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

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**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.

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## 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.[1] All substances have demonstrated significant and durable tumor responses with significant prolonged progress-free and overall survival.[2-4] 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.[5] 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.[3,4] 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

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**Table 1.** Course of disease from diagnosis of the primary tumor in 08/2006 until death of the patient due to metastatic disease.

| | |
|---|---|
| 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-$\alpha$ (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 19$^{th}$ week of gestation |
| 03/2015 | Surgical resection of lymph node metastases (R2)Histological examination of tumor tissue: melanoma metastasis. Mutation analysis of tumor tissue: wildtype for BRAF, NRAS and c-KIT |
| 03/2015 | Termination of pregnancy |
| 04/2015 | Surgical resection of abdominal lymph node metastases (R2) |
| 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 | Tumordebulking 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 |

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 MRI scan of the brain performed 2 d later showed a decrease of inflammation in the periorbital region whereas the signs of hypophysitis had improved only slighly. 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.

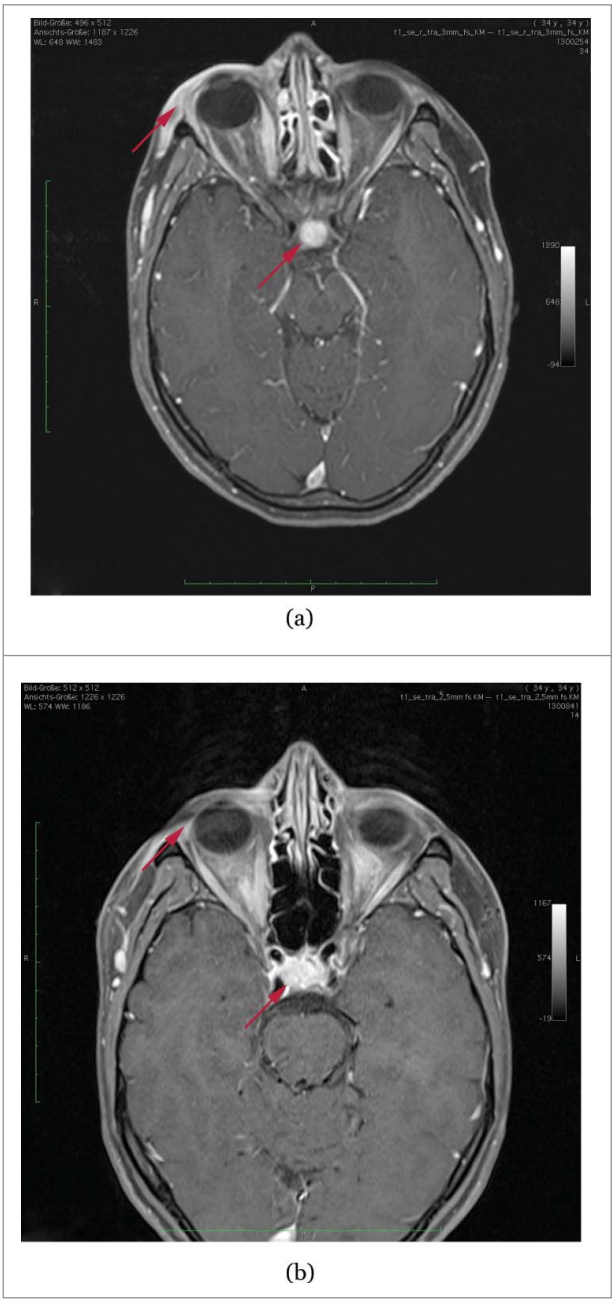

**Figure 1.** Gadolinium-enhanced T1-weighted MR images of the brain show increased contrast uptake (red arrows) and enlargement of the right lateral orbital region and pituitary gland on the day of diagnosis (A) and 2 d after the beginning of high dose steroid therapy (B).

## 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.[3,4] 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

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 continuitatem* 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.[6-16] 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 und uncommon immune-mediated adverse reactions occurred in the same patient.

Whether autoimmunity in patients with melanoma undergoing immunotherapies with i.e. interferon-$\alpha$, 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.[17] and that immune-related adverse events such as vitiligo and autoimmune thyreoiditis were associated with responses to ipilimumab, at the cost of considerable toxicity.[18,19] 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.[20] This regrettably applies to our patient who showed no tumor response, neither under ipiliumab nor under nivolumab treatment.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

## References


[1] Callahan MK, Flaherty CR, Postow MA. Checkpoint blockade for the treatment of advanced melanoma. Cancer Treat Res 2016; 167:231-50; PMID:26601865; http://dx.doi.org/10.1007/978-3-319-22539-5_9

[2] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373:23-34; PMID:26027431; http://dx.doi.org/10.1056/NEJMoa1504030

[3] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363:711-23; PMID:20525992; http://dx.doi.org/10.1056/NEJMoa1003466

