

Microcellular Variant of T-Prolymphocytic Leukemia Mimicking CLL

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Abstract

61-year-old female was referred to our center for management of progressing chronic lymphocytic leukemia (B-CLL), diagnosed 4 years ago based upon lymphocytosis and smudge cells present on peripheral blood smear. At initial assessment she had erythematous papulomatous skin rash, hepatosplenomegaly, diffuse lymphadenopathy, pleural effusions. Peripheral blood (PB) showed anemia (hemoglobin 110 g/L, mean corpuscular volume 101fL), elevated white blood cell count ($199 \times 10^9/\text{mL}$) with lymphocytosis. Bone marrow examination revealed interstitial and intra-sinusoidal marrow infiltration with small to intermediate size mature lymphocytes with minimal cytoplasm, condensed chromatin and indistinct nucleoli. No cells with large nucleoli typical of prolymphocytes were seen. Cells were positive for CD2/3/4/5/7, negative for CD20/23/8, had normal female karyotype. B-cells appeared exceedingly rare. Skin biopsy and pleural fluid cytology showed similar findings. Based on morphology and immunohistochemistry a provisional diagnosis of mature T-cell leukemia/lymphoma was made. Because of the discordance between laboratory and clinical findings, additional investigations were requested, which showed that the lymphoma cells were positive for TCL-1, CD30. The diagnosis was revised to T-cell prolymphocytic leukemia (T-PLL), small cell variant, without evidence of previously diagnosed B-CLL.

Treatment/prognosis of B-CLL and T-PLL differ significantly. PB lymphocytosis should not be assumed as CLL but confirmed by flow cytometric evaluation. Diagnosis of prolymphocytic leukemia should be made based on combination of clinical, morphological and immunophenotypic features.

Keywords: T-Prolymphocytic Leukemia (T-PLL); Lymphocytosis; Chronic Lymphocytic Leukemia (CLL); Smudge Cells

Introduction

A 61-year-old female was referred to our cancer center for progressing chronic lymphocytic leukemia (CLL), diagnosed four years ago elsewhere. Until recently she had an indolent course, but over the last two months she had rapidly increasing lymphocytosis and generalized skin rash. At initial assessment she had ECOG status 1, normal respiratory and cardiovascular exams, generalized diffuse lymphadenopathy, limited erythematous papulomatous skin rash, and mild hepatosplenomegaly. Peripheral blood (PB) investigation revealed mild anemia (Hb 110 g/L, MCV 101fL), lymphocytosis ($191 \times 10^9/\text{mL}$) and few smudge cells. PB lymphocytes were small to intermediate size with minimal cytoplasm, condensed chromatin and indistinct nucleoli (Figure 1A). Preliminary diagnosis of CLL was made and original flow cytometry (FC) report was requested. Skin lesion was biopsied, and staging computer tomography (CT) scans were arranged. Since the patient was asymptomatic, we put her on active surveillance.

Within two weeks her condition deteriorated rapidly and she was admitted with progressive fatigue, ascites, and dyspnea secondary to large pleural effusions. Her lymphocytosis increased to $303 \times 10^9/\text{mL}$. CT abdomen/pelvis/chest confirmed lymphadenopathy above and below diaphragm, with the largest lymph node measuring 3 cm. Transformation into aggressive lymphoproliferative malignancy (LPM) was suspected and she underwent bone marrow aspiration and biopsy. While waiting for the results of the investigations she received a short course of prednisone with no success.

Bone marrow examination revealed interstitial and intrasinusoidal marrow infiltration with small to intermediate size lymphocytes with

minimal cytoplasm, condensed chromatin and indistinct nucleoli (Figure 1B). No cells with large nucleoli typical of prolymphocytes were seen. Cells were positive for markers CD2/3/4/5/7, negative for CD20/23/8 (Figure 1C; CD3 immunostain), and had normal female karyotype. B-cells appeared exceedingly rare. Skin biopsy (Figure 1D) and pleural fluid analysis showed similar findings. Based on morphology and immunohistochemistry a provisional diagnosis of mature T-cell leukemia/lymphoma was considered. She started chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), however her condition deteriorated after the first cycle. She remained in-patient, required chest tube with ongoing drainage and recurrent paracentesis, and skin rash progressed to approximately 75% of her body surface area.

Because of discordance between laboratory and clinical findings further investigations were requested. These showed the lymphoma cells were positive for TCL-1 and CD30. The diagnosis was revised to T-cell prolymphocytic leukemia (T-PLL), small cell variant. While reviewing patient's original data we realized that no FC from PB was done originally. B-CLL had been incorrectly diagnosed based solely on lymphocytosis and presence of smudge cells in PB.

