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T-Cell Prolymphocytic Leukaemia: A Case Series

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Abstract: *T-prolymphocytic leukaemia (T-PLL) is a rare mature T-cell lymphoproliferative disorder. It is seen more often in middle-aged and elderly individuals with a median age of onset of 65 years and a male predominance of 2:1. Patients present with hepatosplenomegaly, lymphadenopathy, 15% may have serous effusions and approximately 20% have skin involvement. The white cell count is often above 200 x 10^9/l, and the tumour cells are CD3+, CD4+ or CD8+ (co-expression of CD4 and CD8 in 25%), CD7+, and are CD25-. The disease has an aggressive clinical course due its inherently chemoresistant nature, with a median survival of 7 months on conventional chemotherapy. We report4 patients diagnosed with T-PLL all presenting within a year to academic hospitals in the Johannesburg area of South Africa. There is a scarcity of information on T-PLL in South Africa where Human-immunodeficiency virus (HIV)-related haematological malignancies predominate in clinical practice.*

Key words: *T-cell prolymphocytic leukaemia, aggressive course, poor prognosis, South Africa*

I. Introduction

T-cell prolymphocytic leukaemia (T-PLL) is a rare and aggressive diseaseclassified by the World Health Organisation under the mature T-and NK-cell neoplasms(1). Among the mature lymphocytic leukaemias in those aged >30 years old, it represents only 2%. It has a male predominance (2:1) and a median age of onset of 65 years(1).

Patients usually present with hepatosplenomegaly and generalised lymphadenopathy. Some patients have serous effusions (15%), and up to 20% may have skin involvement. The white cell count is often above 200 x 10^9/l, and anaemia and thrombocytopenia may be present. The tumour cells are intermediate in size with prominent nucleoli morphologically, and express CD3, CD4 (or CD8, with co-expression of CD4 and CD8 seen in 25% of cases), and CD7. Unlike adult T-cell leukaemia/lymphoma, they usually lack expression of CD25, and hypercalcaemia is not a feature(1).

The course is an aggressive one with resistance to conventional chemotherapy and a median survival of 7 months(1-4). The median survival is improved with the use of alemtuzumabmonotherapy (a monoclonal agent against CD52) to approximately one year(2, 5-7), although some patients have been reported to survive more than 5 years on this treatment (2). Further improvements in survival and a possible cure lie with the use of allogeneic stem cell transplant where a median survival of approximately 3 years has been reported(8, 9). However, this therapeutic strategy is challenging both in terms of difficulty achieving remission and transplant related morbidity and mortality in a patient population that is often older with co-morbid conditions.

In South Africa, the Human Immunodeficiency Virus (HIV)-related haematological malignancies dominate clinical practice. There is no published information regarding the prevalence of T-PLL in South Africa, including case reports. In this context, we report on 4patientswith T-PLL, all of whom presented to academic institutions in the Johannesburg area in 2015.

Clinical Presentation

Two male patients and two female patients presenting with T-PLL in 2015 are described.Clinical features are shown in table 1. The mean age at presentation was 61.3 years (range = 39 years-72 years). All patients experienced at least one constitutional symptom for a mean of 5.3 months(range = 1 month - 1 year) prior to presentation. On examination,all patients had pallor, lymphadenopathy and hepatosplenomegaly. Patient 4 had a left-sided pleural effusion. Flow cytometric analysis of this pleural fluid revealed a population of approximately 94% lymphocytes which were CD2+, CD3+, CD4+, CD7+, CD8- and CD25-.

A striking feature in patients 1, 2 and 4 was a widespread skin rash, which was at least part of the reason for their presentation to hospital. In patient 1 this was described by the dermatologists as eczematous plaques on the trunk, arm, back and limbs with an erythematous, oedematous background involving 80% of the body, and clinically in keeping with erythroderma. The skin involvement in patient 2 was similar and is depicted in the images of figure 1, described as xerotic and erythematous on the arms, face, trunk, back and legs. Additionally, bullous lesions were noted on the feet, legs, buttocks and back, most of which had ruptured. Patient 4 had likely skin involvement across the face, chest and legs although a skin biopsy was never performed.A skin punch biopsy was performed in patients 1 and 2(figure 1). Both cases demonstrated a marked dermal infiltration of CD3+, CD4+, and CD8- lymphocytes.

