De Novo Deletion 17p (del17p) in an Adult T-Cell Prolymphocytic Leukemia as a Rare Presentation

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Abstract: T-Cell Prolymphocytic leukemia is a rare and aggressive lymphoproliferative disease which is unresponsive to conventional chemotherapy. We present a case of 72 years old female hospitalized in July 2018 in National Institute of Blood diseases and BMT, Karachi, Pakistan, having lymphadenopathy, splenomegaly, and leukocytosis with lymphocytosis, thrombocytopenia and peripheral smear showed predominant population of mature looking lymphocytes. Immunophenotyping shows CD45 (+), CD3(+), CD4(+), CD5(+), ZAP70(+), CD38(*)*, CD25(*)* and negative CD19, CD20, CD10, CD11c, CD8, FMC, Kappa & Lambda and cytogenetics by FISH showed del17p53 in 35% of interphase nuclei. In patients of T-PLL, del 17 p53 has never been reported previously.

Keywords: del17p, T-cell, Prolymphocytic, Leukemia, Lymphoproliferative, CLL.

BACKGROUND

T-cell Prolymphocytic leukemia (T-PLL) is a rare mature T-cell lymphoproliferative disorder with post-thymic immunophenotype. T-PLL is characterized by an aggressive clinical course that is not responsive to conventional chemotherapy. Previously this disease was known as T-cell chronic lymphocytic leukemia (T-CLL), to avoid confusion with more indolent B-cell lymphoma, B-Cell Chronic lymphocytic leukemia (B-CLL); it is renamed as T-cell prolymphocytic leukemia (T-PLL) [1]. It presents at an advanced age and carries a dismal prognosis [2]. The incidence of T-Cell PLL is less than 5%. In general, the treatment outcome is favorable in B-cell CLL as compare to T-cell CLL.

In the peripheral blood there is usually a significant lymphocytosis, which often exceeds 100 x10⁹/L with more than 90% of these cells are circulating prolymphocytes. Thrombocytopenia and anemia are seen in half of the cases [3].

Most of T-PLLs shows mature post-thymic CD2+, CD3+, CD7+, CD4+, CD8− immunophenotypes, but cases with CD4+, CD8+ and CD4−, CD8+ are also frequently observed [4].

The role of del17p is relatively well documented in cases of B-cell CLL, but there is no such defined role in T-Cell PLL. The aim of this paper is to present a rare type of T-cell Prolymphocytic leukemia case with del17p which is nonresponsive to conventional chemotherapy and has an aggressive clinical course and shorter survival.

CASE PRESENTATION

A 72 years old woman, known case of Type-2 Diabetes Mellitus, presented to the hematology clinic with complaints of generalized weakness for 2 months. On physical examination, she had generalized lymphadenopathy along with moderate hepatosplenomegaly. Laboratory investigations showed Hemoglobin 11.8g/dl, total leucocyte count 199.45x10⁹/L, and a platelet count of 35x10⁹/L. Microscopic examination of peripheral smear showed absolute lymphocytosis of 93%, with predominant population of mature looking lymphocytes, medium in size and of round shape, having regular cellular margin with intermediate nuclear-cytoplasmic ratio and scanty amount of cytoplasm. Nuclear margins were intact with clumped chromatin pattern and inconspicuous nucleoli. Pleomorphic lymphoid cells (4.3%) suggesting a prolymphocytic variety were also present (Fig. 1.). Bone marrow was not done because of the general condition of patient.

Fig. (1). Peripheral Smear Showing Abnormal Mature Looking Lymphocytes.
Flow cytometric immunophenotyping found 85.7% lymphocytes (forward light scatter properties). These lymphocytes showed following findings: CD45 (+), CD3(+), CD4(+), CD5(+), ZAP70(+), CD38(+)*, CD25(+)* and negative CD19, CD20, CD10, CD11c, CD8, FMC, Kappa & Lambda. In addition, it showed 0.7% benign lymphocytes, 1.97% benign T-lymphocytes and 8.37% granulocytes and precursors. Molecular cytogenetics on peripheral blood by Fluorescence In-Situ Hybridization (FISH) showed del17p in 70 (35%) inter-phase nuclei whereas 130 cells (65%) showed normal signal pattern (Figs. 2, 3). Taking into account the clinical, morphological and immunophenotypic features, a diagnosis of “T-Cell Prolymphocytic Leukemia” was considered.

