Balkan Med J 2024;41:312-3

Guillain-Barre Syndrome due to Adjuvant Therapy with Dabrafenib Plus Trametinib

Aslı Geçgel[1], Sercan Ön[2], Yeliz Çiftçi[3], Oğuzcan Özkan[1], Fatma Pınar Açar[1], Burçak Karaca[1]

[1]Clinic of Medical Oncology, Ege University Hospital, İzmir, Türkiye
[2]Clinic of Medical Oncology, İzmir Bayraklı City Hospital, İzmir, Türkiye
[3]Clinic of Neurology, Bakırçay University Çiğli Training and Research Hospital, İzmir, Türkiye

The incidence of cutaneous melanoma continues to increase worldwide and is associated with a significant risk of mortality. The surgical removal of melanoma in its early stages is usually curative. Nevertheless, patients with resected stage IIB-IV melanoma face a heightened risk of relapse and mortality. To mitigate this risk, systemic adjuvant therapy is required.[1]

Adjuvant administration of a combination of dabrafenib and trametinib yielded a significantly reduced risk of recurrence and enhanced survival outcome in patients diagnosed with stage III melanoma and carrying the BRAF V600E or V600K mutation (hazard ratio 0.51).[2] With the increased use of these agents for melanoma and other indications, clinicians should be aware of rare but potentially life-threatening side effects associated with these medications.

Guillain-Barre syndrome (GBS) is an ascending acute immune-mediated polyneuropathy triggered by infections, vaccinations, and drugs. It is a potentially life-threatening disease characterized by rapid and symmetrical progression of weakness in the extremities. GBS is associated with the use of antibiotics, anti-tumor necrosis factor agents, antimotility drugs, and immune checkpoint inhibitors.[3,4] Only a few cases of BRAF-MEK-induced GBS have been reported.[5-7] Herein, we aim to heighten clinicians' awareness of a relatively uncommon scenario by presenting a patient with stage III malignant melanoma who developed GBS secondary to the administration of adjuvant dabrafenib and trametinib.

A 55-year-old male was admitted to the dermatology unit because of changes in the size, shape, and color of a nevus located beneath the right scapula. An excisional biopsy was performed, which revealed a superficial spreading type of malignant melanoma that originated from a dermal congenital nevus, classified as pTIIIa. The tumor continued to grow at the lateral excised margin after reexcision and sentinel lymph node biopsy were performed in November 2022. No residual disease was found in the tumor bed or axilla.

During the follow-up, ultrasound revealed suspicious lymph nodes in the right axilla. On positron emission tomography/computed tomography, the lymph nodes in the bilateral submandibular chains exhibited millimeters of mild fluorodeoxyglucose (FDG) uptake (SUV: 4.7), and a lymph node in the right axilla demonstrated FDG uptake. In April 2023, a right-sided axillary dissection was performed. Histopathological examination of the specimen revealed melanoma metastasis in one of the 16 dissected lymph nodes. The metastatic lymph node was 3 cm in diameter. The molecular test for BRAF V600E mutation was positive. The patient was referred to the medical oncology unit, and adjuvant treatment with dabrafenib (2x150 mg/day) and trametinib (2 mg/day) was initiated in May 2023 for the stage IIIc melanoma.

Approximately two months after initiating treatment, the patient presented with complaints of left-sided drooping of the mouth, difficulty in speaking, difficulty in swallowing, and weakness in both lower extremities. A physical examination revealed unilateral peripheral facial paralysis, and deep tendon reflexes in all four limbs could not be elicited. Brain magnetic resonance imaging did not reveal any abnormalities. Vitamin B12, folate, and creatine phosphokinase levels were within their normal ranges. The viral serology results were negative. A lumbar puncture was performed, and biochemical evaluation of the cerebrospinal fluid (CSF) revealed a protein level of 154.9 mg/dL and a glucose level of 75 mg/dL. CSF microscopy and cytology yielded negative results. Electromyography (EMG) revealed normal sensory conductions, an ulnar F-latency of

Corresponding author: Burçak Karaca, Clinic of Medical Oncology, Ege University Hospital, İzmir, Türkiye

e-mail: karacaburcak@hotmail.com

Received: February 02, 2024 **Accepted:** February 21, 2024 **Available Online Date:** 04.07.2024 • **DOI:** 10.4274/balkanmedj.galenos.2024.2024-1-86

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: A.G. 0000-0001-6942-9858; S.Ö. 0000-0003-1461-7485; Y.Ç. 0009-0007-6304-2944; O.Ö. 0000- 0002-4075-7775; F.P.A. 0009-0000-2749-8732; B.K. 0000-0003-2638-1625.

***This manuscript has been presented in a Melanoma Bridge congress 2023 as a poster in November 30th-December 2nd 2023, Naples (Italy).**

Cite this article as: Geçgel A, Ön S, Çiftçi Y, Özkan O, Açar FP, Karaca B. Guillain-Barre Syndrome due to Adjuvant Therapy with Dabrafenib Plus Trametinib. Balkan Med J.; 2024; 41(4):312-3.

30.8 (upper limit) with 80% persistence, and an inability to elicit a tibial F-response.

