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T Prolymphocytic Leukemia, a rare disease, case presentation with typical pathological findings and review of management

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Introduction

Prolymphocytic leukemia (PLL) is a rare disease, accounting for < 2% of lymphoid leukemias [1]. There are 2 quite different entities with distinct pathologic features and different therapeutic strategies, T-cell and B-cell [2]. T-PLL is more common [3]. Although termed 'prolymphocytic,' T-PLL is characterized by the proliferation of post-thymic T-lymphocytes. It is estimated that physicians will see a case of T-PLL every five to ten years [4]. Over the last 15 years, 3 cases of T-PLL were diag-nosed in our center. We present here the latest case, with typical pathological findings.

Case presentation

A 63-year-old British gentleman, previously healthy with good performance, presented with fatigue for 6-8 weeks with puffiness of face and eyelids and weight loss of 5 kilograms. Physical exam showed periorbital edema and conjunctival injection, cervical lymphadenopathy, and hepatosplenomegaly. Initial complete blood count (CBC): white blood cells (WBCs) 331.9 x10^9/L(4.0-10.0), with 94% lymphocytes, hemoglobin (Hb) 119 gm/L(130-170), platelets (Plts) 128 x10^9/L (150-400). Lactate dehydrogenase 10.4 µkat/L (2.1-3.7), , uric acid 537 µmol/L (210- 420). Abdomen ultrasound showed markedly enlarged spleen (20.3 cm).

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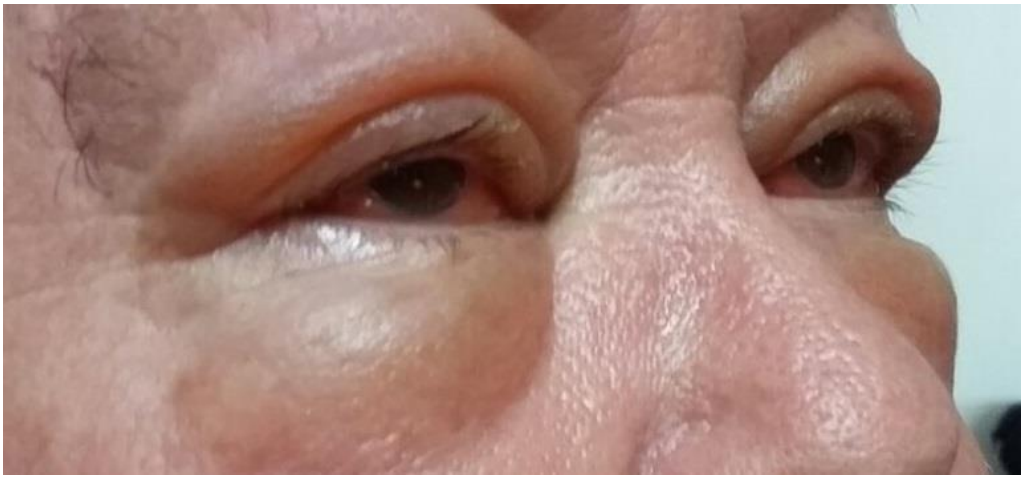


Figure 1 Periorbital edema and conjunctival injection

The peripheral blood smear showed profound leukocytosis with 94% abnormal lymphoid cells. The cells were small to medium in size with high nucleo-cytoplasmic ratio, moderately condensed chromatin and almost all with prominent nucleolus. Substantial number of the cells show irregular nuclear contour with short indentation. The cytoplasm was basophilic agranular and many cells show irregular cytoplasmic protrusions (Figure 2).

