Neurological Sciences (2023) 44:3335–3339
https://doi.org/10.1007/s10072-023-06827-4

LETTER TO THE EDITOR

CNS demyelination associated with nilotinib

Ezgi Erturul[1] · Belgin Kocer[1] · Saliha Gokce[1] · Murat Ucar[2]

Received: 14 January 2023 / Accepted: 3 April 2023 / Published online: 3 May 2023
© Fondazione Società Italiana di Neurologia 2023

Introduction

As treatment options for cancer and autoimmune diseases are developing each day, iatrogenic central demyelination case reports are increasing in number. Tumor necrosis factor-alpha inhibitors and immune-checkpoint inhibitors are the most frequently reported agents in iatrogenic central nervous system demyelination cases [1]. Recently, there have been reports on iatrogenic peripheral and central demyelination associated with tyrosine kinase inhibitors. Nilotinib is a second generation tyrosine kinase inhibitor targeting the Bcr-abl translocation, and used in chronic myeloid leukemia (CML) [2]. A possible central demyelination associated with the use of nilotinib will be presented in this case report.

Case

Twenty-nine-year-old female patient presented with the complaint of diplopia in all directions with bilateral ataxia. The patient had a known history of CML with a duration of 8 years. During the disease course, she used several medications including 9 months of imatinib, almost 5 years of dasatinib, and 2 years of 800 mg per day nilotinib respectively. She had no history of radiotherapy. In the initial neurological examination, bilateral internuclear ophthalmoplegia, vertical nystagmus with upward and downward gaze, left intentional tremor, and right dominant bilateral ataxia were detected. Cranial magnetic resonance imaging (MRI) scans revealed multiple demyelinating lesions. A lesion was localized adjacent to the occipital horn of the lateral ventricle, within the white matter with an open ring contrast enhancement and diffusion restriction. Another lesion was localized in the right temporal cortical-juxtacortical area with homogenous contrast enhancement. There were demyelinating lesions without contrast enhancement in bilateral brachium pontis and bilateral periventricular white matter. Cervical MRI showed periependymal multi-segmental T2 hyperintensities without contrast enhancement on C3-C7 vertebral levels (Fig. 1). ANA IFA was 2 positive, but other vasculitis-related biomarkers were negative. Cerebrospinal fluid (CSF) examinations including CSF culture, Gram-Wright-ARB stains, tuberculosis PCR, cytology, Rose Bengal, and Monospot tests turned out to be unremarkable. CSF oligoclonal band (OCB) occurred to be type 3 positive and IgG index was high (0.71/0.20–0.60 in normal value), with these results, the patient was diagnosed with multiple sclerosis according to 2017 Revised McDonald criteria. Thus, nilotinib therapy was terminated. Ten days of 1 g/per day intravenous methylprednisolone was administered, the treatment then was continued with 48 mg per day oral methylprednisolone tablets; dose reduction was made gradually over 2-week period. Clinical improvement was observed on the third day of the intravenous methylprednisolone treatment and after the 2 weeks of oral corticosteroid therapy, neurological examination of the patient was normal. It was decided to proceed treatment with dimethyl fumarate. In the third month follow-up, neurological examination of the patient was totally normal. The cranial and cervical MRI scans revealed regression in the previous lesion sizes (Fig. 2); however, new lesions were detected on the right frontal and the splenium of the corpus collosum (Fig. 3). Bosutinib, another tyrosine kinase inhibitor, was administered by the hematology department, because of the Bcr-abl translocation positivity.

Discussion

Medications can cause demyelination due to immune system deregulation by the activation of $CD8^+$ T cells and apoptosis of regulatory T cells, or chemical-induced

