Case Reports in Oncology

Case Rep Oncol 2017;10:1112–1115

DOI: 10.1159/000484553
Published online: December 18, 2017

Case Report

Herpes Encephalitis: A Mortal Complication in a Patient Treated with Immunosuppressive Drugs because of Immune-Related Adverse Events after Ipilimumab Treatment

Lieke van Montfort[a] Caroline M. Loos[b] Monique Anten[b]
Rob L.H. Jansen[a]

[a]Department of Medical Oncology, Maastricht University Medical Center, Maastricht, The Netherlands; [b]Department of Neurology, Maastricht University Medical Centre, University Maastricht, Maastricht, The Netherlands

Keywords
Melanoma · Immunotherapy · Side effects · Neuro-oncology tumor necrosis factor · CTLA-4 antigen · Ipilimumab · Herpes simplex encephalitis

Abstract
Until a few years ago, metastatic melanoma had a poor prognosis with limited treatment options. These therapeutics options and thereby median survival have increased obviously over 5 years with the arrival of immunotherapeutic drugs like ipilimumab, nivolumab, and pembrolizumab. Nowadays, ipilimumab is often used in patients with metastatic melanoma. In this paper, we report a case of a 68-year-old man who developed, and eventually died of, herpes encephalitis after introducing ipilimumab as treatment for metastatic melanoma. To our knowledge, this is the first report in which herpes encephalitis as a complication after ipilimumab and infliximab treatment is described and we would like to make physicians aware of this possible serious neurological complication, especially when a patient has a history of herpes simplex infection.

KARGER

Rob L.H. Jansen, MD, PhD
Division of Medical Oncoloy, Department of Internal Medicine, Grow – School for Oncology and Developmental Biology, Maastricht University Medical Centre
P. Debyelaan 25, NL–6229 HX Maastricht (The Netherlands)
E-Mail rob.jansen@mumc.nl

Introduction

A melanoma is a malignant tumour originating in melanocytes with, until recently, a poor prognosis and limited treatment options in case of metastatic disease as occurs in 11% of the patients. However, therapeutic options have increased obviously over the last years and nowadays, immune-stimulating drugs like cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) receptor inhibitors and programmed cell death protein 1 (PD1) antibodies are the main drugs in the treatment of metastatic melanoma [1].

Ipilimumab, a CTLA4 receptor inhibitor that interferes with the natural immune response of the body towards cancer cells, has become available for the treatment of patients with unresectable stage III or stage IV melanoma since 2011 [1]. As a result of its mechanism of action, ipilimumab can cause some serious immune-related adverse events (irAEs) [2, 3]. IrAEs are estimated to occur in 64% of the patients; however, the majority of this irAEs can be graded by using the common toxicity criteria as grade 1 or 2 adverse events. Grade 3 or 4 adverse events occur in 17.8% of the patients. The skin and gastrointestinal tract are most commonly affected. Endocrine, hepatic, and neurologic events are less common [4].

Here we present a patient who developed herpes encephalitis after he was treated with immunosuppressive drugs because of irAEs caused by ipilimumab treatment.

Case Presentation

A left-handed 68-year-old Caucasian man was previously known with atrial fibrillation, herpes encephalitis (1990), and primary melanoma stage I in 2001. In 2014, metastatic disease was demonstrated and ipilimumab treatment (3 mg/kg) was initiated. Two months later he developed hypophysitis grade II and colitis grade III, treated with high doses of corticosteroids (up to 2 mg/kg). As the colitis was refractory on December 3, treatment with a TNF-alpha inhibitor (infliximab) was initiated.

On December 24, the patient presented at the local emergency department with acute confusion, speech disorder, and weakness of the right arm and leg. Brain CT showed an old left temporal lesion with no signs of recent ischemia or intracerebral hemorrhage, and intravenous thrombolysis was given for the treatment of an acute ischemic stroke. The patient was transported towards a tertiary centre for a possible intra-arterial thrombolytic treatment. However, during transport, the patient developed clonic seizures of the right side of the body and eventually a status epilepticus. The differential diagnosis included a symptomatic status epilepticus in acute stroke or a late-onset symptomatic status epilepticus related to the old lesion in the left temporal lobe. A brain CT angiography showed no occlusion of the left arteria cerebri media; therefore, there was no indication for intra-arterial treatment. The patient was admitted to the intensive care unit.

Because of respiratory insufficiency and a refractory status epilepticus, the patient was intubated and sedated. Four days after admission, the patient developed fever over 40°C, for which he was empirically treated with intravenous antibiotics. Additional laboratory tests showed normal infection parameters and no obvious focus for infection could be found (X-ray, urine, and blood cultures). On December 28, the patient developed new clonic seizures and eventually a new status epilepticus, which were treated with antiepileptic drugs. On January 1, a lumbar puncture was performed because of persistent epileptic seizures. Liquor examination demonstrated lymphocytic pleiocytosis (96 × 10^6/L leukocytes) , elevated protein levels (1.0 g/L), and a positive polymerase chain reaction assay for herpes simplex virus

type I (cycle threshold 38). Intravenous treatment with acyclovir was initiated for the duration of 10 days. On January 4, all sedative medication was ceased and no clinical signs of epilepsy were observed. On January 5, a brain MRI was performed, which showed findings compatible with the MR findings of herpes simplex encephalitis. On January 26, the patient died.