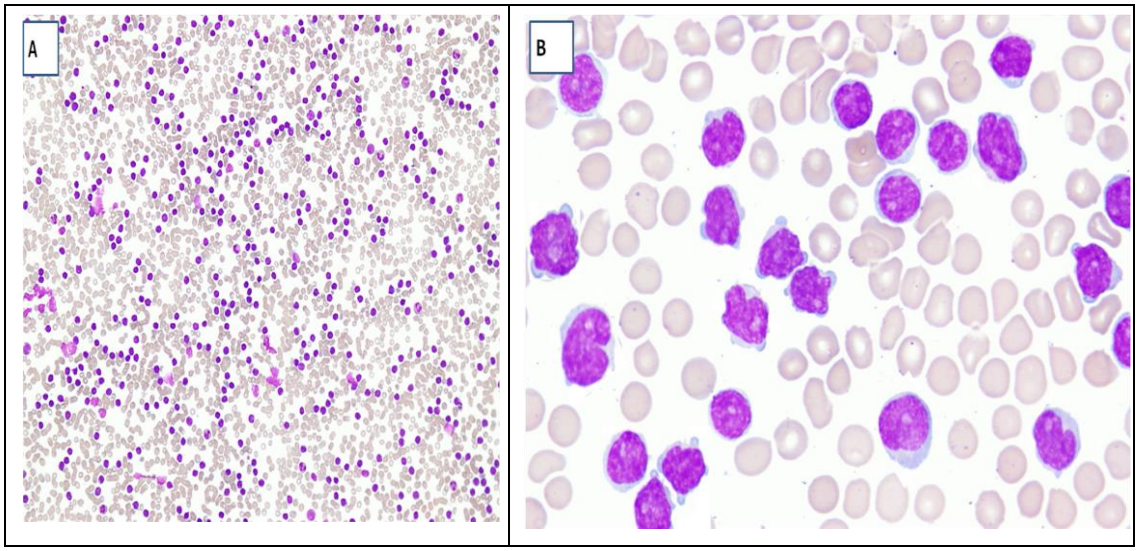


Figure 2 Peripheral blood smear. A, there is remarkable leukocytosis and lymphocytosis. B, the lymphocytes are small to medium with high nucleo-cytoplasmic ratio, moderately condensed chromatin, prominent nucleoli and many show irregular nuclear contour with short indentation. The cytoplasm is basophilic agranular and many cells show irregular cytoplasmic protrusions (Wright stain x1000)

Flow cytometry on peripheral blood revealed one homogenous abnormal population positive for cluster of differentiation 45 (CD45) and express the pan T-cell markers (CD3, CD2, CD5 and CD7). All were positive for CD4, T-cell receptor (TCR) alpha/beta, CD43 and BCl2 with partial expression of CD38. These cells were negative for CD56, CD57, CD16, CD25, CD103, CD10, CD117, Terminal deoxynucleotidyl transferase (TdT), CD1a and CD34. (Figure 3A)