✉ Ezgi Erturul
ezgiierturul@gmail.com

[1] Department of Neurology, Gazi University School of Medicine, Ankara, Turkey

[2] Department of Radiology, Gazi University School of Medicine, Ankara, Turkey

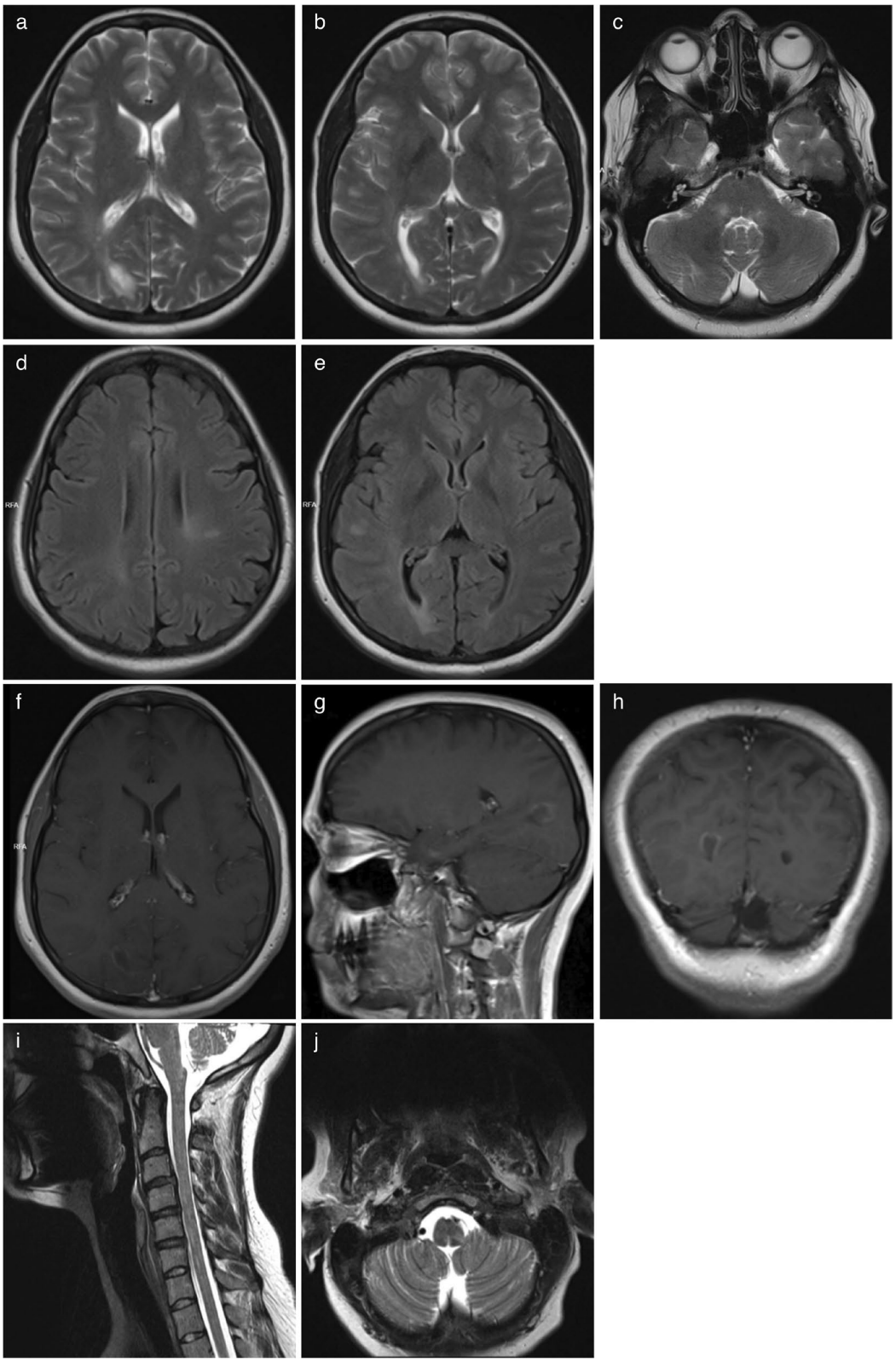


Fig. 1 Demyelinating lesions in the right temporal cortical-juxtacortical area, adjacent to occipital horn of the lateral ventricle and bilateral brachium pontis on axial T2 and FLAIR cranial MR scans (**a–e**). Demyelinating lesion adjacent to occipital horn with open ring contrast enhancement on the axial-sagittal and coronal post-contrast T1 cranial MRIs (**f–h**). Periependymal multi-segmental T2 hyperintensities at C3–C7 vertebral levels on sagittal and axial T2 cervical MRI scans (**i–j**)