The preliminary laboratory findings are shown in table 1 and include a marked leucocytosis (mean total white cell count =345.06 x 10^9/L (range 204.15- 632.90x 10^9/L); mean malignant cell count = 326.07 x 10^9/l (range 191.90 – 607.56 x 10^9/L)). Indeed, patient 4 required leucophoresis for a presenting leucocytosis greater than 600 x 10^9/L. In addition, all patients presented with anaemiaand patients 1 and 3 had a thrombocytopenia. Also of note was that all patients tested HIV and HTLV-1 negative and there was no hypercalcaemia. The peripheral blood smears showed significant malignant lymphocyte populations as shown in figure 1.These cells were CD3+, CD4+, CD5+ and CD7+ on flow cytometry, but CD1a-, CD8-, CD25- and TdT-. Of interest is that the tumour populations in patients 1 and 2 also had aberrant expression of the myeloid markers CD13 and CD33. Bone marrow aspirate and trephine biopsy (figure 1) demonstrated extensive infiltration by the tumour populations, contributing to the cytopenias seen.

Clonality was established on PCR of T-cell receptor generearrangement analysis. Unfortunately,the samples submitted for cytogenetics failed to yield any metaphases for analysis in patient 2, but he was positive for 17p (p53) deletion, and negative for 11q23 (ATM) deletion on fluorescence in situ hybridisation (FISH). The other patients were both negative for 17p (p53) and 11q23 (ATM) deletions, although patient 1 did have a rearrangement of 14q32. Using the laboratory findings inconjunction with the clinical context of these patients withgeneralised lymphadenopathy, hepatosplenomegaly, a pleural effusion andskin involvement,a diagnosis of T-cell prolymphocytic leukaemia was made.

The patients were initially managed supportively with intravenous fluids, analgesia and allopurinol. Patient 2 was also treated with cloxacillin for superficial cellulitis. Following diagnosis, all patients received combination chemotherapy detailed in table 1 with blood product support for any ensuing cytopenias. Despite this treatment, none of the patients entered remission. Sadly, patient 1 demised from a presumed pulmonary thromboembolic event following a haemodynamic collapse and signs of acute right heart failure, although no thrombus was visualised on bedside echocardiography. He was too unstable for more definitive imaging and demised despite best available therapy. Patient 2 demised from neutropenic sepsis complicated by hypokalaemia and acute kidney injury secondary to *Clostridium difficile* diarrhoea. Patient 3 demised from neutropenic sepsis complicated by acute kidney injury.Patient 4 demised from fungal sepsis. The mean overall survival was 6.3 monthswith a range of 1 month to 7 months.

II. Discussion And Conclusion

T-cell prolymphocytic leukaemia is a rare and aggressive mature lymphoproliferative disorder. It's occurrence in the South African population has not been well described. The four patients described here demonstrated some heterogeneity in terms of age at presentation as well as gender. The two male patients and the older female patient were more typical in terms of age at presentation, as well as skin involvement. All patients did have typical clinical and pathological features interms of lymphadenopathy, hepatosplenomegaly and bone marrow involvement by a population of CD3/4/7+ and CD1a/TdT/CD8/CD25- cells. The extent of skin involvement in the two male patients was unusual and may be due to late presentation.

Poor prognostic markers for an already aggressive disease include high white cell count, and reduced tumour doubling time (2). These were factors in play for all four patients, and contributed to theirpoor survival. Patient 3 was atypical in terms of age at presentation. Her improved survival despite lack of alemtuzumab compared to the two male patients may have been at least in part related to her younger age. Conventional combination chemotherapy used forthe treatment of T-PLL has had poor outcomes with a median survival of 7 months reported in a retrospective series of 70 patients in the United Kingdom (6). The current treatment preferred in published series is that of alemtuzumabmonotherapy followed by a stem cell transplant(either

autologous or allogeneic) as a consolidation measure, which can improve overall survival beyond 4 years in selected patients (2, 9). However,it is unclear due to limited patient numbers whether autologous or allogeneic transplant is superior. Unfortunately, alemtuzumab was not used for the first 3 patients described in this case seriesdue to the ill health of these patients. It is available on a compassionate basis and was used in the fourth patient once she had clinically stabilised. None of the patients entered a complete remission whereby a stem cell transplant could have been considered.

