Hepatosplenic T-cell lymphoma: A case series

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Hepatosplenic T-cell lymphoma (HSTCL) is a rare type of Non-Hodgkin Lymphoma (NHL), grouped under the mature or peripheral T-cell lymphomas. It is characterised by extranodal infiltration and proliferation of malignant T-cells within the sinusoids of the liver, sinuses and red pulp of the spleen, and the bone marrow. The tumour cells express CD2 and CD3, but are CD4, CD5 and CD8 negative and express a clonally restricted gamma–delta (or less commonly alpha–beta) T-cell receptor. The disease has an aggressive clinical course associated with a poor prognosis. We highlight and report three patients from South Africa with HSTCL, all of whom had hepatosplenomegaly and cytopaenias, and despite being HIV seronegative and immunocompetent, had a poor outcome, with a mean survival of 7.5 months in the two evaluable patients. This rare entity has not previously been reported from South Africa and as yet needs to be adequately characterised in a population where lymphoma is the most common haematological malignancy in adults, and where approximately two thirds of the adult lymphoma population are HIV seropositive.

KEYWORDS: Hepatosplenic T-cell lymphoma; Hepatosplenomegaly; Cytopaenias; Aggressive course; Poor prognosis; South Africa

Hepatosplenic T-cell lymphoma (HSTCL) is a rare subset of the peripheral T-cell lymphomas, with less than one hundred case reports in the literature. It has been estimated to contribute only 1.4% of all T-cell lymphomas.[1] It was first described as a separate entity amongst the peripheral/mature T-cell lymphomas in the 1990 REAL (Revised European American Lymphoma) classification.[2] It is characterised by malignant T-cell proliferation with a predisposition for the sinusoids of the liver, sinuses and red pulp of the spleen, and the sinuses of the bone marrow; expression of gamma–delta (γδ) (or less commonly alpha–beta) T-cell receptor (TCR) as part of the malignant T-cell clone; and a very aggressive clinical course with poor prognosis (median overall survival of 11 months),[3,4] although a more recent report suggests improved outcome and survival with intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation.[5]

HSTCL is more common among young males in their teenage years and in young adulthood. Approximately 10–20% of patients have a history of immunosuppression, either through treatment for malignancy (such as in Hodgkin Lymphoma or acute myeloid leukaemia), inflammatory conditions (e.g. infliximab use in inflammatory bowel disease), or solid organ transplants.[6,7] The majority of patients have liver, spleen, and bone marrow involvement at presentation. As a result they tend to be jaundiced, anaemic, have prominent hepatosplenomegaly, minimal lymphadenopathy, and constitutional or 'B' symptoms. Thrombocytopaenia is commonly seen, although this may be part of a broader pancytopaenia. The cause of

Table 1. Clinical characteristics of the patients with HSTCL.

	Patient 1	Patient 2	Patient 3
Presentation			
Age at presentation (years)	21	23	42
Gender	M	M	M
Self-reported duration of symptoms	2 weeks	4 months	2 months
Functional status	2	2	4
Fever	+	+	+
Night sweats	+	+	+
Fatigue	+	+	+
LOW/LOA	+	+	+
Abdominal pain/ swelling	+	+	–
Mucous membrane bleeding	–	+	–
Examination			
Pallor	+	+	+
Jaundice	–	+	–
Petechiae	–	+	–
Ecchymosis	–	+	–
Lymphadenopathy	Shotty generalised	Shotty generalised	Shotty generalised
Hepatomegaly	8 cm below costal margin	15 cm below costal margin	10 cm below costal margin
Splenomegaly	22 cm below costal margin	15 cm below costal margin	6 cm below costal margin
Management			
a. Supportive	+	+	+
b. Specific			
Chemotherapy regime:			
CHOP	+	+	+
CHOEP	+	–	–
CNOP-M	+	–	–
FCM	+	+	–
FCR	–	+	–
FCRM	–	+	–
Survival	12 months	3 months	<1 month (3 days)

CHOP – cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; CHOEP – CHOP plus etoposide, CNOP-M – cyclophosphamide, novantrone, oncovin, prednisone, methotrexate; FCM – fludarabine, cyclophosphamide, mitoxantrone; FCR – fludarabine, cyclophosphamide, rituximab; FCRM – FCR plus mitoxantrone.

the cytopaenias is multifactorial: marrow infiltration, splenic sequestration, haemolytic anaemia, immune-mediated thrombocytopaenia, or haemophagocytic syndrome either alone or in combination. Neutropaenia is less commonly encountered. Peripheral blood spill of malignant cells occurs in the leukaemic phase of the disease.[4,7] The immunophenotype of the malignant cells is typically: CD2+, CD3+, γδTCR+, CD4−, CD5−, CD8−, CD±56.[8] An isochromosome of the long arm of chromosome 7 (i(7)(q10)) is a recurrent genetic abnormality described in HSTCL either in isolation or in association with

Table 2. Laboratory features of patients with HSTCL at CHBAH.