[4] Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, Lebbe C, Baurain JF, Testori A, Grob JJ, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364:2517-26; PMID:21639810; http://dx.doi.org/10.1056/NEJMoa1104621

[5] Bowyer S, Prithviraj P, Lorigan P, Larkin J, McArthur G, Atkinson V, Millward M, Khou M, Diem S, Ramanujam S, et al. Efficacy and toxicity of treatment with the anti-CTLA-4 antibody ipilimumab in patients with metastatic melanoma after prior anti-PD-1 therapy. Br J Cancer 2016; 114(10):1084-9; PMID:27124339; http://dx.doi.org/10.1038/bjc.2016.107

[6] Borodic GE, Hinkle D. Ipilimumab-induced orbital inflammation resembling Graves disease with subsequent development of systemic hyperthyroidism from CTLA-4 receptor suppression. Ophthal Plast Reconstr Surg 2014; 30:83; PMID:24398505; http://dx.doi.org/10.1097/IOP.0000000000000033

[7] Bronstein Y, Ng CS, Hwu P, Hwu WJ. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. AJR Am J Roentgenol 2011; 197:W992-W1000; PMID:22109345; http://dx.doi.org/10.2214/AJR.10.6198

[8] Faje AT, Sullivan R, Lawrence D, Tritos NA, Fadden R, Klibanski A, Nachtigall L. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. J Clin Endocrinol Metab 2014; 99:4078-85; PMID:25078147; http://dx.doi.org/10.1210/jc.2014-2306

[9] Henderson AD, Thomas DA. A case report of orbital inflammatory syndrome secondary to ipilimumab. Ophthal Plast Reconstr Surg 2015; 31:e68-70; PMID:24814274; http://dx.doi.org/10.1097/IOP.0000000000000081

[10] Hunter G, Voll C, Robinson CA. Autoimmune inflammatory myopathy after treatment with ipilimumab. Can J Neurol Sci 2009; 36:518-20; PMID:19650371; http://dx.doi.org/10.1017/S0317167100007939

[11] Lecouflet M, Verschoore M, Giard C, Gohier P, Le Corre Y, Milea D, Martin L. Orbital myositis associated with ipilimumab. Ann Dermatol Venereol 2013; 140:448-51; PMID:23773743; http://dx.doi.org/10.1016/j.annder.2013.02.029

[12] McElnea E, Ni Mhealoid A, Moran S, Kelly R, Fulcher T. Thyroid-like ophthalmopathy in a euthyroid patient receiving Ipilimumab. Orbit 2014; 33:424-7; PMID:25207976; http://dx.doi.org/10.3109/01676830.2014.949792

[13] Min L, Vaidya A, Becker C. Thyroid autoimmunity and ophthalmopathy related to melanoma biological therapy. Eur J Endocrinol 2011; 164:303-7; PMID:21088057; http://dx.doi.org/10.1530/EJE-10-0833

[14] Papavasileiou E, Prasad S, Freitag SK, Sobrin L, Lobo AM. Ipilimumab-induced Ocular and Orbital Inflammation-A Case Series and Review of the Literature. Ocul Immunol Inflamm 2016; 24:140-6; PMID:25760920

[15] Sheik Ali S, Goddard AL, Luke JJ, Donahue H, Todd DJ, Werchniak A, Vleugels RA. Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphocyte antigen 4 blockade. JAMA Dermatol 2015; 151:195-9; PMID:25321335; http://dx.doi.org/10.1001/jamadermatol.2014.2233

[16] Sheldon CA, Kharlip J, Tamhankar MA. Inflammatory orbitopathy associated with ipilimumab. Ophthal Plast Reconstr Surg 2015; PMID:26068559; http://dx.doi.org/10.1097/IOP.0000000000000509

[17] Gathings R, Lewallen R, Yosipovitch G. Immunotherapy-induced leukoderma from treatment of melanoma with IL-2: a case report and a review of the literature. Acta Derm Venereol 2015; 95:197-200; PMID:24820241; http://dx.doi.org/10.2340/00015555-1897

[18] Bouwhuis MG, Ten Hagen TL, Eggermont AM. Immunologic functions as prognostic indicators in melanoma. Mol Oncol 2011; 5:183-9; PMID:21367679; http://dx.doi.org/10.1016/j.molonc.2011.01.004

[19] Bouwhuis MG, Ten Hagen TL, Suciu S, Eggermont AM. Auto immunity and treatment outcome in melanoma. Curr Opin Oncol 2011; 23:170-6; PMID:21150603; http://dx.doi.org/10.1097/CCO.0b013e328341edff

[20] Bottoni U, Paolino G, Ambrifi M, Didona D, Albanesi M, Clerico R, Lido P, Brachini A, Corsetti P, Richetta AG, et al. Association between autoimmune disease and cutaneous melanoma with regard to melanoma prognosis. Clin Exp Dermatol 2015; 40:254-9; PMID:25475359; http://dx.doi.org/10.1111/ced.12531