Although T-PLL is rare, as these cases illustrate, clinicians need to be aware of this entity in order to expedite timely referral to a clinical haematology or medical oncology unit as early treatment is critical to more favourable outcomes.

Ethics approval

Ethics approval for this study was gained from the Human Research Ethics Committee (Medical) of the University of Witwatersrand, Johannesburg, South Africa.

Conflicts of Interest

All the authors declare that there are no conflicts of interest.

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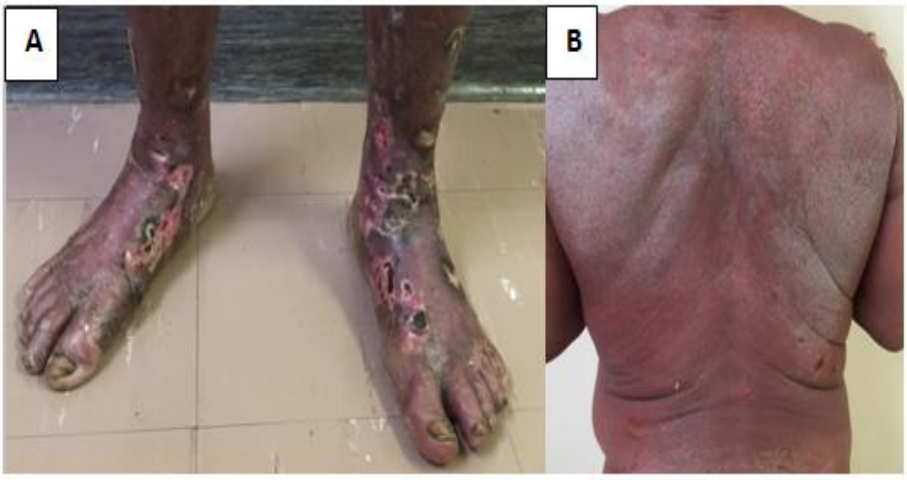

