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LETTER TO THE EDITOR

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Dasatinib-associated follicular lymphoid hyperplasia: First pediatric case report and literature review

This 14-year-old male was diagnosed with chronic myeloid leukemia (CML) in July 2013. He initially received imatinib for 5 months, but was then switched to dasatinib (100 mg/day) due to arthralgia. Five months later, he developed hyperplasia of a right parotid lymph node. Myeloid cell analysis showed no BCR/ABL rearrangement. Serologic tests for human immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, and toxoplasmosis were negative, as were tests for tuberculosis (Quantiferon-TB, culture of biopsy). Pathologic analysis revealed the presence of voluminous follicles with hyperplastic germinal centers in the cortical region and tangible macrophage bodies in the germinal centers. Immunohistochemistry showed follicles with no BCL-2 expression and germinal centers positive for cluster of differentiation 10. The diagnosis of follicular and interfollicular hyperplasia was established. Six months later, voluminous cervical adenopathies persisted and small subangulomaxillary lymphadenopathies appeared on the left side. Positron emission tomography confirmed the presence of right cervical hypermetabolic lymphadenopathies. Dasatinib was then replaced with nilotinib; two weeks later the lymphadenopathies began to decline and they disappeared completely 3.5 months later.

The temporal relationship between the lymphadenopathies (onset and improvement) and dasatinib treatment are consistent with a causal role of this drug. It has been suggested that, in some patients with advanced CML, high doses of dasatinib increase the risk of opportunistic infections.[1] However, for this patient, all serologic tests were negative and there was no evidence of tuberculosis. A concomitant lymphoproliferative disorder, as reported in a few rare cases of CML, was also excluded.

Fourteen cases of follicular lymphoid hyperplasia (FLH) associated with dasatinib use were identified in the literature (Table 1). All of them displayed cervical lymphadenopathies (range: 8–35 months after treatment) and rarely inguinal or axillary lymphadenopathies.[2–5] Biopsy ruled out the possibility of extramedullary blastic

TABLE 1 Characteristics of clinical reports of follicular lymphoid hyperplasia with dasatinib for CML

References	Number	Age (years)	Dose (mg/day)	Time to onset (months)	Clinical characteristics of lymph nodes	Biopsy	Course	Time to regression (months)
Alshehry et al., *Acta Hematol*., 2015	1	67	100	12	Cervical	Mixed paracortical and follicular lymphoid hyperplasia	Recovery	"Promptly"
Roux et al., *Blood*., 2013	9	24–69, median: 52	100 (N = 7), 80 (N = 1), 50 (N = 1)	9–35, median: 20	Cervical (N = 9), inguinal (N = 1)	Follicular lymphoid hyperplasia, cytogenetic: clonal abnormality (N = 1)	Recovery (N = 9), switch to nilotinib (N = 6)	0.5–2 (N = 9), median: 1
Knott et al., *AVAHO*., 2014	1	37	100	8	Parotid gland, multiple	Follicular and interfollicular lymphoid hyperplasia	Recovery, switch to bosutinib	1
Ozawa et al., *Am J Surg Pathol*., 2015	3	46–62, median: 54	Unknown	18–24, median: 19	Cervical (N = 3), axillary (N = 1)	Follicular lymphoid hyperplasia (N = 3), EBV reactivation (N = 1), progressive transformation of germinal center (N = 2), atypical B cells (N = 1)	Recovery (N = 2), switch onto nilotinib (N = 1), unknown (N = 1)	1.5 (N = 1), unknown (N = 1)

Abbreviations: CML, chronic myeloid leukemia; EBV, Epstein-Barr virus; FLH, follicular lymphoid hyperplasia; TKI, tyrosine kinase inhibitor

transformation of CML in all patients and revealed paracortical hyperplasia in one. Clonal abnormalities were observed in one patient and atypical B cells in another. Dasatinib treatment was discontinued, leading to a regression of lymphadenopathies in 13 patients (range: 2–9 weeks). In eight patients, it was replaced with another tyrosine kinase inhibitor (TKI) (nilotinib: 7; bosutinib: 1) with no recurrence of lymphadenopathy.

The mechanism underlying the FLH remains unknown. TKIs are involved in B-cell activation through the BCR and the Akt/protein kinase B pathways,[6,7] which may could promote B-cell proliferation. The absence of areas of nodal effacement and the characteristics of the germinal center and mantle zones in this case are consistent with an adverse effect of the drug.[4] FLH differs from follicular lymphoma in its absence of BCL-2 gene expression in the B cells of the germinal center and the absence, in almost all cases, of light chain restriction, immunoglobulin gene rearrangement, and t(14, 18) translocation.[8] The absence of recurrence after switching to another TKI may be due to the different degrees of inhibition of different protein kinase targets. The report of a case of clonal abnormalities[2] suggests that dasatinib should be discontinued in patients with FLH, who should be switched onto another TKI, such as nilotinib or bosutinib.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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