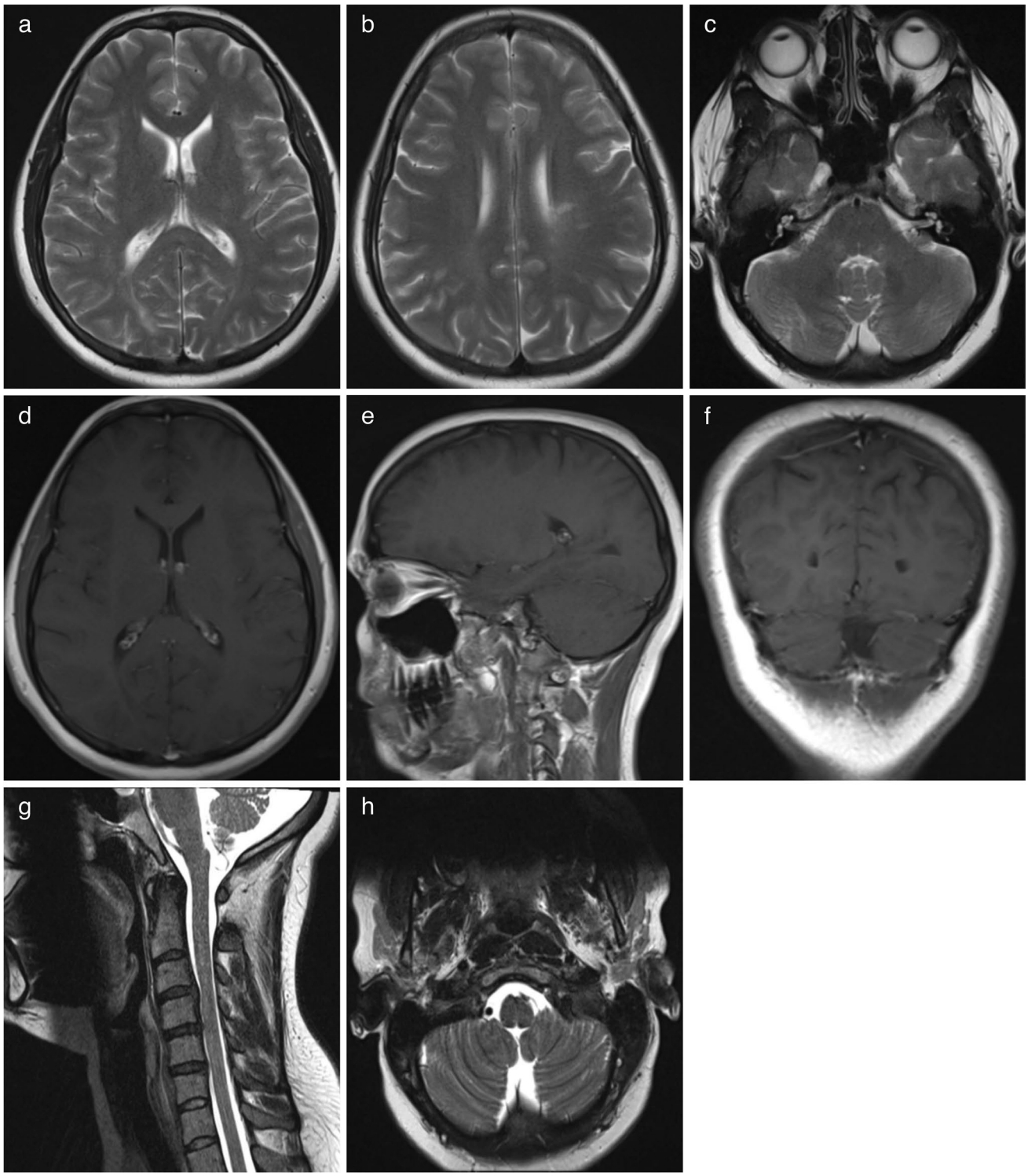


Fig. 2 Regression of previous lesions in the third month follow-up cranial and servical MRIs (**a–h**)

neurotoxicity [3]. The mechanism is not yet to be fully understood. Tumor necrosis factor-alpha inhibitors and immune-checkpoint inhibitors are the most frequently reported agents, but recently, the number of cases reporting iatrogenic central nerve demyelination with tyrosine kinase inhibitors has increased. There are 3 other cases of nilotinib-related demyelination reported in the literature.