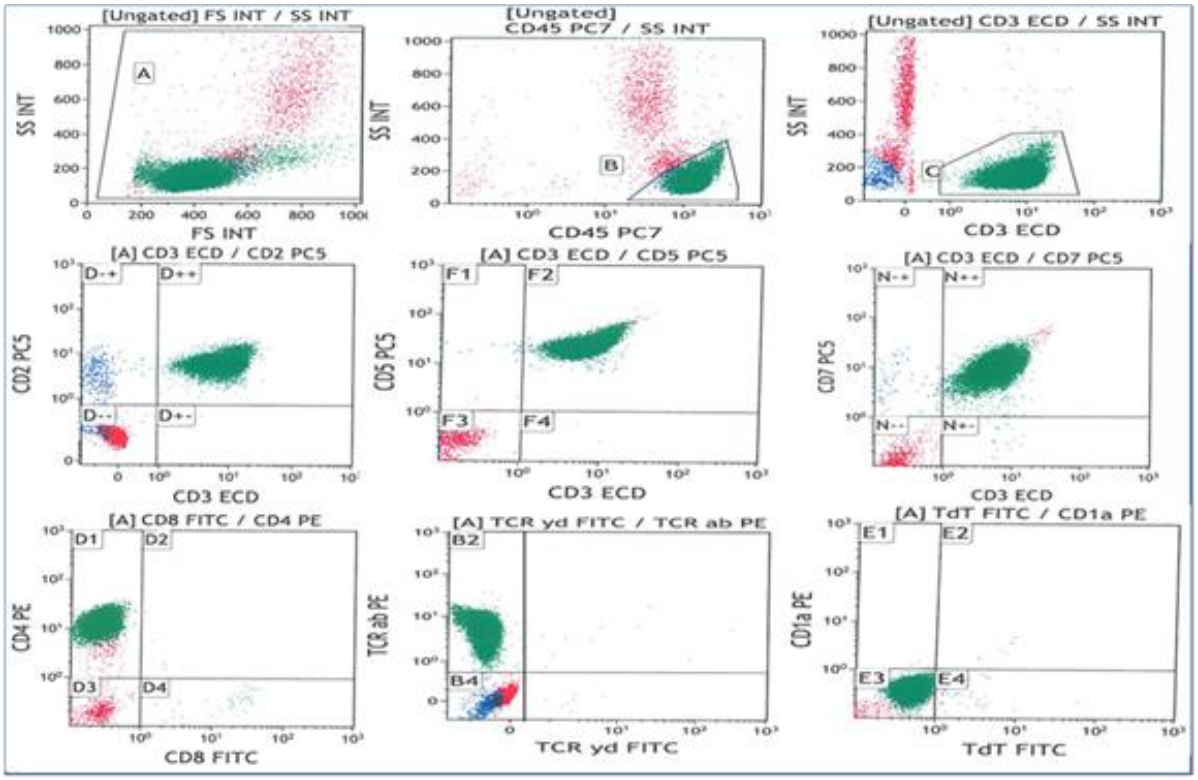


Figure 3A: Flow cytometry analysis shows one homogenous abnormal population with low side light scatter and low to medium forward light scatter expressing CD45, CD3, CD2, CD5, CD7 and CD4 and TCR alpha/beta. The cells are negative for the precursor markers CD1a and Tdt.

TCRVb region analysis by flow cytometry using IO Test Beta Mark TCR Repertoire kit (Beckman