The final diagnosis was a status epilepticus caused by a reactivation of herpes simplex encephalitis in an immunocompromised patient, with a history of herpes encephalitis and metastatic melanoma, which was treated with ipilimumab, corticosteroids, and infliximab.

Discussion

We report here a case of a patient who developed herpes encephalitis while he was treated with immunosuppressive drugs such as infliximab and prednisolone because of the presence of irAEs caused by ipilimumab treatment. Based on the patients past history, the encephalitis most probably concerns a reactivation of the herpes simplex encephalitis of 1990. However, due to missing data about the encephalitis in 1990, a de novo infection caused by (another strain of) herpes simplex virus type 1 cannot be excluded. To our knowledge, this is the first description of a patient with (a reactivation of) herpes encephalitis after treatment with ipilimumab.

Herpes encephalitis in immunocompromised patients, mainly in relation to TNF-alpha inhibitors such as infliximab, is reported in the literature in some case reports [5–7]. Among these, 5 cases are described of patients with TNF-alpha inhibitor therapy and herpes encephalitis. Infection of the herpes virus can be controlled by TNF signalling pathways by mediating cytotoxicity of the infected cells and by regulating immune responses [8]. Some animal models suggest a protective role for TNF-alpha signalling against herpes simplex encephalitis and thereby suggest that the use of TNF-alpha inhibitors could increase the risk of severe herpes encephalitis [9]. Nevertheless, according to the guidelines of infliximab used by gastroenterologists and rheumatologists, the safety tests that have to be performed before the start of infliximab are: screening for tuberculosis by a Mantoux or Quantiferon test; screening for hepatitis B by serum analysis; and anamnesis for a history of heart failure or demyelinating disease [10]. There are no guidelines that advise caution when there is a history of herpes encephalitis.

Conclusion

With the current knowledge, herpes encephalitis in the past medical history is not a contraindication for immunosuppressive treatment such as high doses of corticosteroids or infliximab. However, clinicians have to be aware of the potential association between the treatment of powerful immunosuppressive agents and a (reactivation of) herpes encephalitis. Furthermore, caution is recommended in the immunosuppressive treatment of these kinds of patients with a history of herpes encephalitis.

Statement of Ethics

The authors have no conflicts of interest to disclose.

Disclosure Statement

The authors have no ethical conflicts to declare.

References

1 Postow MA, Callahan MK, Wolchok JD: Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol 2015;33:1974–1982.
2 Dequen P, Lorigan P, Jansen JP, van Baardewijk M, Ouwens MJ, Kotapati S: Systematic review and network meta-analysis of overall survival comparing 3 mg/kg ipilimumab with alternative therapies in the management of pretreated patients with unresectable stage III or IV melanoma. Oncologist 2012;17:1376–1385.
3 Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, Patt D, Chen TT, Berman DM, Wolchok JD: Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015;33:1889–1894.
4 Ibrahim RA, Berman DM, DePril V, et al: Ipilimumab safety profile: summary of findings from completed trials in advanced melanoma. J Clin Oncol 2011;15(suppl):8583.
5 Bradford RD, Pettit AC, Wright PW, Mulligan MJ, Moreland LW, McLain DA, Gnann JW, Bloch KC: Herpes simplex encephalitis during treatment with tumor necrosis factor-alpha inhibitors. Clin Infect Dis 2009;49:924–927.
6 Schepers K, Hernandez A, Andrei G, Gillemot S, Fiten P, Opdenakker G, Bier JC, David P, Delforge ML, Jacobs F, Snoeck R: Acyclovir-resistant herpes simplex encephalitis in a patient treated with anti-tumor necrosis factor-alpha monoclonal antibodies. J Clin Virol 2014;59:67–70.
7 Crusio RH, Singson SV, Haroun F, Mehta HH, Parenti DM: Herpes simplex virus encephalitis during treatment with etanercept. Scand J Infect Dis 2014;46:152–154.
8 Sedy JR, Spear PG, Ware CF: Cross-regulation between herpesviruses and the TNF superfamily members. Nat Rev Immunol 2008;8:861–873.
9 Lundberg P, Welander PV, Edwards CK 3rd, van Rooijen N, Cantin E: Tumor necrosis factor (TNF) protects resistant C57BL/6 mice against herpes simplex virus-induced encephalitis independently of signaling via TNF receptor 1 or 2. J Virol 2007;81:1451–1460.
10 Guideline of remicade, available at www.remicade.com.