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SHORT COMMUNICATION

A rare case of hepatosplenic $\gamma\delta$ T-cell lymphoma expressing CD19 with ring chromosome 7 and trisomy 8

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Abstract

Hepatosplenic T-cell lymphoma (HSTL) is a rare subtype of peripheral T-cell lymphoma predominantly seen in young males. This disease presents with isolated hepatosplenomegaly and thrombocytopenia with sinusoidal infiltration of liver and sinusal infiltration of spleen. Immunophenotype shows positivity for CD3, CD7, TCR$\gamma\delta$ or TCR$\alpha\beta$, CD38 and double negative for CD4, CD8, TdT, CD5, and CD56. Isochromosome 7q with or without trisomy 8 is seen in HSTL. Recently, ring chromosome 7 has also been identified as a new abnormality. We describe the clinical, immunophenotypic and cytogenetic analysis in a 24-year-old woman. We present an unusual case of TCR$\gamma\delta$ positive T-cell lymphoma with aberrant expression of CD19, which is a B-cell lymphoid marker, with amplification of 7q region and subsequent formation of ring chromosome 7 and trisomy 8. This is the second case of HSTL, positive for CD19 and first case presenting with ring chromosome 7 and trisomy 8 in a CD19 positive HSTL which is a rare finding in T-cell lymphoma and needs to be explored further.

Keywords Hepatosplenic T-cell lymphoma, Aberrant expression of CD19, Cytogenetics, Amplification, Ring chromosome.

Introduction

Hepatosplenic T-cell lymphoma (HSTL) is a rare, clinically aggressive subtype of peripheral T-cell lymphoma accounting for less than 5% of all T-cell lymphomas [1], classified as a distinct clinico-pathological entity in the 2008 and 2017 WHO classification [2,3]. This disease predominantly affects young men and usually presents with isolated hepatosplenomegaly and thrombocytopenia. Typical features are sinusoidal infiltration of liver and sinusal infiltration of spleen [4]. The most frequent immunophenotype is CD2+, CD3+, CD4–, CD5–, CD7+/–, CD8-, CD16+/–, CD38+, and CD56+. Majority of cases express $\gamma\delta$ T-cell receptor, however, few cases have been reported expressing $\alpha\beta$ T-cell receptor. Isochromosome 7q with or without trisomy 8 is reported to be the primary cytogenetic abnormality in HSTL [5]. Recently, ring chromosome 7, a rare variant, has also been identified in HSTL [6–8]. Contribution of these aberrations to the pathogenesis of disease is still unknown. Various treatment modalities has been disappointing, with inconsistent response rates, high relapse rates and a short median survival [9]. We describe conventional cytogenetics (CC) and fluorescence in situ hybridization

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(FISH) study in a 24-year-old female diagnosed as hepatosplenic $\gamma\delta$ T-cell lymphoma with aberrant expression of CD19.

Materials and methods

Case report

A 24-year-old female was referred to Tata Memorial Hospital, Mumbai, India with pain in lower limbs, rashes and fever of 2-months duration. Ultrasonography revealed isolated hepatosplenomegaly and no lymphadenopathy. Her liver was enlarged 2 cm and spleen was enlarged 17 cm below coastal margin. Viral serology for hepatitis B and HIV was normal. Peripheral blood work-up revealed low haemoglobin of 6.8 g/dL, low white blood cell count of 3.17 $\times$ 10^9/L and low platelet count of 107 $\times$ 10^9/L with elevated lactate dehydrogenase level of 636 U/L. Morphological and immunophenotypic analysis on bone marrow was suggestive of hepatosplenic gamma-delta T-cell lymphoma diagnosed by presence of 88% atypical lymphocytes and positive for CD3, CD7, TCR$\gamma\delta$, and CD38, aberrant expression of CD19 (Fig. 1) and double negative for CD4, CD5, TdT, CD8, CD20, CD56, and cCD79a. Due to poor general condition, patient was put on supportive care and she passed away two months after the initial diagnosis due to disease related complications.

Conventional cytogenetic and FISH analysis

Conventional karyotyping was performed on unstimulated, direct and 24-h bone marrow cultures. GTG banded metaphases were analyzed and karyotyped as per ISCN 2016 [10]. FISH study was performed according to standard protocols on interphase nuclei using locus specific *CUTL1*: 7q22, D7S2419: 7q36, CEP 7 triple color probe (Kreatech Diagnostics, The Netherlands), CEP 8 DNA probe and sub-telomeric TelVysion Spectrum green labeled 7p probe (Vysis Abbott Molecular, Delkenheim, Germany). Hybridization was performed according to manufacturer's instructions. A total of 200 interphase cells were evaluated. Whole chromosome paint for 7 (Cytocell Ltd., Cambridge) was applied for further confirmation and ten metaphases were analyzed.