Treatment with Alemtuzumab, anti-CD52 antibody, was initiated and within 2 weeks she reached complete remission with complete resolution of symptoms, lymphadenopathy and skin rash. Her lymphocyte count returned to normal, hemoglobin and platelet count improved. She was referred to the allogeneic bone marrow transplantation (Allo-SCT).

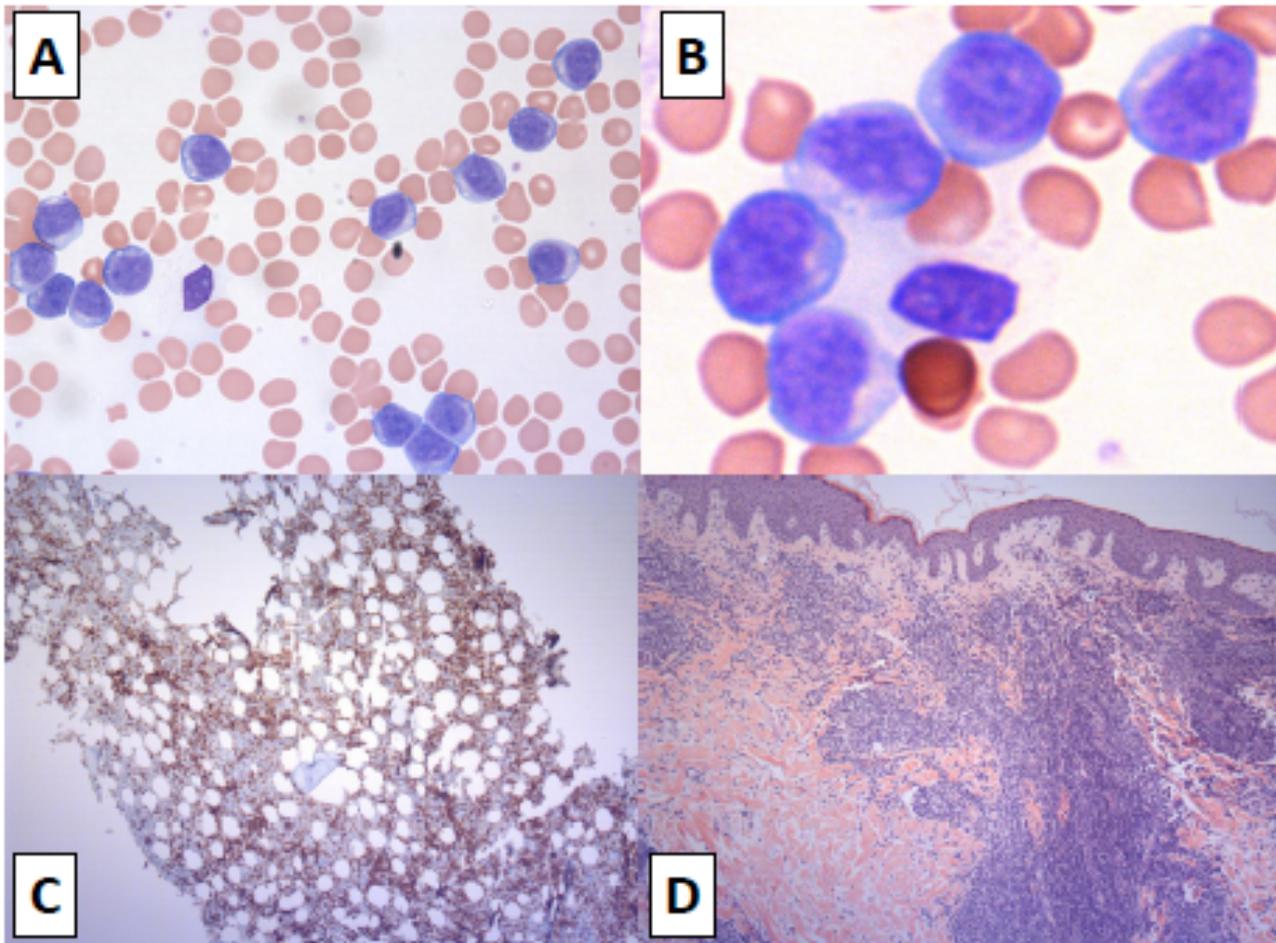


Figure 1: (A) Lymphocytes in peripheral blood, objective $\times 40$; (B) Lymphocytes in bone marrow, objective $\times 60$; (C) Immunostaining for CD3, objective $\times 20$; (D) Skin biopsy, objective $\times 10$

Discussion

There are several teaching points to be discussed in management of such patients.