	Patient 1		Patient 2		Patient 3	
Blood results						
White cell count $\times 10^9$/l	11.21		2.80		44.80 (tumour cells 27.78 $\times 10^9$/l)	
Haemoglobin (g/dl)	10.1		10.1		4.8	
Platelets $\times 10^9$/l	117		29		17	
LDH (U/l)	1167		1256		1885	
Bilirubin (μmol/l) (total/conjugated)	8/4		133/104		26/21	
ALP/GGT (U/l)	93/60		431/228		234/174	
ALT/AST (U/l)	13/34		106/249		13/139	
INR/PTT (s)	1.33/40.6		1.10/53.1		1.40/49.6	
Bone marrow infiltration present	+		+		+	
Immunophenotype	Flow cytometry	IMH	Flow cytometry	IMH	Flow cytometry	IMH
CD1a	ND	–	ND	ND	ND	ND
CD2	ND	ND	+	ND	+	ND
CD3	ND	+	Equivocal	+	+	+
CD4	ND	Occasional +	ND	Equivocal	–	ND
CD5	ND	–	–	–	Subgroup +	ND
CD7	ND	–	+	ND	+	ND
CD8	ND	–	–	–	–	ND
CD16	ND	ND	ND	ND	+	ND
CD30	ND	–	ND	–	+	ND
CD34	ND	–	ND	–	–	ND
CD43	ND	+	ND	ND	ND	ND
CD56	ND	Subgroup weakly +	ND	Weakly +	–	ND
TdT	ND	–	ND	–	ND	–
EBER ISH	ND	ND	ND	–	ND	ND
Cytogenetics/FISH					Failed	
Isochrome 7 q–	+		+		No result	
Trisomy chromosome 8	ND		+		No result	

IMH: immunohistochemistry of the bone marrow trephine/liver biopsy, EBER ISH: Epstein–Barr virus-encoded small RNA in situ hybridisation. ND: not done.

other abnormalities, most notably trisomy 8, with the combination of these two abnormalities being highly suggestive of HSTCL.[9]

There is no standard treatment regime that is described for this aggressive disease, and reported results of therapeutic interventions are generally disappointing and have limited efficacy. A variety of chemotherapeutic regimes have been used; from standard CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone), CHOP-like regimens, purine analogues, monoclonal antibodies (e.g. alemtuzumab), platinum-based regimes, ICE (ifosfamide, carboplatin, etoposide) and IVAC (ifosfamide, etoposide, high-dose cytarabine).[5,10] In the last decade, however, there have been a number of reports of the successful use of allogeneic stem cell transplants (SCT), which appears

