Annals of Hematology (2019) 98:205–207
https://doi.org/10.1007/s00277-018-3381-y

LETTER TO THE EDITOR

Autoimmune myelitis in a CLL patient undergoing treatment with ibrutinib

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Received: 23 April 2018 / Accepted: 21 May 2018 / Published online: 26 May 2018

Dear Editor,

A 46-year-old male patient was diagnosed with chronic lymphocytic leukaemia (CLL) (IGHV mutated, normal karyotype, CD38+, ZAP70+, *TP53* status not assessed) 14 years ago. Previous therapies consisted of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), FCR (fludarabine, cyclophosphamide, and rituximab), and rituximab plus bendamustine. However, 2 months after a third-line therapy, he required further treatment due to bulky lymphadenopathy, pronounced constitutional symptoms, and lymphocyte doubling time < 3 months (absolute lymphocyte count of 79,6 G/l, platelets 103 G/l, haemoglobin 135 g/l). Cytogenetics revealed a normal karyotype. Ibrutinib 420 mg/day was started and well tolerated resulting in an immediate and complete resolution of B-symptoms and > 70% regression of lymphadenopathy. However, after 1 month, he was referred to our hospital due to paraesthesia's starting in the left foot and spreading within hours to the right leg, the pelvic floor, and the genital area, accompanied by bladder dysfunction. Cerebrospinal fluid (cytology, cell count, chemistry, isoelectric focusing, PCR tests for adenovirus, HSV1/2, VZV, CMV, EBV, HHV6, and toxoplasmosis) and serological analyses (including *Treponema pallidum*, *Borrelia burgdorferi*, HIV) were normal. Of note, his past medical history was negative for any neurological or autoimmune disease, and thorough neurological and medical assessment revealed no further symptoms. MRI showed signal enhancements of the spinal cord at the thoracolumbar transition and at height TH7 (Fig. 1); cerebral MRI was normal. Based on these findings and the clinical presentation with absence of any signs of infectious disease, a diagnosis of autoimmune myelitis was rendered. Treatment with methylprednisolone 1 g OD over 5 days was administered leading to a prompt but slow neurological improvement while ibrutinib was continued. After 2 months, the bladder dysfunction had completely disappeared but paraesthesias persisted, although to a lesser extent. After 10 months, most neurological symptoms have disappeared with only a slight hypaesthesia of the pelvic floor remaining. Ibrutinib was given for a total of over 2 years, and no further myelitis or other autoimmune symptoms were noted.

To the best of our knowledge, this is the first report of an autoimmune myelitis occurring during treatment with ibrutinib. Ibrutinib has been shown to ameliorate CLL-associated autoimmune phenomena but may in turn trigger other inflammatory processes [1, 2]. Besides the inhibition of Bruton's tyrosine kinase (Btk), ibrutinib also inhibits interleukine-2-inducible T cell kinase (ITK) leading to a Th1 shift due to a decrease in downstream activation of Th2 cells. This imbalance leads to a decrement of potentially autoreactive Th2 cells but also to a pro-inflammatory response of Th1 cells [3, 4]. Th1-mediated immune responses are mainly driven by INF-γ, TNF-α, and IL-2 and associated with various autoimmune disorders including multiple sclerosis and transverse myelitis [5]. Indeed, ibrutinib has been shown to induce such autoimmune phenomena, particular within the first months of treatment (e.g., skin lesions). They seem to be steroid-responsive or even only transient in nature [6, 7]. Although cases of autoimmune phenomena triggered by ibrutinib have been described, and the abovementioned influences of ibrutinib illustrate its impact on autoimmune responses, it has to be admitted that the myelitis possible developed in parallel but not because of ibrutinib treatment.