Coulter, Brea, CA, USA) using the panel of 24 monoclonal antibodies to TCR Vb families showed restricted expansion of region 13.1 in 99%. (Figure 3B)

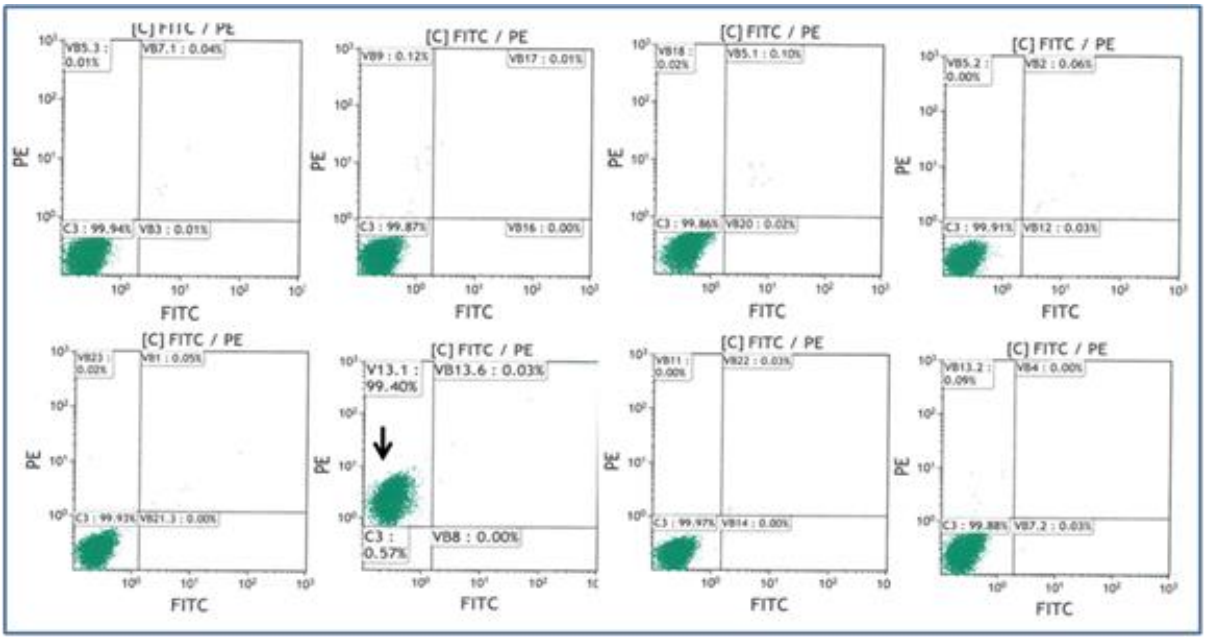


Figure 3B: TCRVb region analysis using IO Test Beta Mark TCR Repertoire kit (Beckman Coulter, Brea, CA, USA) including the panel of 24 monoclonal antibodies to TCR Vb families showed restricted expansion of region 13.1.

