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RESEARCH ARTICLE

CD5-negative, CD10-negative small B-cell leukemia: variant of chronic lymphocytic leukemia or a distinct entity?

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Abstract

75 yrs female presenting with 3 months duration of anemia, fever ,bony pains and loss of appetite with CBC revealing Hb. 6.6g/dl, TLC 5.0 x 10^9 /L, DLC N55, L32, and M8. Platelets 094x10^9 /L. PBF showed scanty number of smudge cells and no roulex formation. Bone marrow aspiration and imprints showed markedly hyper cellular marrow with 80% mature lymphocytes. The Plasma cells were (3.5%). Trephine biopsy also showed hypercellular marrow with infiltration by lymphomononuclear cells. Serum electrophoresis showed M-spike while as markers were negative for CD 5, CD 10, Cyclin D, and Bcl 2 was immunoreactive in all hematopoietic cells. Patient was treated with CVP regimen and went in remission and is currently following with normal clinical examination and normal CBC. We strongly believe that this could be a variant of chronic lymphocytic leukemia with CD 5, CD10 negative markers.

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INTRODUCTION

75 years female known case of hypertension, subclinical hypothyroidism on levothyroxine 50 µg daily was evaluated outside SKIMS from April 16th 2012 to April 21st 2012 for symptomatic anemia,fever and bony pains of 3 months duration without any history of bleeding from any site. This was associated with loss of appetite. Physical

examination of the patient showed pallor, single right axillary lymph node 1 x 1.5 cms firm smooth and non tender. There was no organomegaly.
Investigations revealed, CBC Hb. 6.6g/dl, TLC 5.0 x 10^9 /L, DLC N55, L32, and M8. Platelets 094x10^9 /L, MCV 101.9fL, MCH 31.9 pg, MCHC 31.3g/dl. PBF showed scanty number of smudge cells and no roulex formation. Serum chemistry revealed blood glucose (random) 175 mg/dl, bilirubin of 0.63 mg/dl, ALT 17 u/l, ALP 253 u/l, TP 9.3 g/dl, alb 3.02 g/dl, globulin 6.2, Urea 28 mg/dl, creatinine 0.9 mg/dl and LDH 221 u/l.
Chest X ray was normal and did not show any lytic lesion.
Skeletal survey – normal, no lytic lesion seen
Serum electrophoresis: monoclonal gammapathy (M-spike) seen in beta globulin.
Bone marrow aspiration and imprints showed markedly hyper cellular marrow. The marrow was almost completely replaced by lymphocytes (80%). Plasma cells were (3.5%). The rest of the cells were normal myeloid and erythroid cells. Megakaryocytes were rarely seen.
H & E from trephine biopsy shows high cellular marrow with infiltration by lymphomononuclear cells. Normal marrow tissue markedly depleted.
CD markers were CD2- 4.70%, CD3- 3.40%, CD4- 4.10%, CD5- 13.10%, CD8- 3.8%,CD13- 4.60%, CD16- 3.20%, CD23- 4.80% , CD19- 88.40%, CD20- 92.80%, CD22- 82.50%, CD23- 4.80%, CD25- 30.30%, FMC-7 68.20%, sIgM 90.60%, Kappa 95.30%, Lambda 4.40%, CD103- 0.50%, CD10- 0.30%, CD 45- 9.90%, HLA DR- 91.00%, CD11c- 0.90%, CD56- 3.5%. Gated lymphocytes were highly positive for CD19, kappa, CD 20, sIgM, FMC-7, CD22, CD45 and HLADR. Moderately positive for CD25 and negative for CD3, CD4, CD8, CD13, CD16, CD5,CD103, CD10, Lambda, CD 2,CD 23,CD 11c,CD56.
CD19 gated cells were 83.6 % positive for CD38 and 0.4 % positive for ZAP-70
Serum and urine electrophoresis – M band seen in serum: urine no M band seen.
Immunoglobulin quantification Ig G 17.3g/l (reference range 7.0 – 16.0), Ig M 9.25g/l (reference range 0.4-2.4), IgA 1.21g/l (0.7 – 4.0)
Bcl2- immunoreactive in all hematopoietic cells.
Cyclin D – non immunoreactive.
With this back ground patient was diagnosed as CD5 negative CLL and was started on CVP (injection Cyclophosphamide 750 mg /m^2 d1, injection Vincristine (VCR) 1.4 mg /m^2 (max 2 mg), tab Prednisolone 60 mg /m^2 d1 to d5. On 2nd cycle of CVP injection VCR was replaced with injection Vinblastine as patient developed VCR induced peripheral sensory neuropathy. Currently patient has received 6th cycle of CVP with normal physical examination with and normal CBC.

