normal values for routine parameters and for thyroid-stimulating hormone (TSH). Hyponatriemia as sign of cortisol deficiency was not present. A prescription for ibuprofen (administered 2 times daily in a dosage of 400 mg) was given which helped to manage the pain at first. Two days later, as the headache did not subside, the patient was examined again. She then presented a light periorbital swelling and was examined from a neurologist and an ophthalmologist who both could not find any cause for the symptoms. A CT scan of the head and brain, a cerebrospinal fluid puncture and a measurement of the intraocular pressure were performed and did not show any abnormalities. Again, laboratory testing was normal. Pain medication was adapted and the patient left with the requirement to contact us if the headache would get worse. Almost a week later, the patient was emergently seen. She was experiencing an excruciating headache with nausea and had been...
vomiting. Periorbital swelling had increased. Laboratory results showed thyroid malfunction and a MRI scan of the brain confirmed the diagnosis of hypophysitis (Fig. 1). In addition, a cellulitis of the periorbital subcutaneous fat tissue was observed (Fig. 1). The patient was treated with dexamethasone in a dosage of 4 mg every 6 hours. After the first dose, she already experienced a relief of her symptoms. One day later, the symptoms and swelling declined almost completely, but vitiligo began to develop on the face of the patient. A hormone substitution with hydrocortisone and levothyroxine was begun. The vitiligo continued to spread over the next weeks and finally involved more than half of the body surface area. A tumor staging showed progressive disease and treatment with the anti-PD1 antibody nivolumab was initiated. However, metastases grew rapidly and the patient developed multiple brain metastases. She died 12 months after detection of first distant metastases.

**Discussion**

Ipilimumab is an anti-CTLA4 antibody approved for the treatment of metastatic melanoma. The most common side-effects include auto-immune mediated colitis and hypophysitis. The onset of these side-effects is often difficult to recognize because of the lack of specific symptoms. In the case presented here, the diagnosis of headache as a sign of hypophysitis was blurred because the patient was waiting for her menstrual period and had already experienced similar headaches as signs of a premenstrual syndrome. Other symptoms suspicious for hypophysitis such as nausea or fever were not present at first. Furthermore, laboratory testing initially did not show any abnormalities such as disbalanced thyroid

| Year | Event | Details |
|------|-------|---------|
| 08/2006 | Excision of primary melanoma (amelanotic, tumor thickness > 1.7 mm, Clark level IV) right thigh |
| 09/2006 | Sentinel lymph node biopsy and lymph node dissection right groin (2/8 nodes positive) |
| 10/2006-08/2007 | Adjuvant therapy with interferon-α (high-dose) |
| 2008 | First pregnancy |
| 03/2009 | Birth of a healthy baby girl |
| 02/2015 | Second pregnancy, detection of intraabdominal lymph node metastases during ultrasound examination at 19th week of gestation |
| 03/2015 | Surgical resection of lymph node metastases (R2) |
| 04/2015 | Termination of pregnancy |
| 04/2015-06/2015 | Therapy with ipilimumab (3 cycles), termination due to side effects |
| 07/2015-09/2015 | Therapy with nivolumab (3 cycles), termination due to progression of disease |
| 10/2015 | Tumor debulking of abdominal metastases |
| 12/2015 | Progressive disease with development of multiple brain metastases and pulmonary metastases |
| 12/2015 | Whole brain radiation (36 Gy) |
| 02/2016 | Death of the patient due to further tumor progression |

Figure 1. Gadolinium-enhanced T1-weighted MR images of the brain show increased contrast uptake (red arrows) and enlargement of the right lateral orbital region and pituitary gland on the day of diagnosis (A) and 2 d after the beginning of high dose steroid therapy (B).
hormones. As the periorbital swelling occurred, the clinical presentation mimed a slight case of angioedema. It must remain unclear if the swelling should be interpreted as an independent event of immune-mediated infiltration and inflammation or if it represents a *per continuatatem* effect due to the inflammation of the pituitary gland. The former scenario seems to be more likely as there are more than 10 similar cases published in the literature so far reporting that ipilimumab therapy may induce orbital myositis and orbital inflammation.  

In our patient, application of corticosteroids was performed delayed, because brain MRI scans had been inconspicuous first. We therefore recommend that every patient should be sensitized to report any symptoms that develop during or after treatment with immunostimulating drugs and that MRI of the head and brain should be performed immediately in every patient who presents with an unusual headache.

To our knowledge this is the first case in which this combination of common and uncommon immune-mediated adverse reactions occurred in the same patient.

Whether autoimmune in patients with melanoma undergoing immunotherapies with i.e. interferon-α, interleukin-2, ipilimumab, nivolumab or pembrolizumab is associated with increased response rates and prolonged survival is still discussed controversially. There are reports that the development of leukoderma or vitiligo was associated with a better prognosis, and that immune-related adverse events such as vitiligo and autoimmune thyroiditis were associated with responses to ipilimumab, at the cost of considerable toxicity. However, there are other studies that report that development of autoimmune diseases whether they were tumor-associated or drug-induced was not associated with a better prognosis. This regrettably applies to our patient who showed no tumor response, neither under ipilimumab nor under nivolumab treatment.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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