Bone marrow aspirate was remarkably hypercellular and extensively infiltrated with abnormal lymphoid cells comprising approximately 75% of total nucleated cells, morphologically similar to those seen in peripheral blood. The biopsy showed extensive diffuse infiltration with small to moderately sized lymphoid cells with prominent nuclear irregularity (Figure 4A&B). The immunophenotype was confirmed by immunohistochemistry and the cells were positive for CD3, CD5, CD7, CD2, CD4, BCL2 as well as for Zap70. BCL6 was uniformly negative.

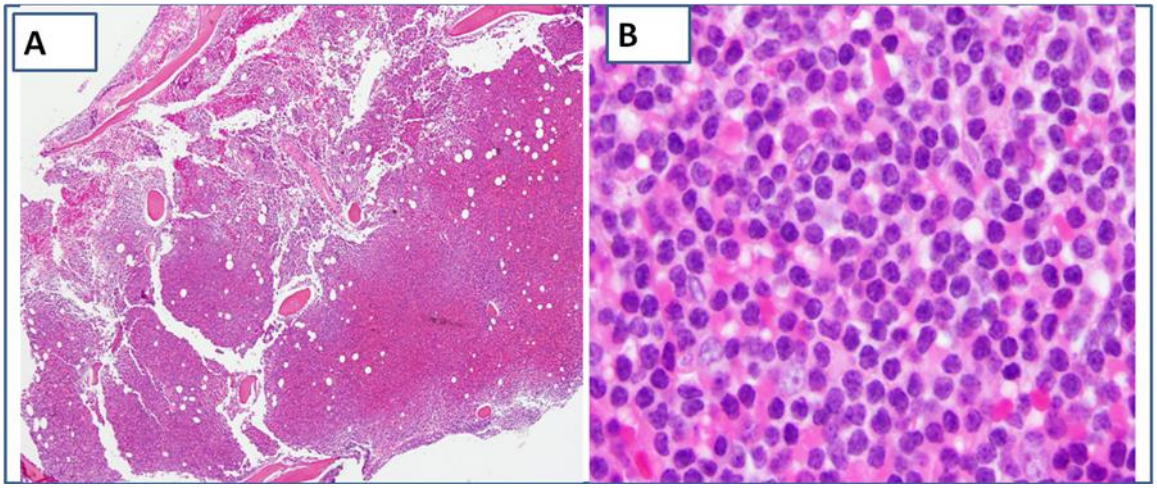
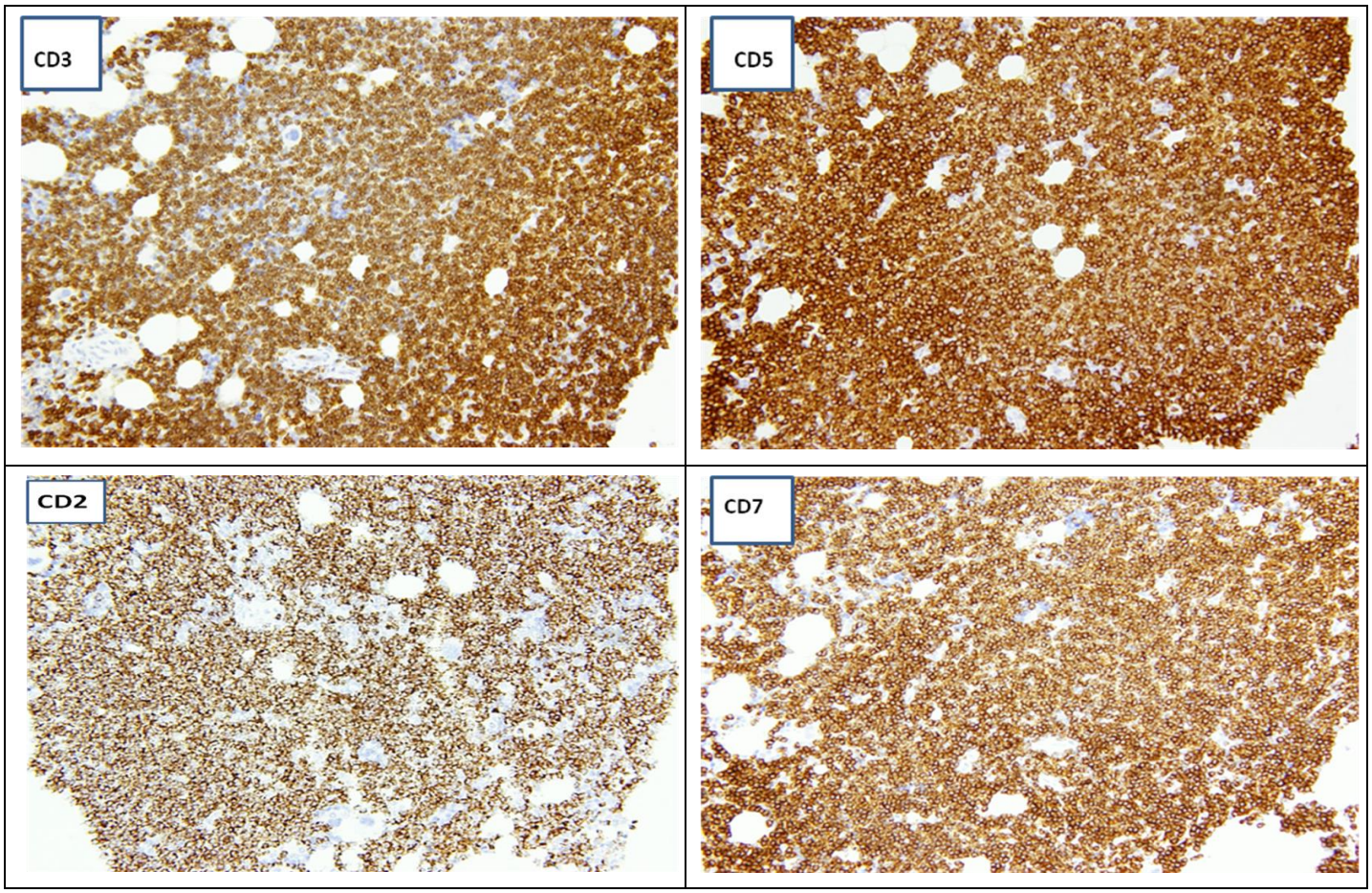


