Case Report

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

Zara-tul-Ain Bashir[1,*], Saima Siddiqui[2], Jawwad Hassan[2], Tahir Sultan Shamsi[1]

[1]*Department of Clinical Hematology, National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan.*

[2]*Department of Immunology & Cytogenetics, National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan.*

Abstract: T-Cell Prolymphocytic leukemia is a rare and an agressive 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 del17 p53 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 x10^9/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 199.45x10^9/L, and a platelet count of 35x10^9/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.

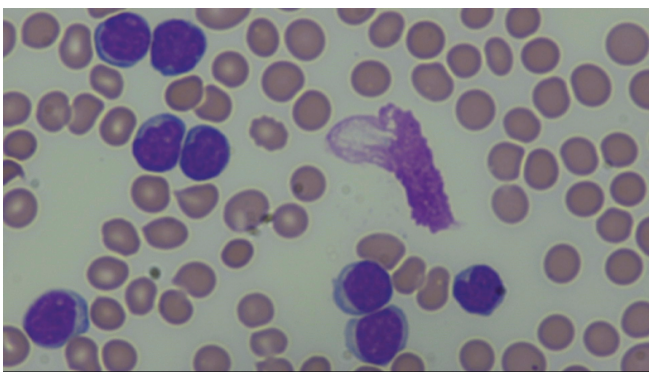

Fig. (1). Peripheral Smear Showing Abnormal Mature Looking Lymphocytes.

*Address correspondence to this author at the Department of Clinical Hematology, National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan. E-mail: zara_malik08@hotmail.com

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.

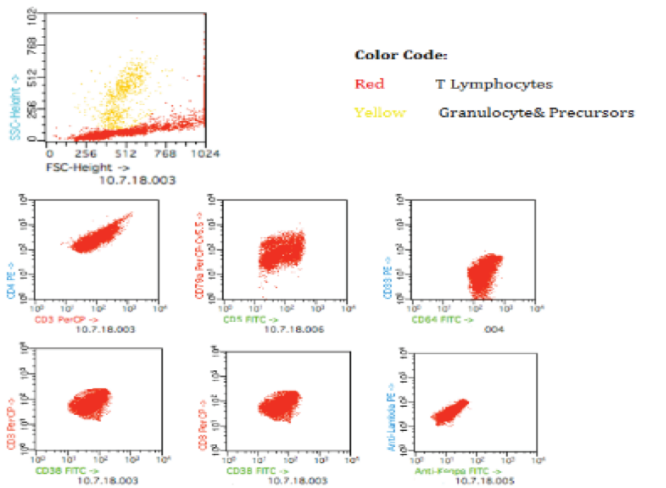

Fig. (2). Dot and Plot Representation of Immunophenotypical Markers.

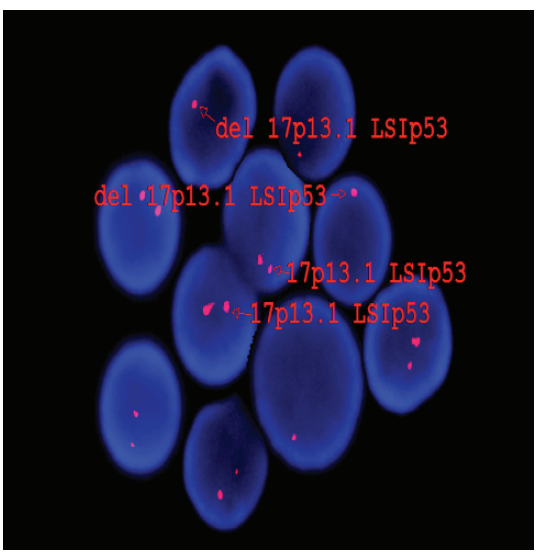

Fig. (3). Detection of LSI p53 (17p13.1) Gene Deletion by Using FISH.

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 Sezary syndrome/ mycosis fungoides, large granular lymphocytic (LGL) leukemia (T-y lymphoproliferative disorder), adult T-cell leukemia [human T-cell lymphotrophic virus-l (HTLV- 1) associated], and T-ceIl 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 ll 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 isomeration [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.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Delgado P, Starshak P, Rao N, Tirado CA. A comprehensive update on molecular and cytogenetic abnormalities in T-cell prolymphocytic leukemia (T-pll). J Assoc Genet Technol 2012; 38(4): 193-8.