Discussion.

Chronic lymphocytic leukemia (CLL) is a neoplastic disease characterized by accumulation of small, mature-appearing lymphocytes in blood, marrow and lymphoid tissues. CLL is the most prevalent leukemia in western societies and very uncommon in Eastern Asia. The age adjusted rate of CLL in the United States is 4.2/100,000 persons as determined by the international agency for Research on cancer of the World health organization. In 98% of the patients, the disease is of the B-lineage; less than 2 % of patients have T-cell lineage leukemia.

Chronic lymphocytic leukemia is the most common type of leukemia in the United States and Europe, constituting about 30% of all leukemias and 80% of chronic lymphoproliferative disorders (1). Further, it is the most common form of a heterogeneous group of small “chronic “ B-cell lymphoproliferative disorders (SBLPD) which also encompass prolymphocytic leukemia (PLL), hairy cell leukemia (HCL), and leukemic phase of non-Hodgkin’s lymphoma (NHL). The latter category includes follicular (FL), mantle cell (MCL), marginal-zone (MZL), and lymphoplasmacytic lymphoma (LPL), as well as small lymphocytic lymphoma (SLL), which is essentially equalent to CLL. Immunophenotypic (IP) analysis is germane to the distinction of these entities, with the increasing use of flow cytometry for the evaluation of such cases leading to greater diagnostic precision and accuracy. For example, CD 5 usually present in a minor subset of normal B cells is characteristically only expressed by CLL and MCL, thereby distinguishing these entities from other SBLPD. However, several recent studies of CLL have identified a subset of ‘CD5-negative CLLS. (2,3,4)

A number of studies have used the term “CD5-negative CLL” which reportedly constitute 0% to 36% of CLL (2, 3, 4). While this terminology is intellectually and biologically unsatisfying, most of these CD5-negative CLLs can be further sub classified in to other categories such as PLL, HCL, LPL, or the leukemic phase of non-Hodgkin’s lymphoma. However, only rare cases of CD5-negative CLL are reported to represent marginal-zone lymphoma in leukemic phase (5).

There has been a tendency to “lump” together CD5-negative CLL, such cases show sufficiently diverse features with variable expression of different markers, including inappropriate inclusion of disparate entities. Generally, such cases have a somewhat inferior prognosis when compared with “typical” CLL (6,7). However, it has also been demonstrated [6] that although CD5-negative CLL patients had borderline shorter survival and higher Rai stage than the CD5-positive patients, the only factor that significantly affected the prognosis was the density of sIg, with bright fluorescence being associated with a poorer prognosis. The adverse prognostic effect of high-density sIg in this group of CD5-negative CLL was also recognized in other studies (8, 9)

Immunophenotypic analysis is required to separate the biologically and clinically heterogeneous SBLPD from one another (10). Quite specific Immunophenotypic profiles, together with the clinical, morphological and genetic features, are integral to the precise diagnosis. Accordingly, CLL/SLL is essentially defined by a rather characteristic antigenic profile, i.e., co expression of CD5 and CD23 monoclonal B cells together with a diminution in the density of expression of number of other antigens, such as CD20, and CD79b sIg.