Figure 4: BMB. A, show hypercellular marrow with extensive diffuse infiltration (H&E, x100). B, the cells are small to medium in size and show irregular nuclear contour (H&E, x1000)



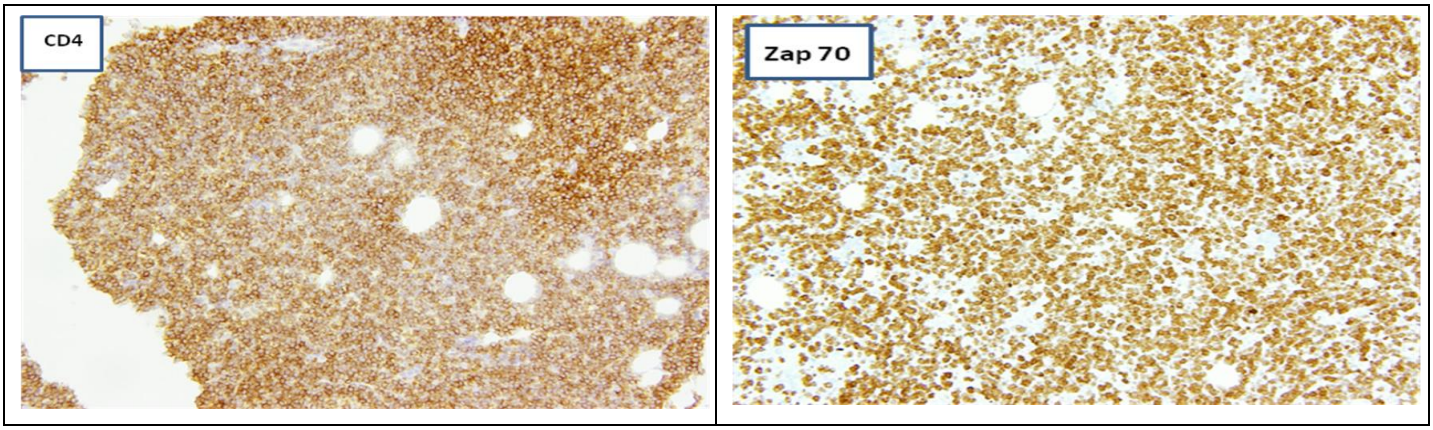


Figure 5: Immunohistochemistry performed on bone marrow biopsy. The abnormal lymphoid cells are positive for CD3, CD5, CD2, CD7, CD4 and Zap70 (20x)

Table 1 - Clinical and Laboratory Characteristics of T-PLL

Category	Characteristic Findings
Clinical features	Median age 61 years
	Male:Female 2:1
	Splenomegaly, lymphadenopathy, skin rash, edema, and pleuroperitoneal effusions
	Very high WBC
Morphology	Basophilic prolymphocytes with cytoplasmic blebs
	Small cell (20%) and SS (5%) variants
Immunophenotype	CD2+, CD3+, CD5+
	CD7++, CD52++
	CD4/CD8 variable
	CD1a-, TdT-, CD25±
Cytogenetics	t(14,14), inversion 14, t(X,14), iso8q, complex
Oncogenes	*TCL-1, MTCP-1, ATM, JAK3, STAT5b*
Differential diagnosis	B-PLL, T-LGL leukemia, ATLL, SS
Prognosis	Median survival 7 months with conventional therapy; 20 months with alemtuzumab; 48 months with alemtuzumab + HSCT

TCL-1, T-cell leukemia-1 gene; MTCP-1, Mature T-Cell Proliferation 1 gene; *ATM,* ataxia-telangiectasia mutated gene; JAK-3, Janus kinase 3 gene; STAT, signal transducer and activator of transcription; T-LGL, T large granular lymphocytic leukemia; SS, Sezary syndrome; ATLL, adult T cell leukemia lymphoma; B-PLL, B-cell prolymphocytic leukemia; and HSCT, hematopoietic stem cell transplant

Reference 4

Based on the morphology and the immunophenotypic profile, a diagnosis of CD4+/CD8− T-prolymphocytic leukemia was made.

FISH analysis revealed *ATM* deletion at 11q22 and TRA/D rearrangement in 93% of the cells analyzed and karyotype was complex with multiple numeric and structural abnormalities including inv (14)(q11.2q32); Karyotype: 43,XY, del(11) (q14), add(11) (p15),-13, inv(14) (q11.2q32), der(19)t(13;19) (q11;q13.4),-20,-22[7]/42, idem,-9, add(14) (p11.1), add(17)(p13) [23]

After confirming the diagnosis of T-PLL the patient travelled back to his home country. He was started on treatment with alemtuzumab, then pentostatin was added in week 4, after 10 weeks of treatment he achieved complete remission. After that he received reduced intensity conditioned allogeneic stem cell transplant from a matched brother, complicated by mild acute graft versus host disease. Until the time of writing this report he was doing fine.

Discussion

T-PLL is rare, and despite the advances in the understanding of the biology of this disease, the prognosis still remains poor with a short survival and no curative therapy [5].

Because T-PLL is rare, it is difficult to diagnose and sometimes misdiagnosed as chronic lymphocytic leukemia (CLL) or other disorders which results in poor outcome in this aggressive disease with peculiar treatment strategy. Our patient has typical morphologic, immunophenotyping and cytogenetic characteristics typical for T-PLL (outlined in table 1).