The clinical and diagnostic test findings were deemed to be consistent with acute polyneuropathy. The patient was diagnosed with GBS based on the elevated CSF protein level, and plasmapheresis was initiated. The patient underwent plasmapheresis five times, with sessions scheduled every other day. In the third week after the onset of symptoms, a repeat EMG revealed normal sensory conductions. The patient's GBS was attributed to the side effects of dabrafenib and trametinib. Thus, the drugs were discontinued.

GBS is not a single clinical entity. It is a complex clinical condition, often presenting with acute demyelinating neuropathy or, in some cases, axonal loss. The diagnosis of GBS relies on clinical features, supplemented by CSF and electrodiagnostic study findings.[8] EMG can support the diagnosis of GBS and provide prognostic information. In cases similar to our patient's, the earliest findings may include prolonged or absent F-waves. Signs of demyelination, such as slowing of nerve conduction and prolongation of distal latencies, can also be observed. Anti-ganglioside antibodies may be beneficial for patients presenting with atypical clinical signs.[9] According to a pharmacovigilance study, neurological side effects, including seizures (0.4%), peripheral neuropathies (0.4%), and GBS (0.05%), are very rare with the combined use of dabrafenib and trametinib. Other BRAF-MEK inhibitor combinations are associated with a higher GBS risk (0.1%-0.5%).[10]

The optimal management of GBS involves intravenous immunoglobulin administration or plasma exchange in addition to supportive care. Given the potential progression of symptoms, prompt diagnosis and treatment are crucial because respiratory muscles can be affected.

GBS is considered an immune-mediated polyneuropathy, and specific antibodies are found in patients diagnosed with GBS. However, it remains unclear whether BRAF-MEK inhibitor combinations trigger antibody production. Case reports indicate that patients have benefited from plasmapheresis or intravenous immunoglobulins. Upregulation of MAPK signaling in leukocytes has been observed in patients with GBS.[11] Although this pathway plays a role in neuronal myelination, evidence suggesting that the inhibition of the MAPK pathway could lead to GBS is lacking.

The decision to rechallenge or continue the use of this drug presents a clinical dilemma. Although, there is a risk of disease recurrence and progression, the reintroduction of dabrafenib and trametinib could lead to GBS recurrence. GBS has recurred in two of three reported cases when the treatment was continued.[5-7]

Recognition of this rare side effect, which has been reported only a few times and early administration of treatment are vital. GBS should be considered when neurological side effects such as weakness, cranial nerve involvement, and sensory changes are observed in patients receiving BRAF-MEK inhibitor combinations.

Authorship Contributions: Design- A.G., B.K., Supervision- B.K., Data Collection and Processing- Y.Ç., O.Ö., F.P.A., Writing- A.G., S.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: The authors declared that this study received no financial support.

REFERENCES

1. Kobeissi I, Tarhini AA. Systemic adjuvant therapy for high-risk cutaneous melanoma. *Ther Adv Med Oncol.* 2022;14:17588359221134087. **[CrossRef]**
2. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med.* 2017;377:1813-1823. **[CrossRef]**
3. Awong IE, Dandurand KR, Keeys CA, Maung-Gyi FA. Drug-associated Guillain-Barré syndrome: a literature review. *Ann Pharmacother.* 1996;30:173-180. **[CrossRef]**
4. Li Y, Zhang X, Zhao C. Guillain-Barré Syndrome-Like polyneuropathy associated with immune checkpoint inhibitors: a systematic review of 33 cases. *Biomed Res Int.* 2021:2021:9800488. **[CrossRef]**
5. Taha T, Tzuk-Shina T, Forschner I, Bar-Sela G. Acute motor and sensory axonal neuropathy related to treatment with MEK inhibitors in a patient with advanced melanoma. *Melanoma Res.* 2017;27:632-634. **[CrossRef]**
6. Batra J, Ankireddypalli A, Kanugula AK, Gorle S, Kaur J. Guillain-Barre Syndrome secondary to the use of dabrafenib and trametinib for the treatment of advanced thyroid carcinoma. *Cureus.* 2023;15:e35069. **[CrossRef]**
7. Maurice C, Marcus B, Mason W. Guillain-Barre syndrome after treatment with dabrafenib for metastatic recurrent melaloma. (P4.232). *Neurology.* 2015;84:232. **[CrossRef]**
8. Meirson T, Asher N, Bomze D, Markel G. Safety of BRAF+MEK inhibitor combinations: severe adverse event evaluation. *Cancers.* 2020;12:1650. **[CrossRef]**
9. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* 2014;371:1877-1888. **[CrossRef]**
10. Sudulagunta SR, Sodalagunta MB, Sepehrar M, et al. Guillain-Barré syndrome: clinical profile and management. *Ger Med Sci.* 2015;13:Doc16. **[CrossRef]**
11. Uncini A, Kuwabara S. The electrodiagnosis of Guillain-Barré syndrome subtypes: Where do we stand? *Clin Neurophysiol.* 2018;129:2586-2593. **[CrossRef]**
12. Meirson T, Asher N, Bomze D, Markel G. Safety of BRAF+MEK inhibitor combinations: severe adverse event evaluation. *Cancers.* 2020;12:1650. **[CrossRef]**
13. Chang KH, Chuang TJ, Lyu RK, et al. Identification of gene networks and pathways associated with Guillain-Barré Syndrome. *PLoS One.* 2012;7:e29506. **[CrossRef]**