

LETTER TO THE EDITOR

## Hepatosplenic $\alpha\beta$ T-cell lymphoma arising after long-term azathioprine therapy successfully treated with allogeneic bone marrow transplant

Sandra Bašić Kinda<sup>1</sup>, Nadira Duraković<sup>1</sup>, Snježana Dotlić<sup>2</sup>, Ranka Serventi Seiwert<sup>1</sup>, Sanja Davidović Mrsić<sup>3</sup>, Klara Dubravčić<sup>4</sup> & Igor Aurer<sup>1</sup>

<sup>1</sup>Division of Hematology, Department of Internal Medicine, <sup>2</sup>Department of Pathology and Cytology, <sup>3</sup>Department of Pediatrics and <sup>4</sup>Clinical Institute of Laboratory Diagnosis, Clinical Hospital Center Zagreb and University School of Medicine, Zagreb, Croatia

Hepatosplenic T-cell lymphoma (HSTCL) is a rare entity characterized by thrombocytopenia, hepatosplenomegaly, systemic symptoms and no lymphadenopathy, occurring predominantly in young males. Lymphoma primarily involves spleen and liver, and has a typical immunophenotype (CD2+, CD3+, CD4–, CD5–, CD7+, CD8–) [1], commonly expressing NK-related antigens CD16 and CD56 [2]. Isochromosome 7q is frequently observed, sometimes accompanied by trisomy 8 [1,3]. Two subtypes are described: a more common form expressing  $\gamma\delta$  TCR chain and a rarer form expressing  $\alpha\beta$  TCR chain [3]. HSTCL has a distinctly aggressive course and rarely responds to conventional chemotherapy [1,3]. There is no recommended treatment, and the few patients that achieved long term survival had received allogeneic bone marrow transplantation (alloBMT).

Recently, there have been reports of HSTCL arising after long term therapy with thiopurines and anti-TNF therapy in young males with inflammatory bowel disease [4]. It is believed that thiopurine-induced damage, particularly damage specific to chromosome 7 previously shown in patients with rheumatologic diseases [5], and not anti-TNF therapy, is crucial for development of HSTCL in this patient population [4].

We report a case of a patient with history of Crohn's disease, treated with azathioprine for over 7 years. He presented with thrombocytopenia and splenomegaly, which were perceived as immune thrombocytopenia and treated with corticosteroids. Splenectomy was undertaken and histopathology report was not indicative of hematologic disease. As his symptoms evolved, he developed fever, elevated transaminases, persistent thrombocytopenia, and his general condition started to deteriorate. Re-evaluation was done at our institution: bone marrow biopsy was morphologically normal, but immunophenotyping revealed an increased population of CD2+ CD3+ CD4– CD7+ CD5– CD56+ T-cells. Liver biopsy confirmed diagnosis of hepatosplenic  $\alpha\beta$  T-cell lymphoma (Figure 1A). Upon re-review of histologic specimens, both bone marrow and spleen were found to be

infiltrated. Cytogenetic examination of bone marrow was normal, but FISH revealed duplication of 7q31 chromosome (Figure 1B).

Review of literature revealed there is no recommended potentially curative treatment for this disease, so treatment with asparaginase-containing high-dose chemotherapy (HOVON 70 protocol) was started. At the end of induction cycle his platelets and liver transaminases normalized. Patient continued treatment receiving consolidation, intensification and interphase according to the same protocol, until an unrelated bone marrow donor was identified.

Prior to BMT, re-staging showed disease to be in complete remission and FISH was negative. He received myeloablative conditioning consisting of high dose cyclophosphamide and total-body irradiation. Apart from one episode of febrile neutropenia and deep vein thrombosis, transplantation course was uneventful. On day +25 his bone marrow showed engraftment of all three lineages, 100% donor-derived. Patient was readmitted on day +55 for high fever, poor general condition and elevated liver transaminases; he was found to have Epstein Barr virus reactivation and treated with rituximab. No further complications occurred. Since patient showed no signs of GVHD cyclosporine was stopped at day 180. Regular check-up done 1 year post-transplant showed no signs of disease. Unfortunately, on day +381 he was readmitted because of sepsis. Beta-hemolytic *Streptococcus* was isolated from blood; he had rapidly progressing multi-organ failure and succumbed three days later. Post-mortem analysis showed no evidence of lymphoma.