The leukemic lymphocytes in T-PLL are usually CD4+/CD8-, however, significant number are doubly positive for CD4 and CD8, or are positive for CD8 and rarely are doubly negative for CD4 and CD8. CD7 is usually expressed in T-PLL [6]. CD7 expression help in diagnosis of T-PLL as it is usually downregulated or lost in most other T cell neoplasms. Herling et al. in their study on 102 cases of mature T-cell leukemia including 38 T-PLL, CD7 was expressed in 95% of leukemic cells of T-PLL cases tested with less positivity in the other mature T cell neoplasms [7].

A study from MD Anderson Cancer Center involving 97 patients with T-PLL showed that sixty-nine (71%) patients had a complex karyotype (CK), 27 (28%) had a normal karyotype (NK), and one (1%) patient had two cytogenetic aberrations. There were no significant differences between these groups in gender, age, complete blood count and other clinical parameters. In the CK group, the most common aberrations involved 14q (n=45) and 8q (n=38). Patients with a CK had a significantly poorer OS than patients with a NK (14 vs 43 months, P = 0.0016) [8].

There are no large studies regarding the management of this disease, suggested approach by German CLL study group is induction by fludarabine, mitoxantrone, and cyclophosphamide (FMC), for up to 4 cycles, was followed by alemtuzumab (anti-CD52 monoclonal antibody) consolidation, up to 12 weeks [9]. MD Anderson Cancer Center suggested alemtuzumab in combination with pentostatin [10]. British group from the Royal Marsden Hospital suggested alemtuzumab (intravenous rather than subcutaneous route of administration [11]) as front-line therapy, followed by HSCT, with addition of pentostatin (a purine analog) in specific cases [1,4,10,12] Comparison between different studies is showed in table 2. Consolidation with stem cell transplant, preferably allogeneic if the patient is fit, or otherwise autologous, is associated with positive outcome (table 3).

A recent study by Dholaria BR et al [15] involving 11 patients with T- PLL also showed similar results, with Median PFS and OS were 15 months (95% CI=12–99) and 56 months (95% CI=15–56). The 4-year PFS and OS were 45% (95% CI=13–78%) and 57% (95% CI=25–89%), respectively. In this study most patients

received alemtuzumab-based first line systemic therapy (82%) and were al-lografted in CR1.

One question with unclear answer is the mechanism of ophthalmic manifestations in T-PLL. Nasz KJ reported a case of T-PLL presenting with periorbital edema [16], our patient has clear conjunctival injection and periorbital edema (as shown in figure 1), it seems that leukemic prolymphocytes can infiltrate the conjunctiva and cause the redness seen in such cases [17], but it is unclear whether the same mechanism plays a role in periorbital edema.

Conclusion:

T-PLL is rare and outcome is poor, alemtuzumab should be the first line treatment since it has improved the outcome, but consolidation with stem cell transplant (preferentially allogeneic) is needed to maintain the response. Multicenter collaborative effort is required to conduct appropriate clinical trials.

Table 2: Summary of treatment trials with > 10 patients

Reference	Regimen	Number of patients	CR	ORR	Median PFS	Median OS
Dearden et al [4] 2012	Alemtuzumab (IV)	39 pretreated	60%	76%	7 months	10 months
Dearden et al [11] 2011	Alemtuzumab (IV)	32 previously untreated	81%	91%	67% at 1 year	37% at 4 years
Hopfinger et al [9] 2013	FMC then Alemtuzumab (IV)	9 pretreated; 16 previously untreated	24% (FMC); 48% (alemtuzumab)	92% for all 25; patients; 68% after FMC; 95% in 21 patients receiving alemtuzumab	11.5 months	17.1 months
Ravandi et al [10] 2009	Pentostatin + Alemtuzumab (IV)	13 (treated + untreated)	62%	69%	7.8 months	10.2 months
Herbaux et al [13] 2015	Bendamustine	9 pretreated, 6 untreated	20%	53%	5 months	8.7 months
CR: complete remission, ORR: overall response rate, PFS: progression free survival, OS: overall survival						

Table 3: Outcomes for patients with T-PLL treated with alemtuzumab alone or followed by autologous or allogeneic HSCT (14)