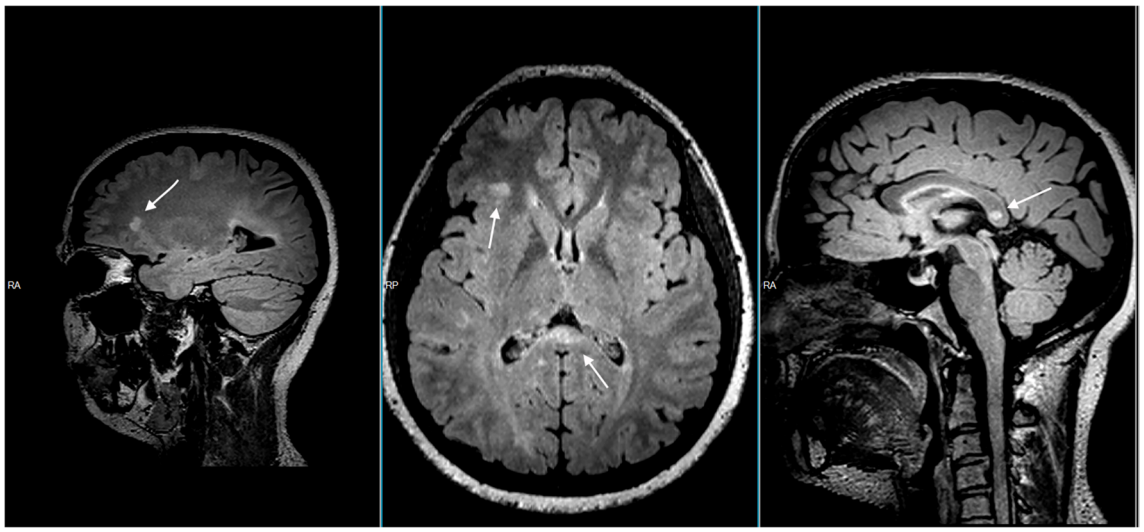


Fig. 3 New lesions in the right frontal and the splenium of the corpus collosum in the third month follow-up FLAIR cranial MRI scans

The first case is a 36-year-old male patient followed up with CML for 5 years and has been using nilotinib for 3 years. The patient's symptoms include right facial paralysis and weakness affecting the right extremities. Multiple demyelinating lesions were observed in the cranial MRI scans. Nilotinib therapy was terminated and the patient's symptoms were regressed with intravenous methylprednisolone. The second case is a 39-year-old female patient followed up with CML, who has a history of using nilotinib for 2 years. Multiple demyelinating lesions were observed in the cranial and cervical MRI of the patient who had a complaint of paresthesia in the right neck and arm. During the follow-ups, the patient's complaints were regressed spontaneously without the termination of nilotinib treatment [2]. The third case is a 62-year-old female patient followed up with CML, using nilotinib for 5 years. She was presented with descending extremity weakness and subjective sensory defect for 10 days. Subsequently, the patient developed dyspnea and urgent intubation was required. In the neurological examination, quadriparesis and areflexia were detected without an objective sensory defect. While the cranial MRI of the patient was reported to be normal, hyperintensity compatible with demyelinating lesions was observed at C2–C7 spinal levels in the cervical MRI. CSF examination revealed albuminocytological dissociation (protein: 82 mg/dl, leukocytes 8/uL). Nilotinib was ceased and intravenous immunoglobulin therapy was initiated. There was minimal improvement observed in patient's complaints [4]. Agents used prior to nilotinib were not reported in the mentioned cases. In our case, there was also a history of using other tyrosine kinase inhibitors, such as imatinib and dasatinib, before the nilotinib treatment. A history of multiple drug use with the same mechanism of action may increase the possibility of CNS demyelination.