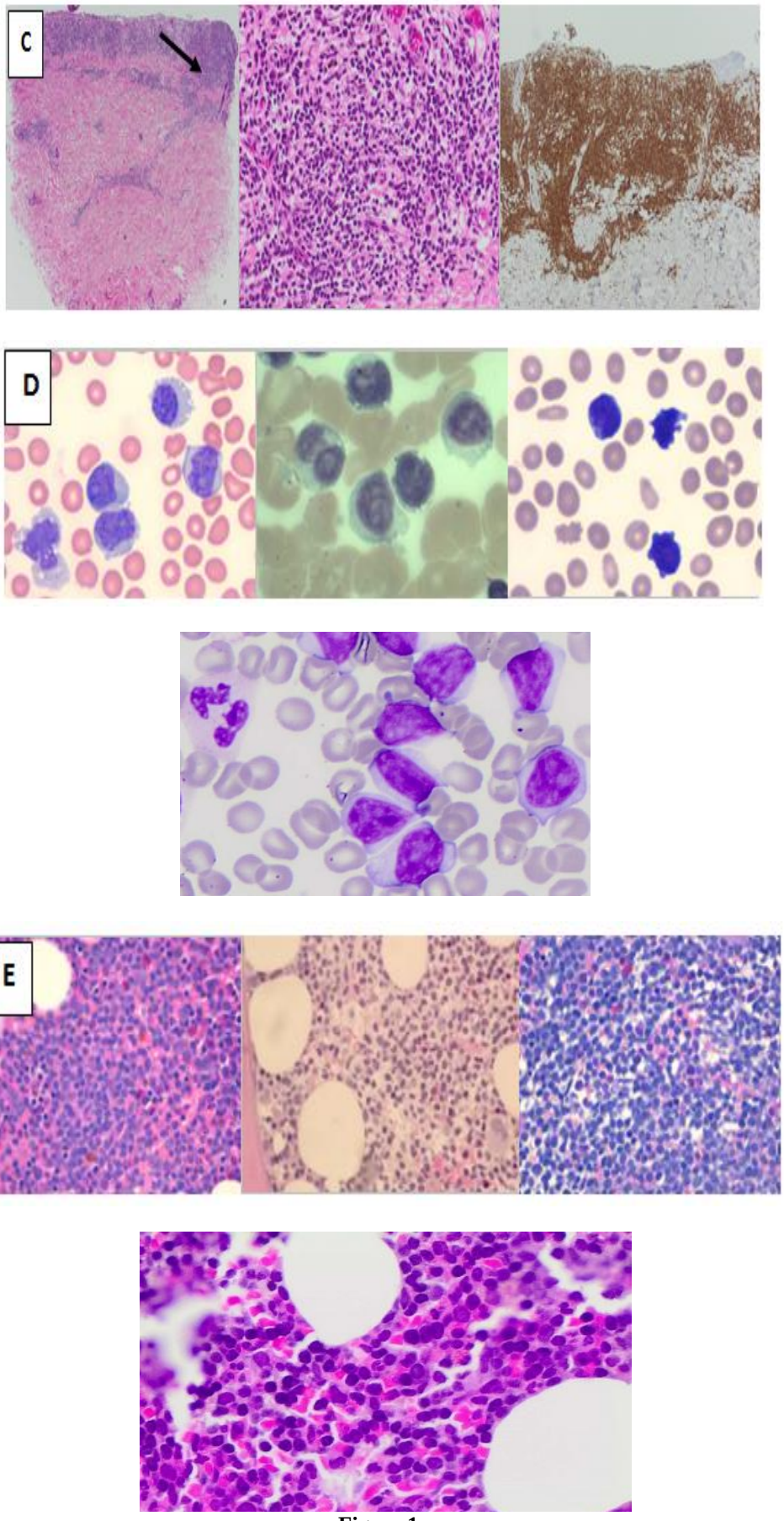

Figure 1.

Panels A and B. Pictures depicting the patient 2's blistering rash with a bullous eruption of the feet **(A)**, and erythroderma of the back **(B)**.

Panel C. Skin biopsy of patient 2 of a blistering lesion depicted in image A. The dermis shows a superficial and deep dense atypical lymphoid infiltrate (arrow), predominantly in a perivascular location. This infiltrate is composed of small to intermediate-size atypical lymphocytes with scant pale cytoplasm. They have cerebriform nuclei with inconspicuous nucleoli. Occasional admixed small reactive lymphocytes are also present. The tumour cells expressed CD3 and CD4, the latter of which is shown in the far right image of the panel.

Panel D: Images from the peripheral blood; left to right patients 1,2,3 and 4.

Panel E: Trephine biopsy (BMT); left to right patients 1,2,3 and 4.

Patient 1: The tumour cells weremorphologically pleomorphic, ranging in size from intermediate to large. They had a pale basophilic cytoplasm with coalescent vacuolation, mature chromatin and a single large prominent nucleolus. The nuclear contours were irregular in some. On BMT the tumour cells were distributed both interstitially as well as in a sheet-like pattern in areas. They were intermediate to large in size, with dispersed nuclear chromatin, irregular nuclear contours and a bulky eosinophilc cytoplasm. A single prominent nucleolus was appreciated in some. The tumour cells were estimated to comprise ~70% of the cells present on a CD3 stain. **Patient 2:**The malignant cells represented ~95% of the white cell differential count. Morphologically they were small to medium in size,some with a high N:C ratio and others with more abundant pale basophilic cytoplasm and prominent nucleoli. The BMT expanses are moderately hypercellular owing to extensive diffuse infiltrate of intermediate sized primitive cells, with a N:C ratio, primitive nuclear chromatin and many with conspicuous nucleoli. Nuclear folding is evident. Haemopoiesis is scattered interstitially.**Patient 3:**The tumour cells were morphologically small to intermediate in size with hyperchromatic nuclear chromatin and deeply basophilic cytoplasm. Many had irregular nuclear contours and/or prominent cytoplasmic blebbing. Nucleoli were not conspicuous. The BMT was extensively infiltrated by these tumour cells, which had irregular nuclear contours, moderately dispersed nuclearchromatin and multiple pin prick nucleoli. They were estimated to comprise >95% of the cells present on a CD3 stain. **Patient 4:** The malignant cells represented ~93% of the white cell differential count. Morphologically they were intermediate in size with a single prominent nucleolus, variable amounts of cytoplasm, some demonstrating cytoplasmic blebbing. The BMT was hypercellular due to extensive interstitial infiltration by the tumour population with partial displacement of normal haemopoiesis.

