To the editor:

Reversible lymph node follicular hyperplasia associated with dasatinib treatment of chronic myeloid leukemia in chronic phase

Dasatinib is a tyrosine kinase inhibitor licensed in the treatment of chronic myeloid leukemia (CML) known to exert immunomodulatory effects in vitro and in vivo.1 We report on 9 chronic phase CML patients who developed follicular lymphoid hyperplasia (FLH) apparently caused by dasatinib, an unreported adverse event related to this drug.

Patients received dasatinib at 100 mg (n = 7), at 80 mg (n = 1), or at 50 mg (n = 1) daily for chronic phase CML, either frontline as part of the Optimized Tyrosine kinase Inhibitors Monotherapy (OPTIM) dasatinib trial (EudraCT number 2008-006854-17)2 (n = 2) or after intolerance (n = 2), or suboptimal response/resistance (n = 5) to imatinib. From our first line patients included in the prospective academic OPTIM dasatinib trial, the estimated order of frequency of FLH might be 0.7% (2 of 291). Sex ratio of female to male was 3:6. Sokal scores were low (n = 2), intermediate (n = 1), and high (n = 6). Median age at FLH diagnosis was 52 years (range, 24-69 years).

All patients presented with progressive cervical lymph node enlargement after median treatment duration of 20 months (range, 9 to 35 months). One patient presented additionally inguinal lymph node enlargement. At the time of discovery, 8 patients were in complete cytogenetic response associated with a major molecular response (n = 3) or with a complete molecular response (n = 3). Clinical examination revealed no local or systemic infectious disease. Toxoplasmosis, viral and autoimmune disorders assessments failed to show any active disease. Tomodensitometry confirmed absence of additional localization. In 1 patient, nodes enlargement was associated with peripheral lymphocytosis related to an increase of natural killer cells and CD8+ T-cells, but not to B-cells, as previously described.1 All patients underwent a lymph node biopsy that revealed an FLH (Figure 1A), and an extramedullary blastic transformation of CML was ruled out. Lymph node immunostaining showed a follicular reactive phenotype CD10/bcl2 (see Figure 1B). Cytogenetic analysis of lymph node revealed in 1 patient as clonal abnormality (Figure 1C) without IGH/BCL2 rearrangement detected by standard fluorescence in situ hybridization (data not shown) and clonality assessment showed a DJ-JH rearrangement (Figure 1D). However, the frequency of rearrangement could be underestimated because clonality was searched only in some patients, but not all,

Figure 1. Example of follicular hyperplasia features in a patient. (A) At low power examination, the lymph node architecture is preserved with florid follicular hyperplasia. Large follicles show irregular borders, a prominent germinal center, and sometimes enlarged mantle zone (original magnification ×2.5). (B) Reactive germinal centers show a bcl2/bcl6/CD10 immunostaining pattern (original magnification ×2.5). (C) The karyotype of lymphadenopathy after G-banding was as follows: 46,XY.add(1)(q41),der(14)[1][1:14][q24;p32][8]/46XY[12]. Derivative chromosomes are marked by arrows. (D) Polymerase chain reaction heteroduplex analysis of incomplete Ig heavy chain (IGH) DH-JH rearrangement: detection of a slight homoduplex band (280 bp).
according to availability of material and techniques in each hospital. Philadelphia chromosome was undetectable, ruling out a localized lymphoid blast crisis of CML.

Dasatinib was discontinued in all patients, leading to a complete disappearance of node enlargement within a median time of 1 month (range, 15 days to 2 months). The majority of patients were challenged with nilotinib (n = 6), with 2 patients who remained free of tyrosine kinase inhibitor because of a long-lasting complete molecular response and 1 patient who underwent an allogeneic stem cell transplantation.

FLH is characterized with follicular centers hyperplasia related to B lymphocyte stimulation. Dasatinib is an inhibitor of the SRC family kinase. Lyn, an Src family protein, is expressed in B lymphocytes and is a regulator of B-cell antigen receptor via Akt/PKB overexpression was associated with pro-antigen receptor signaling was identified as a new mechanism in lymphoma and Akt/PKB overexpression was associated with progression of tumor in humans. Considering cytogenetic clonal abnormalities observed in 1 patient, malignant transformation into lymphoma cannot be eliminated. We recommend a systematic search for lymph node enlargement by physical examination in patients treated with dasatinib. A diagnosis of FLH should trigger dasatinib discontinuation.

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References


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