Nilotinib causes inhibition of platelet-derived growth factors receptors (PDGFRs) activation [5]. Platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are expressed in many cell types including the neuronal progenitors, neurons, astrocytes, and oligodendrocytes. PDGF-mediated signaling is involved in neurogenesis, cell survival, synaptogenesis, modulation of ligand-gated ion channels, and development of specific types of neurons. PDGF-AA has been shown to function as a potent mitogen for oligodendrocyte progenitors [6].

The presence of oligodendrocyte progenitors in white matter with ongoing neuroinflammation and in normal-appearing white matter in multiple sclerosis suggests a potential role of oligodendrocytes in myelin repair [7]. Because the PDGFRs are expressed in oligodendrocytes and have a role in myelin repair, blockage of this receptor by nilotinib may facilitate central demyelination. Inversely, PDGFRα's ligand PDGF-CC maintains blood-brain barrier function and integrity, so Zeitelhofer and colleagues affirm that blocking PDGF-CC leads to amelioration of a MS-like neuroinflammation [8]. Consequently, PDFR and their receptors have a different mechanism that is not fully understood yet and nilotinib may be causing central demyelination through these receptors.

In CML and MS coexistence, DMF is preferable agent. For AML differentiation therapy, low-toxic vitamin D derivative/DMF combination could be a new approach for clinical trials [9]. DMF is also being investigated as a new therapeutic agent in T-cell leukemia [10, 11].

When iatrogenic CNS demyelination is suspected, the possible causative agent should be terminated and

immunosuppressive treatment should be administered if necessary. Patient with multiple sclerosis should be followed closely both clinically and radiologically, and the initiation of the disease-modifying agent should not be delayed. In addition, drug selection is important in the coexistence of multiple sclerosis and autoimmune diseases or malignancy. The drug chosen should preferably be effective in both diseases, and if there is no such option, it should at least not worsen the prognosis for the other disease.

Declarations

Ethics approval This paper was approved by the Ethical committee from the blinded manuscript.

Informed consent Informed consent was received from patient.

Conflict of interest The authors declare no competing interests.

References

1. Kumar N, Abboud H (2019) Iatrogenic CNS demyelination in the era of modern biologics. Mult Scler 25(8):1079–1085
2. Rekhi E, Pryce A, Sohal M et al (2016) CNS demyelination in patients on nilotinib treatment for CML. J Neurol Neurosurg Psychiatry 87(12):e1
3. Rimkus CM, Schoeps VA, Boaventura M et al (2021) Drug-related demyelinating syndromes: understanding risk factors, pathophysiological mechanisms and magnetic resonance imaging findings. Mult Scler Relat Disord 55:103146
4. Judge C, Moheb N, Melinosky C (2019) Nilotinib-associated demyelinating disease: case report. Neurol 92(Supplement1):P.22-093
5. Liu Y, Wang Z et al (2011) Inhibition of PDGF, TGF-β, and Abl signaling and reduction of liver fibrosis by the small molecule Bcr-Abl tyrosine kinase antagonist Nilotinib. J Hepatol 55:612–625
6. Betsholtz C (2004) Insight into the physiological functions of PDGF through genetic studies in mice. Cytokine Growth Factor Rev 15(4):215–228
7. Wilson H, Scolding N, Raine C (2006) Co-expression of PDGF a receptor and NG2 by oligodendrocyte precursors in human CNS and multiple sclerosis lesions. J Neuroimmunol 176:162–173
8. Zeitelhofer M, Adzemovic M et al (2020) Blocking PDGF- CC signaling ameliorates multiple sclerosis- like neuroinflammation by inhibiting disruption of the blood–brain barrier. Sci Rep 10(1):22383
9. Nachliely M, Trachtenberg A et al (2019) Dimethyl fumarate and vitamin D derivatives cooperatively enhance VDR and Nrf2 signaling in differentiating AML cells in vitro and inhibit leukemia progression in a xenograft mouse model. J Steroid Biochem Mol Biol 188:8–16
10. Xu JG, Cheng Q et al (2022) Effect of dimethyl fumarate (DMF) on T-cell acute lymphoblastic leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 30(1):1–5
11. Maeta T, Sato T et al (2022) Dimethyl fumarate induces apoptosis via inhibiting NF-κB and STAT3 signaling in adult T-cell leukemia/lymphoma cells. Anticancer res 42(5):2301–2309

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.