Presence of smudge cells in PB is suggestive but is not diagnostic for CLL

Smudge cells (SC), also known as “basket cells” or “Gumprecht cells”, are often reported in PB smears in patients with lymphocytosis. SCs are remnants of cells that lack any identifiable cytoplasmic membrane or nuclear structure. Blasts and lymphoid cells are fragile and crush easily with mechanical pressure during the PB smear processing, resulting in SC [1]. SC is not unique to CLL, but is seen more frequently and in higher numbers in CLL than in other conditions, both neoplastic and reactive. SC of non-lymphoid origin can also be seen in degenerating samples. Normal specimens may contain 0.01% of SC, in patients with severe infections/burns 0.1 to 0.3%, in acute leukemia’s 1 to 3%, and in CLL up to 20% or higher. Percentage of SC in PB smears is not helpful as a morphologic finding for the differentiation between CLL and other B-cell malignancies [2] but may reflect burden of the disease in patients with confirmed, early stage CLL. Presence of more than 30% SC was associated with shorter median progression-free period compared with patients who had less than 30% SC [3].

PB lymphocytosis should not be assumed as CLL, but investigated by morphology on PB smear and flow cytometry

In addition to acute and chronic leukemias, including T-PLL, there are several LPM presenting with different degree of PB lymphocytosis (Table 1). Overall frequency of PB lymphocytosis in LPM, excluding chronic leukemia, is almost 30% as shown by a combination of morphology and flow cytometry [4]. T-PLL is usually associated with marked lymphocytosis $>100,000/\text{mL}$. A half of the patients present with absolute lymphocyte count $>200,000/\text{mL}$ [5]. T-prolymphocytes are usually easy to recognize by morphology: small to medium-sized lymphoid cells with non-granular basophilic cytoplasm, round, oval or markedly irregular nuclei and a visible nucleolus. However, in 25% of cases cells are small with indistinct nucleolus, called “small cell T-PLL variant” [6].

In addition to blood smear review PB lymphocytosis should be evaluated by FC for presence and absence of specific antigens (immunophenotype) of individual cells. In the assessment for LPM FC provides information about cell lineages (T-/B- or NK- lymphoid cells), determination of maturity (mature T/B-lymphoid cells vs blasts), detection and documentation of abnormal cell phenotype (immunoglobulin light chain class restriction and aberrant antigen expression) and level of antigen expression (intensity of staining by fluorochrome labeled antibodies) [7]. Immunophenotype for classical and small cell variant T-PLL is identical.

Type of LPM	Percentage of PB involvement	Degree of lymphocytosis	Specific morphological features	Most common markers
Chronic lymphocytic leukemia	100	variable, usually increases with disease progression	small lymphocytes with clumped chromatin and scanty cytoplasm	weak CD20, CD5+, CD23+
Splenic marginal zone lymphoma	80	moderate	small to medium-sized villous lymphocytes with abundant cytoplasm	variable B-cell phenotype
Mantle cell lymphoma	48	common; some patients have marked, mimicking PLL	small to medium sized cells (centrocyte-like)	variable phenotype; Cyclin D1
Diffuse large B-cell lymphoma	32	mild to moderate	large lymphoid cells, diffuse growth pattern	variable, B-cell phenotype
Follicular lymphoma	20	mild	Small to medium size, angulated, elongated and cleaved nuclei	BCL-2+, BCL-6+, CD10+, CD5-
Lymphoplasmacytic lymphoma	10	mild, lower than in CLL	small cells with plasmacytic differentiation	phenotype not typical for CLL, often CD23(-),
T-prolymphocytic leukemia	100	>100,000/mcl	markedly irregular nuclei and a visible nucleolus	CD2+, CD3+, CD52+, TCL-1+
T-large granular lymphocytic leukemia	100	2-20,000/mcl	large lymphocytes with abundant cytoplasm and granules	CD3, CD8, T-cell receptor Alpha/beta
Hairy cell leukemia	variable, from absent to leukemic presentation	usually mild, except HCL variant, presents with marked lymphocytosis (>50,000/mcl)	small to medium-sized cells with pale blue, abundant cytoplasm with circumferential "hairy projections"	CD20 (b)+, CD22 (b)+, CD11c (b)+, CD25+, CD103+, slg (i), CD123+

Note: LPM=lymphoproliferative malignancy; PB= peripheral blood; CD = cluster of differentiation; mcl=microliter; CLL= chronic lymphocytic leukemia

Table 1: Most common lymphoproliferative malignancies presenting with peripheral lymphocytosis