In conclusion, we describe the occurrence and successful treatment of autoimmune myelitis in a CLL patient shortly

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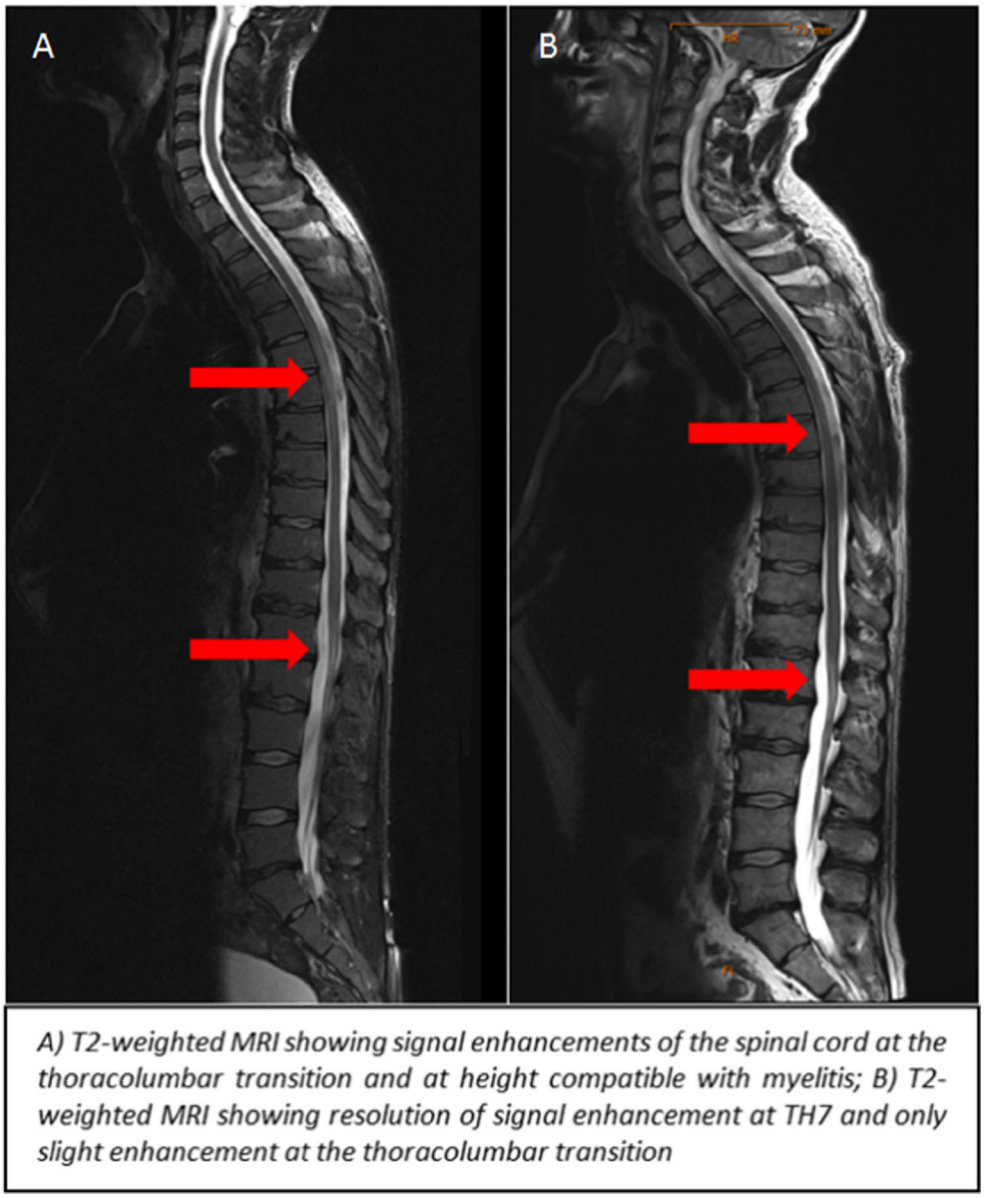

Fig. 1 **a** T2-weighted MRI showing signal enhancements of the spinal cord at the thoracolumbar transition and at height compatible with myelitis. **b** T2-weighted MRI showing resolution of signal enhancement at TH7 and only slight enhancement at the thoracolumbar transition

after initiation of ibrutinib. Thus, clinical surveillance of patients receiving ibrutinib for uncommon toxicities should also include the central nervous system.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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