Results

Conventional karyotyping by GTG banding revealed clonal abnormalities of ring chromosome 7 with trisomy 8 resulting in an abnormal karyotype as 47,XX,r(7)(p13q36),+8 in 15 of 20 metaphases (Fig. 2(A)).

Interphase FISH with triple color LSI 7q22, 7q36, CEP 7 probe revealed presence of 2 copies of centromeric region of chromosome 7 with 6–7 copies of 7q22 region indicating amplification of 7q22 sequences and loss of terminal 7q36 region in 90% cells (Fig. 2(B)). Sub-telomeric 7p probe showed absence of one 7p signal indicating deletion. CEP 8 revealed three copies of chromosome 8 indicating trisomy 8 in 90% cells. Further analysis by metaphase-FISH with whole chromosome paint 7 revealed one normal copy of chromosome 7 and the other showed ring chromosome 7 (Fig. 2(C) and (D)).

Discussion

To the best of our knowledge, presence of ring chromosome 7 with trisomy 8 in an aberrant CD19 positive hepatosplenic $\gamma\delta$ T-cell lymphoma is a new finding and not yet reported in literature. HSTL is a rare disease with a highly aggressive clinical course mostly seen in young men. By conventional cytogenetics (CC) and fluorescence in situ hybridization (FISH) studies, HSTL have been characterized by the presence of an isochromosome 7q [i(7)(q10;q10)], an unbalanced structural abnormality in which the p arm gets deleted, q arm is duplicated and forms a mirror image. This abnormality occasionally appears as sole abnormality and may play a primary role in pathogenesis of the disease. Amplified 7q sequences indicate progression and have been seen during evolution of the disease [5]. The present case displayed common clinical, morphological and immunophenotypic features of HSTL except for aberrant expression of CD19. Cytogenetically, ring chromosome 7 was present with trisomy 8 which was confirmed by metaphase-FISH. Interphase-FISH with loci-specific 7q22, 7q36 and sub-telomeric 7p probe revealed amplification of 7q22 region probably causing excess of oncogenes, with loss of tumor suppressor genes; TCRγ and TCRβ gene present on 7p14.1 region and 7q34 region respectively. Trisomy 8 was an additional abnormality associated with disease progression. Review of literature showed six cases with ring chromosome 7, Shetty et al. [6] reported presence of ring chromosome 7 in a case of seven-year-old male patient by FISH studies. Similarly, Tamaska et al. [7] found ring chromosome 7, trisomy 8 and der(19) by conventional cytogenetics and confirmed it using LSI 7q31 and CEP 7 probes in a 62-year-old female patient. These patients carried typical immunophenotypic characteristics. However, to the best of our knowledge, ours is first case from India reporting r(7) with trisomy 8 in a case of HSTL expressing aberrant CD19 in a young female patient. Patkar et al. [8] has reported a case of HSTL with aberrant CD19 expression but cytogenetically could not confirm the abnormalities due to poor morphology of chromosomes, although gain 7q31 was found by FISH studies. Aberrant expression of CD19 is commonly detected in acute myeloid leukemia and has been described in only a single case of mature peripheral T-cell NHL and hypothesized that it may be due to expression of transcription factor B-cell specific activator protein (BSAP), encoded by *PAX5* gene [11]. Multiple copies of i(7q10) [5] or amplified 7q sequences [6,7] suggests that chromosome 7 carries critical genes for the development of this disease. Combined gene expression profiling and array-based comparative genomic hybridization (CGH) of several HSTL tumors showed downregulation of 7p genes, particularly *CYCS, IKZF1, HUS1* and *CBX3* and upregulation of 7q genes including putative oncogene *PTPN12* [12]. Ferreiro et al. [13] studied six HSTL tumors positive for i(7)(q10) including HSTL-derived cell line and three cases with r(7) using high resolution array CGH, hypothesized that loss of 7p22.1p14.1 is a critical pathogenetic event contributing to development of HSTL, whereas gain of 7q22.11q31.1 provides growth advantages and contributes to chemoresistance of the tumor.