Skin biopsy: Stained with Hematoxylin and Eosin. Image left x10 magnification. Image centre x40 magnification. Image right x20 magnification. Peripheral blood stained with May-Grünwald Giemsa, 1000× magnification. Bone marrow trephine stained with Hematoxylin and Eosin, 400× magnification.

Table 1. Clinical features and laboratory results of patients with T-PLL at presentation

	Patient 1		**Patient 2**		**Patient 3**		**Patient 4**	
PRESENTATION								
Age at presentation (years)	69		65		39		72	
Ethnicity	Black		Black		Black		Caucasian	
Gender	Male		Male		Female		Female	
Self-reported duration of symptoms (months)	12		1		6		2	
Performance status (ECOG)	1		3		2		2	
BLOOD RESULTS								
Total White Cell Count $x10^9/l$	204.15		319.40		223.78		632.90	
Malignant Cell Count $x10^9/l$	191.90		303.43		201.40		607.56	
Haemoglobin (g/dl)	10.1		13.5		6.0		10.6	
Platelets $x10^9/l$	82		227		50		143	
Lactate dehydrogenase (U/l)	1846		768		1384		925	
Uric acid (mmol/l)	0.40		0.38		1.02		0.24	
IMMUNOPHENOTYPE	Flow cytometry	IMH	Flow cytometry	IMH	Flow cytometry	IMH	Flow cytometry	IMH
CD1a	-	ND	-	ND	-	ND	-	ND
CD2	-	ND	-	ND	+	ND	++	ND
CD3	++	ND	++	+	++	+	++	ND
CD4	++	+	++	+	-	+	++	ND
CD5	++	ND	++	ND	++	ND	++	ND
CD7	++	ND	++	ND	+	ND	++	ND
CD8	-	-	-	-	++	-	-	ND

CD25	-	ND	-	ND	-	ND	-	ND
CD56	ND	ND	ND	ND	++	ND	ND	ND
TdT	-	ND	-	ND	-	ND	-	ND
Aberrant CD13	+	ND	+	ND	-	ND	ND	ND
Aberrant CD33	+	ND	+	ND	-	ND	ND	ND
T cell receptor PCR	monoclonal		monoclonal		monoclonal		monoclonal	
Cytogenetics/FISH								
11q23 deletion (ATM)	-		-		-		-	
17p deletion (P53)	-		+		-		-	
Chromosome 14 abnormalities	Rearrangement of 14q32 detected by FISH		Failed		-		-	
MANAGEMENT								
Specific Chemotherapy Regimes	CHOP x 2 cycles		Cyclophosphamide, daunorubicin, L-aspariginase, vincristine, prednisone, and intrathecal prophylaxis (methotrexate and hydrocortisone) x 1 cycle		CHOP x 1 cycle FCM x 3 cycles		ChP x 2 cycles FC x 1 cycle Alemtuzumab x 1 cycle	
Survival	2 months		1 month		6 months		7 months	

ELISA: enzyme-linked immunosorbent assay; IMH: Immunohistochemistry of the skin biopsy; ND: Not done; PCR: polymerase chain reaction; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; FCM: fludarabine, cyclophosphamide, mitoxantrone; ChP: Chlorambucil, prednisone.