[2] Vivekanandarajah A, Atallah JP, Gupta S. Case Report: T-cell prolymphocyticleukaemia (T-PLL): A rare disease with a grave prognosis. BMJ Case Rep 2013; 2013: bcr2013009808.

[3] Pawson R, Schulz TF, Matutes E, *et al*. The human T-cell lymphotropic viruses type 1/11 are not involved in T Prolymphocyticleukaemia and large granular lymphocytic leukaemia. Leukemia 1997; 11(8): 1305-11. DOI: 10.1038/sj.leu.2400725

[4] Dürig J, Bug S, Klein-Hitpass L, *et al*. Combined single nucleotide polymorphism-based genomic mapping and global gene expression profiling identifies novel chromosomal imbalances, mechanisms and candidate genes important in the pathogenesis of T-cell prolymphocytic leukemia with inv (14)(q11q32). Leukemia 2007; 21(10): 2153. DOI: 10.1038/sj.leu.2404877

[5] Hoyer JD, Ross CW, Li CY, *et al*. True T-cell chronic lymphocytic leukemia: a morphologic and immunophenotypic study of 25 cases [see comments]. Blood 1995; 86(3): 1163-9.

[6] Galton DA, Goldman JM, Wiltshaw E, *et al*. Prolymphocyticleukaemia. Br J Haematol 1974; 27(1): 7-23 DOI: 10.1111/j.1365-2141.1974.tb06769.x

[7] Catovsky D, Galetto J, Okos A, *et al*. Prolymphocyticleukaemia of B and T cell type. Lancet 1973; 2(7823): 232-4. DOI: 10.1016/S0140-6736(73)93135-8

[8] Swerdlow SH, Campo E, Harris N, *et al*. World health organization classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC 2008.

[9] Matutes E, Brito-Babapulle V, Swansbury J, *et al*. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. Blood 1991; 78(12): 3269-74.

[10] Matutes E, Brito-Babapulle V, Yuille M, *et al*. Prolymphocytic leukemia of B- and T-cell types. In: Cheson BD, Ed. Chronic Lymphoid Leukaemias. New York, NY: Marcel Dekker 2001; pp. 525-41.

[11] Planas AT, Zamkoff KW, Poiesz BJ, Kurec AS, Davey FR. T-cell prolymphocytic leukemia with a suppressor phenotype. Ann Clin Lab Sci 1983; 13(3): 193-200.

[12] El-Deiry WS, Kern SE, Pietenpol JA, Kinzler KW, Vogelstein B. Definition of a consensus binding site for p53. Nature Genet 1992; 1(1): 45. DOI: 10.1038/ng0492-45

[13] El-Deiry WS. Regulation of p53 downstream genes. In: Seminars in Cancer Biology. USA: Academic Press 1998; Vol 8, no. 5: pp. 345-57.

[14] Prives C, Hall PA. The p53 pathway. J Pathol 1999; 187(1): 112-26. DOI:10.1002/(SICI)1096-9896(199901)187:1<112::AID-PATH250>3.0.CO;2-3

[15] Oda K, Arakawa H, Tanaka T, *et al*. p53AIP1, a potential mediator of p53-dependent apoptosis, and its regulation by Ser-46-phosphorylated p53. Cell 2000; 102(6): 849-62. DOI: 10.1016/S0092-8674(00)00073-8

[16] Barlev NA, Liu L, Chehab NH, *et al*. Acetylation of p53 activates transcription through recruitment of coactivators/histone acetyltransferases. Mol Cell 2001; 8(6): 1243-54. DOI: 10.1016/S1097-2765(01)00414-2

[17] Zheng H, You H, Zhou XZ, *et al*. The prolyl isomerase Pin1 is a regulator of p53 in genotoxic response. Nature 2002; 419(6909): 849. DOI: 10.1038/nature01116

[18] Zacchi P, Gostissa M, Uchida T, *et al*. The prolyl isomerase Pin1 reveals a mechanism to control p53 functions after genotoxic insults. Springer Nature; 2002;419(6909): 853–7. DOI: 10.1038/nature01120