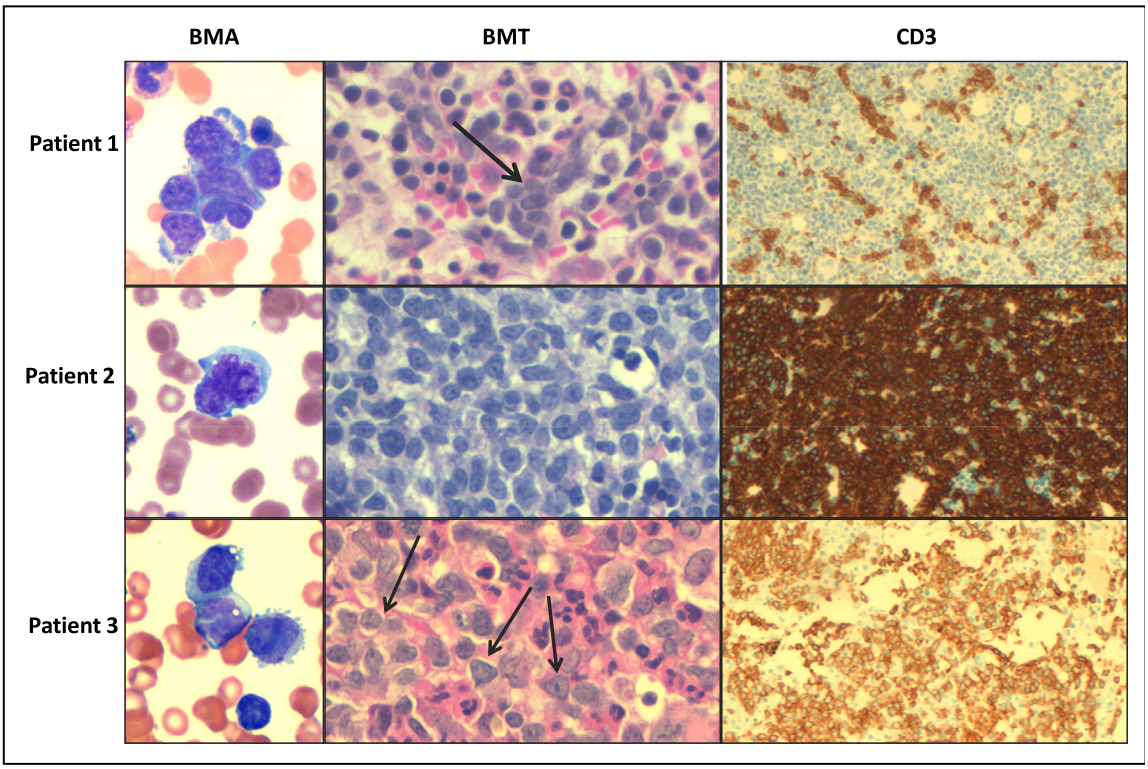

Fig. 1. Bone marrow aspirate, trephine biopsy and CD3 staining of the three cases. Patient 1 had clumps of tumour cells in the bone marrow aspirate, and intrasinusoidal marrow infiltration in the trephine biopsy (see arrow). Patient 2 demonstrated extensive sheet-like infiltration of the bone marrow. Patient 3 exhibited marrow infiltration by a population of tumour cells comprising 50–60% of the cells present. These were distributed interstitially in the trephine biopsy (see arrows). The tumour cells were all predominantly of intermediate size with a moderate amount of palely basophilic cytoplasm. All three cases demonstrated a degree of cytoplasmic blebbing or fimbriation. The nuclear:cytoplasmic ratios were high, and the nuclear chromatin loosely clumped. Only Patient 2 had occasional prominent nucleoli. BMA: Bone marrow aspirate stained with May-Grünwald Giemsa, high power magnification. BMT: Bone marrow trephine stained with hematoxylin and eosin, high power magnification. CD3: Immunohistochemical staining for CD3 on the bone marrow trephine biopsies, low power magnification.

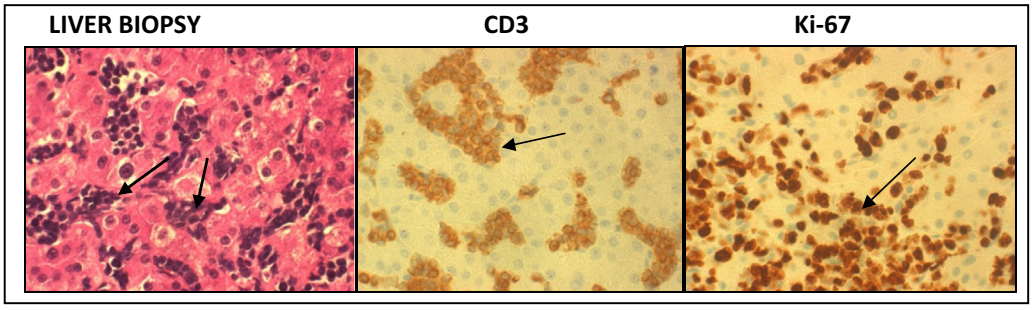

Fig. 2. Liver biopsy from patient 1. Left panel: Infiltration of liver parenchyma by clusters of atypical lymphocytes (see arrows). Centre panel: Atypical lymphocytes are CD3 positive (see arrow). Right panel: Ki-67 stain approaches 100% in atypical lymphocytes (see arrow). Liver biopsy: Stained with hematoxylin and eosin at ×40 magnification. CD3: immunohistochemical staining for CD3.

to be the only therapeutic intervention that has resulted in durable, long term remissions and potential cure of the disease.[5,10,11]

There have been no case reports from South Africa with regard to HSTCL. Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary referral centre in Soweto, Johannesburg. More than two thirds of the adult Non-Hodgkin lymphoma (NHL) patients seen at this hospital are immunocompromised (HIV seropositive) and harbour aggressive B-cell lymphomas such as diffuse large B-cell lymphoma, Burkitt lymphoma and plasmablastic