	Autograft	Allograft	All HSCT	Controls*
No. of cases	15	13	28	23
Median age, y (range)	58 (43-68)	51 (39-61)	55 (39-68)	64 (35-81)
Males:females	8:7	10:3	18:10	16:7
TRM rate, %	7	31	18	NA
Relapse rate, %	60	33	48	96
Median DFS, mo	28	24	24	10
Median OS, mo	52	33	48	20
2-y OS rate, %	78	62	71	31
5-y OS rate, %	40	33	34	0
HSCT indicates hematopoietic stem cell transplant; TRM, transplant-related mortality; OS, overall survival; NA, not applicable; and DFS, disease-free survival				
*Control group: patients who achieved CR and survived at least 6 months.				

References:

1. Dearden C; Management of prolymphocytic leukemia; Hematology Am Soc Hematol Educ Pro-gram. 2015; 2015:361-7.
2. Catovsky D, Galetto J, Okos A, Galton DA, Wiltshaw E, Stathopoulos G; Prolymphocytic leukaemia of B and T cell type; Lancet. 1973 Aug 4;2(7823):232-4.
3. Matutes E, Brito-Babapulle V, Swansbury J et al; Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia; Blood. 1991 Dec 15;78(12):3269-74
4. Dearden C; How I treat prolymphocytic leukemia; Blood. 2012 Jul 19;120(3):538-51.
5. Vivekanandarajah A, Atallah JP, Gupta S; T-cell prolymphocytic leukaemia (T-PLL): a rare disease with a grave prognosis; BMJ Case Rep. 2013 May 2;2013. pii: bcr2013009808.
6. Laribi K, Lemaire P, Sandrini J et al; Advances in the understanding and management of T-cell prolymphocytic leukemia, Oncotarget. 2017 Nov 1;8(61):104664-104686.
7. Herling M, Khoury JD, Washington LT et al; A systematic approach to diagnosis of mature T-cell leukemias reveals heterogeneity among WHO categories; Blood. 2004 Jul 15;104(2):328-35.
8. Hu Z, Medeiros LJ, Fang L et al; Prognostic significance of cytogenetic abnormalities in T-cell prolymphocytic leukemia; Am J Hematol. 2017 May;92(5):441-447.
9. Hopfinger G, Busch R, Pflug N et al; Sequential chemoimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia; Cancer. 2013 Jun 15;119(12):2258-67.
10. Ravandi F, Aribi A, O'Brien S et al; Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms; J Clin Oncol. 2009 Nov 10;27(32):5425-30.
11. Dearden CE, Khot A, Else M et al; Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route; Blood. 2011 Nov 24;118(22):5799-802.
12. Mercieca J, Matutes E, Dearden C; The role of pentostatin in the treatment of T cell malignancies: analysis of response rate in 145 patients according to disease subtype; J Clin Oncol. 1994 Dec;12(12):2588-93.
13. Herbaux C, Genet P, Bouabdallah K et al; Bendamustine is effective in T-cell prolymphocytic leukaemia; Br J Haematol. 2015 Mar;168(6):916-9.
14. Krishnan B, Else M, Tjonnfjord GE et al; Stem cell transplantation after alemtuzumab in T-cell prolymphocytic leukaemia results in longer survival than after alemtuzumab alone: a multicentre retrospective study; Br J Haematol. 2010 Jun;149(6):907-10.
15. Dholaria BR, Ayala E, Sokol L et al, Allogeneic hematopoietic cell transplantation in T-cell prolymphocytic leukemia: A single-center experience; Leuk Res. 2018 Apr;67:1-5
16. Nusz KJ, Pang NK, Woog JJ; Periorbital edema as the initial presentation of T-cell prolymphocytic leukemia; Ophthal Plast Reconstr Surg. 2006 May-Jun;22(3):215-6.
17. Lee SS, Robinson MR, Morris JC, Mirtsching BC, Shen D, Chan CC et al, Conjunctival involvement with T-cell prolymphocytic leukemia: report of a case and review of the literature; Surv Ophthalmol. 2004 Sep-Oct;49(5):525-36.