Acute polyneuropathy in a metastatic melanoma patient treated with vemurafenib and cobimetinib

Annette Compter, MD, PhD; Willem Boogerd, MD, PhD; Johannes V. van Thienen, MD, PhD; Dieta Brandsma, MD, PhD

Practical Implications

Consider polyneuropathy as an immune-mediated side effect of BRAF inhibitors.

We describe a patient with *BRAF* V600E–mutated metastatic melanoma, who developed an acute polyneuropathy during molecular targeted treatment with the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib.

In 2015, a 60-year-old man was diagnosed with *BRAF* V600E–mutated metastatic melanoma. Four weeks after start of treatment with vemurafenib and cobimetinib, he noticed tingling of his feet, spreading to the fingertips in days. He subsequently noted weakness of legs and hands. Neurologic examination showed symmetrical distal paresis, more prominent in legs than in arms, with trace deep tendon reflexes (DTR) of arms and absent DTRs of legs. A distal symmetrical loss of joint position and vibration sensations was found in both legs.

After initiation of treatment with vemurafenib and cobimetinib, both S100B and lactate dehydrogenase showed a major decline, indicating a strong antitumor response. The CK level was normal (19 U/L). MRI excluded cervical compression and leptomeningeal enhancement. CSF analysis showed slightly increased total protein (0.58 g/L) without leukocytosis. Testing for *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, paraneoplastic antibodies, and antiganglioside antibodies was negative.

During hospitalization, the patient developed a rapidly progressive proximal and distal quadriparesis, loss of all DTRs, neuropathic pain, and urinary incontinence. He lost ambulation, and required mechanical ventilation within 1 week after symptom onset. Because he fulfilled the clinical criteria of Guillain-Barré syndrome (GBS)¹ and CSF analysis was compatible with an acute inflammatory polyneuropathy, a 5-day course of IV immunoglobulins (IVIg, 0.4 g/kg daily) was given, with a second cycle 2 days afterwards because of slight initial response and secondary progression thereafter. Three weeks after symptom onset, due to lack of further neurologic improvement after 2 cycles of IVIg, the diagnosis of vemurafenib-induced acute polyneuropathy was considered. Vemurafenib and cobimetinib were discontinued and oral prednisone (1 mg/kg) was started. The patient showed remarkable recovery and mechanical ventilation was discontinued 1 week after discontinuation of vemurafenib and start of prednisone. After 3 months he regained his ability to walk, with major improvement of the paresis of his legs. DTRs and sensory examination were unchanged. Nerve conduction studies (NCS) were performed afterwards and demonstrated absent sensory nerve action potentials of the median, ulnar, and sural nerve, slightly prolonged distal motor latencies of the median, ulnar, and peroneal nerve, and reduced motor nerve conduction velocities of

Departments of Neuro-Oncology (AC, WB, DB) and Medical Oncology (JVvT), Netherlands Cancer Institute–Antoni van Leeuwenhoek, Amsterdam; and Department of Neurology and Neurosurgery (AC), University Medical Center Utrecht, the Netherlands.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article** at Neurology.org/cp.

Correspondence to: a.compter@nki.nl

the ulnar and peroneal nerve, consistent with a symmetrical, length-dependent motor and sensory axonal polyneuropathy.

DISCUSSION

Our patient is the second patient reported with an acute polyneuropathy that appears related to the use of vemurafenib.² Symptoms started within 1 month after start of vemurafenib in both patients. In the other patient, it remained unclear whether the polyneuropathy was related to vemurafenib treatment or to recent treatment with nivolumab, a PD-1 immune checkpoint inhibitor in which polyneuropathy has been described as an immune-mediated adverse reaction.

Clinically our patient fulfilled the Brighton criteria for GBS,¹ with NCS consistent with a multifocal motor and sensory axonal polyneuropathy. The acute polyneuropathy appears related to the use of vemurafenib, because of symptom onset within 1 month after start of vemurafenib and the swift recovery within 1 week after discontinuation of vemurafenib and start of corticosteroids. Corticosteroids can be considered in immune-mediated polyneuropathies.

Previous reports described 4 patients with unilateral or synchronous bilateral facial nerve palsy after start of vemurafenib, which disappeared after vemurafenib discontinuation or start of corticosteroids.^{3–5}

The exact underlying mechanism of vemurafenib-induced facial nerve palsy and acute polyneuropathy remains unclear. The response to corticosteroids in our patient and previously reported patients suggests an immune-mediated effect. BRAF inhibitors seem to increase immune cell recognition of melanoma cells by a hyperactivated T-cell response.⁶ Melanocytes and Schwann cells are both derived from neural crest cells and share surface molecules, such as the gangliosides GM2, GM3, and GD3.⁷ The hyperactivated T-cell response and molecular mimicry of surface molecules might result in autoimmune neuropathies.

Neurologic paraneoplastic syndromes are uncommon in melanoma. Testing for paraneoplastic antibodies in serum and CSF was negative in our patient. Furthermore, the start of neurologic symptoms synchronous with a clear treatment response to vemurafenib and cobimetinib, as shown by the decline in S100B and lactate dehydrogenase, makes a paraneoplastic polyneuropathy less likely. No association between cobimetinib and acute neuropathies has been described.

Our findings suggest that molecular targeted treatment without a direct immune-mediated working mechanism may cause immune-mediated side effects. Attention should be paid to the possibility of immune-mediated neuropathies due to BRAF inhibitors. Treatment of these neuropathies should consist of discontinuation of the BRAF inhibitor and, in case of severe symptoms, corticosteroids.

REFERENCES

1. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011;29:599–612.
2. Johnson DB, Wallender EK, Cohen DN, et al. Severe cutaneous and neurologic toxicity in melanoma patients during vemurafenib administration following anti-PD-1 therapy. *Cancer Immunol Res* 2013;1:373–377.
3. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012;366:707–714.
4. Klein O, Ribas A, Chmielowski B, et al. Facial palsy as a side effect of vemurafenib treatment in patients with metastatic melanoma. *J Clin Oncol* 2013;31:e215–e217.
5. Shailesh FN, Singh M, Tiwari U, Hutchins LF. Vemurafenib-induced bilateral facial palsy. *J Postgrad Med* 2014;60:187–188.
6. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin Cancer Res* 2013;19:1225–1231.

7. Tsuchida T, Saxton RE, Morton DL, Irie RF. Gangliosides of human melanoma. *Cancer* 1989;63: 1166–1174.

Received July 6, 2016. Accepted in final form October 23, 2016.

AUTHOR CONTRIBUTIONS

A. Compter: drafting/revising the manuscript for content, including medical writing for content. W. Boogerd: critical revision of the manuscript for important intellectual content. J.V. van Thienen: critical revision of the manuscript for important intellectual content. D. Brandsma: critical revision of the manuscript for important intellectual content.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

A. Compter and W. Boogerd report no disclosures. J. V. van Thienen received honoraria from serving on the advisory board of Bristol Myers Squibb and Merck Sharp & Dohme. These honoraria have been transferred to the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam. D. Brandsma reports no disclosures. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Discover Altmetrics

See real-time downloads and online activity for articles!

Picked up by 8 news outlets
 Tweeted by 18
 Mentioned in 1 Google+ posts
 12 readers on Mendeley

[See more details](#)

Authors and readers alike can view real-time data on articles including downloads and online activity across multiple sources. Click on the “Article Metrics” link in the right column of an article for details. To learn more about article metrics visit http://www.neurology.org/site/includefiles/article_usage.xhtml.