There is no “classic” IP profile of MZL as is the case for other SBLPDs. The cells express as the B-cells antigen but typically not CD5 or CD10. CD11c, CD23 and CD25 are usually variable. Given the current absence of a “defining” IP, the recently characterized cytogenic and molecular genetic findings are more likely to assume a central role in refining the diagnosis of these diseases. These include trisomy 3, t(11;18) and t(1;14) .(11,12,13)

However, cytogenetics was not informative, and exhaustion of material precluded a molecular evaluation of possible AP12/MLT and IgH/BCL-10 fusions.

There has been case report of CD5 negative CLL with indolent clinical course and autoimmune thrombocytopenia successfully treated with rituximab. Okamoto M et al. CD5-negative chronic lymphocytic leukemia with indolent clinical course and autoimmune thrombocytopenia successfully treated with rituximab; Am J Hematol. 2004 Dec;77(4):413-5

Even when various pathology, laboratory, clinical and even genetic findings may suggest a LPL or MZL, the absence of disease – specific FCIP expression pattern and the absence of disease specific genetic abnormality makes it challenging to make an unequivocal and definitive diagnosis of LPL or MZL solely on blood and marrow studies without a lymph node or tissue biopsy. (14)

In the last few years, one of the progresses in the study of CLL is the flow cytometric documentation of monoclonal B cells in a small number of healthy individuals. This has been called monoclonal B cell lymphocytosis (MBL). Of ten the cells in the MBL are CD 5 positive (termed CLL like cells). In addition to the reported 3.5 % prevalence of the presence of CLL like cells in a study of 910 outpatients over 40 years old, different prevalence rates of MBL and non CLL like clones have been reported. (15)

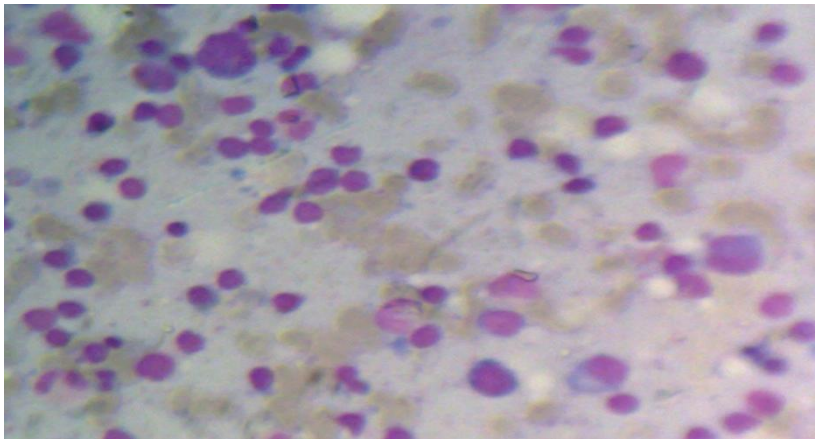

Fig.1 Mature lymphocytes (40X)

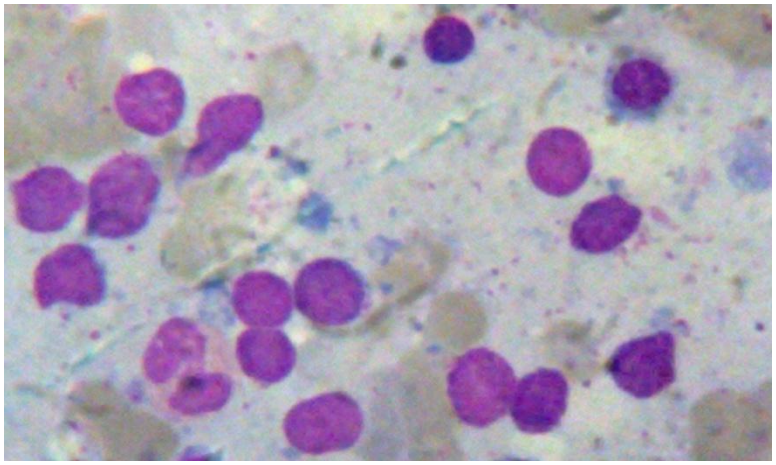

Fig.2 Mature lymphocytes (100X)

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