**Fig. (2).** Dot and Plot Representation of Immunophenotypical Markers.

**Fig. (3).** Detection of LSI p53 (17p13.1) Gene Deletion by Using FISH.

**DISCUSSION**

The chronic lymphoproliferative disorders (CLPDs) include a wide range of disease entities. With the detection of surface membrane markers by the use of immunological techniques, it became evident that the majority of CLPD were of B-cell origin. Less than 5% of the total chronic lymphoproliferative disorders that have been reported are of T-cell origin. These include Sézary syndrome/mycosis fungoides, large granular lymphocytic (LGL) leukemia (T-lymphoproliferative disorder), adult T-cell leukemia [human T-cell lymphotrophic virus-1 (HTLV-1) associated], and T-cell prolymphocytic leukemia (T-PLL). In the past neoplastic disorders of T-cell origins that are morphologic counterpart to B-cell chronic lymphocytic leukemia (B-CLL) has been described [5]. T-cell Prolymphocytic leukemia (T-PLL) was initially described in the 1970’s as a rare haematological malignancy with diverse characteristics and an aggressive clinical course [6-8]. T cell PLL affects individuals over 60 years of age with male preponderance. Massively enlarged spleen is usual; lymphadenopathy is frequent [9-11]. T-prolymphocytes contains a post-thymic (TdT−, CD1a−) T-cell phenotype (CD5+, CD2+, CD7+) with variable expression of CD4 and CD8 [9]. Membrane CD3 is not expressed in all the cases, although this is consistently present in the cytoplasm and expression of CD7 is strong, in contrast to other mature T-cell leukemias, in which this marker is often weakly positive or negative. There may be variable expression of CD25, CD38 and class II HLA-DR.

The TP53 tumor suppressor is a 393-aa transcription factor. In response to genotoxic stresses, p53 binds to specific DNA sequences and trans activates number of genes [12], therefore, arresting cell cycle, repairing damaged DNA, or inducing apoptosis as cell fates [13]. The p53 transactivity is regulated by posttranslational mechanisms such as phosphorylation, acetylation, and prolyl isomerization [14 -18], or by protein–protein interaction [19].

Genetic variations in the tumor suppressor gene TP53 contribute to human cancers in different ways. In most cancers somatic TP53 mutations are most frequent genetic alterations [20]. The antiproliferative role of p53 protein in response to various stresses and during physiological processes such as senescence makes it a primary target for inactivation in cancer [21]. The main modes of TP53 inactivation are single-base substitution and loss of alleles, with inactivation by viral or cellular proteins playing a major role in specific cancers [22]. Second, inheritance of a TP53 mutation causes predisposition to early-onset cancers including, carcinoma of breast, sarcomas, brain tumors, and carcinoma of adrenal glands, defining the Li-Fraumeni (LFS) and Li-Fraumeni-like (LFL) syndromes [23]. Third, TP53 is highly polymorphic in coding and noncoding regions and some of these polymorphisms
have been shown to increase cancer susceptibility and to modify cancer phenotypes in TP53 mutation carriers [24].

Somatic TP53 mutations occur in most of malignancies at rate from 38% – 50% in ovarian, esophageal, colorectal, head and neck, larynx, and lung cancers to about 5% in primary leukemia, sarcoma, carcinoma of testicles, malignant melanoma, and carcinoma of cervix. Mutations are more frequent in advanced stage or in cancer subtypes with aggressive behavior [25-27].

TP53 germline mutations are the underlying cause of LFS (Li-Fraumeni Syndrome), a familial clustering of early onset tumors including sarcomas, breast cancers, brain tumors, and adrenal cortical carcinomas [28, 29]. Other cancers include hematological malignancies, gastric, colorectal, and ovarian cancers, occurring at earlier ages than in the general population [30]. Rarer cancers associated with TP53 germline mutation are choroid plexus carcinoma or papilloma before the age of 15, Wilms’ tumor, and malignant phyllodes tumors [31, 32].

Mutant p53 proteins often accumulate in the nucleus of in situ and metastatic cancer cells, suggesting an oncogenic effect in addition to loss of wild-type suppressor function. TP53 mutation is a useful tumor marker to compare clonality of a tumor, for the follow-up of minimal residual disease, for comparison between primary and recurrent tumors, for tracing the origin of distant metastases and also help to identify early lesions at high risk of malignant evolution [33-35].

In literature search majority of reports of deletion 17p53 is observed in B-cell CLL and of all chromosomal abnormalities, deletion of 17p13 region of chromosome is prognostically least favorable in CLL. In CLL deletion (17p) is known as an independent predictor of poor outcome [36]. CLL patients harboring del (17p) are unresponsive to conventional chemotherapy regimens containing alkylating drugs and purine analogues [37]. Notably, current studies have shown that mutations in TP53 and del(17p), either alone or in combination, are predictive of poor prognosis in CLL in terms of short time to disease progression, short response duration, lack of response to therapy and short overall survival (OS).

According to the best of our knowledge, no case of del17p has been reported in T-cell PLL. We describe a De Novo case of T-PLL with del17p, the aberration was disease associated, as there were also cells detected without that rearrangements.

Prospective studies are needed to identify the striking association between del17p53 and T-PLL as reported here.

CONFLICT OF INTEREST
Declared none.

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REFERENCES
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