Type of LPM	Lymphadenopathy	Splenomegaly	Fatigue	Other/Specific features
Chronic lymphocytic leukemia	variable degree	variable	yes	AIHA, ITP
Splenic marginal zone lymphoma	rare	massive	prominent	AIHA, ITP
Mantle Cell Lymphoma	common, variable degree	common	unusual	extranodal sites: GI tract, Waldeyer ring
Diffuse large B-cell lymphoma	common	rare	unusual	40% extranodal sites at presentation
Follicular lymphoma	almost universally	rare	unusual	widespread at diagnosis, extranodal sites common
Lymphoplasmacytic lymphoma	15-30%, mild to moderate	15-30%, non-massive	usual	hyperviscosity ~ 30%, presence of paraprotein (IgM, IgG)
T-prolymphocytic leukemia	generalized, non-massive	common, usually moderate	variable	skin infiltrates, pleural effusions
T-large granular lymphocytic leukemia	very rare	common: usually moderate	unusual	severe neutropenia; associated with rheumatoid arthritis
Hairy cell leukemia	rare	common, massive	severe	pancytopenia

Note: AIHA= Autoimmune anemia, ITP= Autoimmune thrombocytopenia

Table 2: Clinical features of lymphoproliferative malignancies presented with peripheral lymphocytosis

Diagnosis of T-PLL requires matching of both clinical and pathological findings

Clinical features of LPM presenting with PB lymphocytosis are presented in table 2. In contrast to other LPMs, T-PLL typically presents as an aggressive disease with a median survival of usually less than 1 year. Often, multi-organ involvement with non-bulky lymphadenopathy is presented early at diagnosis. Unusual in B-CLL, but common in T-PLL features

include skin infiltration, nodular, macropapular rash, erythroderma, and less frequently serous effusions, mainly pleural [8]. Anemia and thrombocytopenia are common.

Approximately 15% of patients may be asymptomatic at diagnosis, and this "indolent" phase can persist for a variable length of time. Such cases may show an accelerated course after 2-3 years and in rare cases may extend to several years [9]. Therefore, diagnosis of T-PLL should be made based on combination of clinical presentation, morphological

and immunophenotypic features by FC. T-PLL is usually resistant to conventional chemotherapy and can be rapidly fatal if not treated properly, thus making a correct diagnosis essential. As in our patient the clinical presentation was not consistent with B-CLL or peripheral T-cell lymphoma, therefore we pursued further laboratory diagnostic work-up. When the correct diagnosis of T-PLL was made, we switched therapy from CHOP to alemtuzumab and the patient's condition improved quickly.

Management of T-PLL differs from other LPMs with PB lymphocytosis

Patients with asymptomatic lymphocytosis that is stable or only slowly progressing could be on active surveillance. Since progression may occur rapidly, we suggest referral of T-PLL patients to a cancer center shortly after diagnosis. T-PLL patients should be monitored more frequently than patients with B-CLL. Thus, if needed, treatment should be initiated as early as possible. Debulking therapy with steroids has no or very limited effect in T-PLL. The best treatment is alemtuzumab, and where possible followed by consolidation with allogeneic stem transplant (Allo-SCT). We recommend an early referral to Allo-SCT team, allowing time to identify a suitable donor if Allo-SCT is planned and avoid delays once treatment is initiated.

Alemtuzumab is a humanized IgG1 antibody, which targets the CD52 antigen highly expressed on normal and malignant T- and B-lymphocytes, monocytes, and at particularly high density on T-PLL, but not on hematopoietic stem cells [10]. Single agent Alemtuzumab is efficient in T-PLL with response rate over 90% and better tolerated in T-PLL population with 4-fold fewer infectious complications as compared to relapsed CLL patient group [8]. Infection prophylaxis for *Pneumocystis jirovecii* and herpes viruses, and regular monitoring for cytomegalovirus reactivation help to minimize serious infections. Sequential chemoimmunotherapy based on fludarabine, mitoxantrone and cyclophosphamide induction followed by alemtuzumab consolidation (FCM+A) also seems to offer an alternative to alemtuzumab alone [11]. Bendamustine is an original alkylating agent that shows only partial cross-resistance with other DNA-binding anticancer agents and no cross-resistance with other alkylating agents. Bendamustine is widely used in the treatment of indolent B-cell lymphomas, including CLL. Recent study of bendamustine showed its efficacy and safety in T-PLL, particularly in patients who are refractory to alemtuzumab [12].

In conclusion, PB smudge cells and lymphocytosis are not diagnostic for CLL, but should be further investigated by morphology review and FC. T-PLL is a rare, aggressive disease with unique clinical presentation, laboratory features and requires special management.

Competing Interest

None declared.

The authors have obtained patient consent.

Contributors

Rouslan Kotchetkov collected and interpreted clinical data, performed review of the literature, drafted and revised the manuscript. Russell Price acquired and interpreted pathology images for the publication, and revised the manuscript. All the authors approved the final version to be published and agreed to act as guarantors of the work.

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