[19] Samuels-Lev Y, O'Connor DJ, Bergamaschi D, *et al*. ASPP proteins specifically stimulate the apoptotic function of p53. Mol Cell 2001; 8(4): 781-94. DOI: 10.1016/S1097-2765(01)00367-7

[20] Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. Science 1991; 53(5015): 49-53. DOI: 10.1126/science.1905840

[21] 21Levine AJ. p53, the cellular gatekeeper for growth and division. Cell 1997; 88(3): 323-31. DOI: 10.1016/S0092-8674(00)81871-1

[22] Tommasino M, Accardi R, Caldeira S, *et al*. The role of TP53 in Cervical carcinogenesis. Hum Mutat 2003; 21(3): 307-12. DOI: 10.1002/humu.10178

[23] Li FP, Fraumeni JFJ, Mulvihill JJ, *et al*. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988; 48: 5358-62.

[24] Whibley C, Pharoah PD, Hollstein M. p53 polymorphisms: Cancer implications. Nat Rev Cancer 2009; 9(2): 95. DOI: 10.1038/nrc2584

[25] Wang Y, Helland Å, Holm R, *et al*. TP53 mutations in early-stage ovarian carcinoma, relation to long-term survival. Br J Cancer 2004; 90(3): 678. DOI: 10.1038/sj.bjc.6601537

[26] Wang Y, Kringen P, Kristensen GB, *et al*. Effect of the codon 72 polymorphism (c. 215G> C, p. Arg72Pro) in combination with somatic sequence variants in the TP53 gene on survival in patients with advanced ovarian carcinoma. Hum Mutat 2004; 24(1): 21-34. DOI: 10.1002/humu.20055

[27] ngerød A, Zhao H, Borgan Ø, *et al*. TP53 mutation status and gene expression profiles are powerful prognostic markers of breast cancer. Breast Cancer Res 2007; 9(3): R30.

[28] Li FP, Fraumeni JF, Mulvihill JJ, *et al*. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988; 48(18): 5358-62.

[29] Malkin D, Li FP, Strong LC, *et al.* Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990; 250(4985): 1233-8. DOI: 10.1126/science.1978757

[30] Olivier M, Goldgar DE, Sodha N, *et al.* Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res 2003; 63(20): 6643-50.

[31] Birch JM, Alston RD, McNally RJ, *et al*. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene 2001; 20: 4621-8. DOI: 10.1038/sj.onc.1204621

[32] Gonzalez KD, Noltner KA, Buzin CH, *et al*. Beyond Li-Fraumeni syndrome: Clinical characteristics of families with p53 germline mutations. J Clin Oncol 2009; 27(8): 1250-6. DOI: 10.1200/JCO.2008.16.6959

[33] Dix BR, Robbins PD, Spagnolo DV, Padovan GL, House AK, Iacopetta BJ. Clonal analysis of colorectal tumors using K-ras and p53 gene mutations as markers. Diagn Mol Pathol 1995; 4(4): 261-5. DOI: 10.1097/00019606-199512000-00006

[34] Franklin WA, Gazdar AF, Haney J, *et al*. Widely dispersed p53 mutation in respiratory epithelium. A novel mechanism for field carcinogenesis. J Clin Investig 1997; 100(8): 2133-7. DOI: 10.1172/JCI119748

[35] Montesano R, Hainaut P. Molecular precursor lesions in oesophageal cancer. Cancer Surveys 1998; 32: 53-68.

[36] El Rouby S, Thomas A, Costin D, *et al*. p53 gene mutation in B-cell chronic lymphocytic leukemia is associated with drug resistance and is independent of MDR1/MDR3 gene expression. Blood 1993; 82(11): 3452-9.

[37] Grever MR, Lucas DM, Dewald GW, *et al*. Comprehensive assessment of genetic and molecular features predicting outcome in patients with chronic lymphocytic leukemia: Results from the US Intergroup Phase III Trial E2997. J Clin Oncol 2007; 25(7): 799-804. DOI: 10.1200/JCO.2006.08.3089

Received: September 3, 2018 Revised: November 20, 2018 Accepted: November 23, 2018