So far, a wide range of treatment modalities have been used in treatment of HSTCL with modest results [1,3]. With reported median survival of 8 months, the only treatment that offers substantial chance for long term survival is BMT. To the best of our knowledge, this is fifth case of HS $\alpha\beta$ TCL that was treated with BMT [6–9] and the only one that received intensive remission induction chemotherapy that contained L-asparaginase. Of previously transplanted patients,

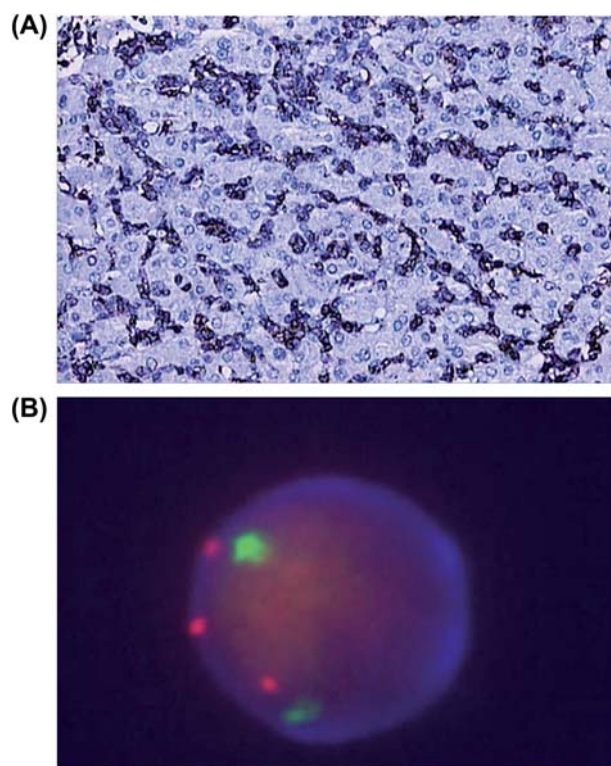


Figure 1. (A) Liver core biopsy, immunohistochemistry, magnification 200x: sinusoids are diffusely infiltrated with lymphatic cells staining positively with CD3. (B) Interphase FISH analysis with Vysis probe, locus specific identifier probe; LSI D7S522(7q31.1-31.3) orange / CEP 7(7p11.1-q11.1) green dual color probe.

3 were alive and well at the time of publication [7–9], while one patient who was transplanted with progressive disease succumbed 2 months after transplant [6]. Chemotherapy that patients received prior to transplantation varied significantly [8,9]. Particularly interesting is the case of a patient that received salvage therapy with alemtuzumab, to which he responded, and was able to proceed to BMT. Same patient relapsed after BMT and responded to DLI [7], which demonstrated the value of adoptive immunotherapeutic induction of GVL effect in the treatment of this disease [7]. Since no particular regimen was found to be superior in remission induction, we decided to treat our patient with intensive chemotherapy regimen containing L-asparaginase. We stipulated that addition of L-asparaginase would have a beneficial

effect based on encouraging results in treatment of extremely aggressive extranodal NK/T-cell lymphoma [10], taking into account that immunophenotype of our patient's lymphoma also expressed CD56.

We believe that patients with HSTCL should receive aggressive treatment, possibly containing L-asparaginase, with the aim to achieve complete remission, followed by alloBMT. Further cooperative studies are warranted in order to establish the best regimen for the treatment of patients with this rare disease.

**Potential conflict of interest:** Disclosure forms provided by the authors are available with the full text of this article at [www.informahealthcare.com/lal](http://www.informahealthcare.com/lal).

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