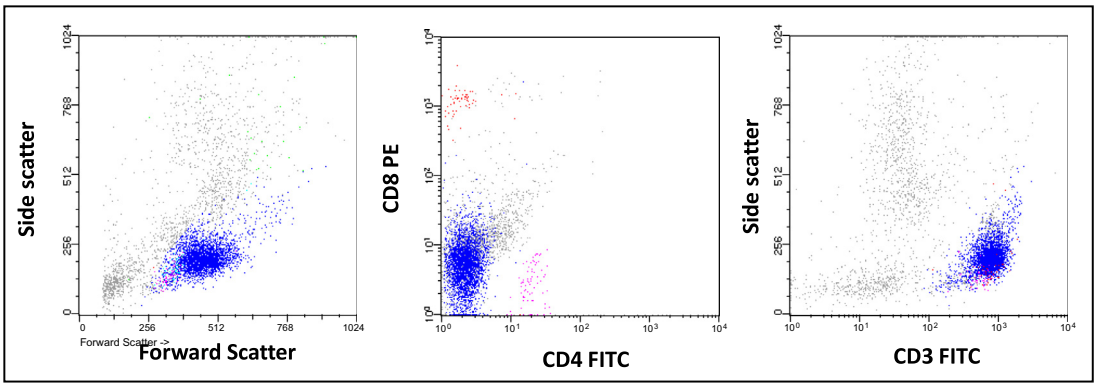

Fig. 3. Flow cytometry findings for patient 3. The lymphoid cells were gated by forward light scatter vs side light scatter. The tumour cells are indicated in blue, and background CD4 and CD8 T-cells in violet and red, respectively. (A) The tumour cells are of intermediate size, are negative for CD4 and CD8 (B) and strongly positive for CD3 (C). FITC, fluorescein isothiocyanate; PE, phycoerythrin.

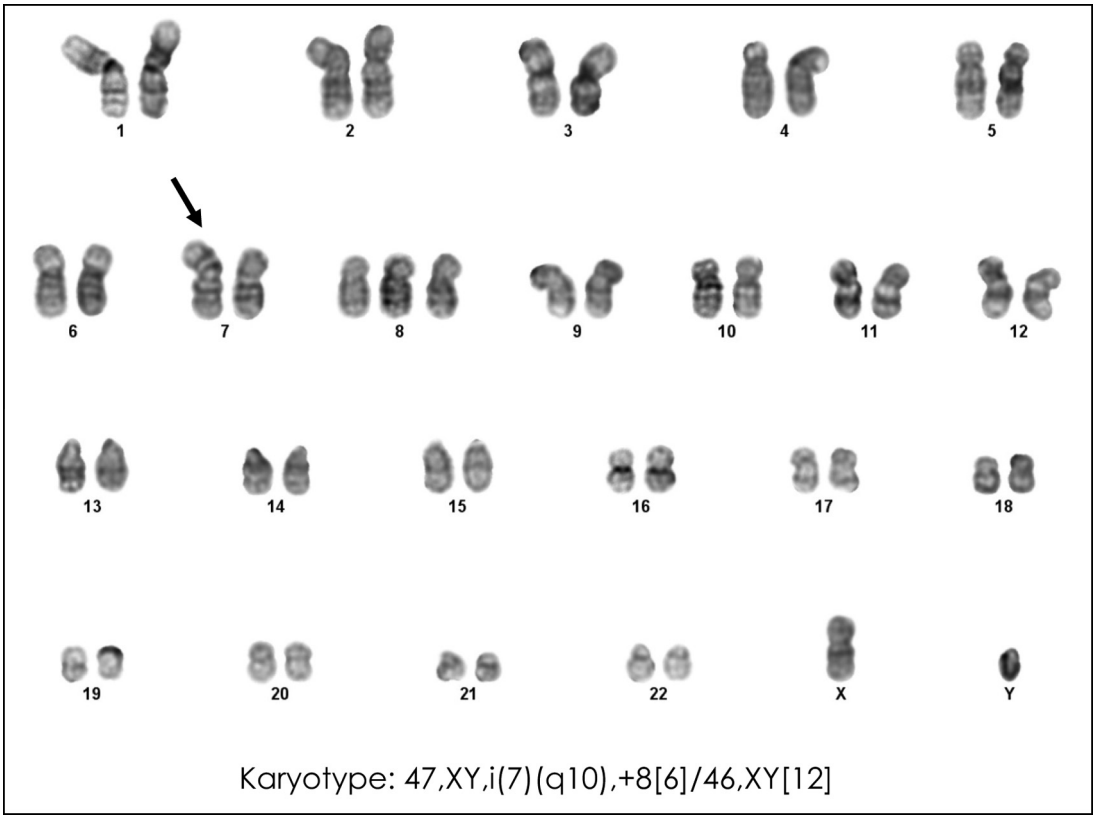

Fig. 4. Conventional cytogenetic studies of patient 2 demonstrating an isochromosome of the long arm of chromosome 7 (see arrow) and trisomy of chromosome 8. Conventional cytogenetic studies using GTW (G-Banding, Trypsin, Wright's stain) were performed, according to standard protocols, on 24 hour unstimulated bone marrow cultures. The results were interpreted using the ISCN (International System for Human Cytogenetic Nomenclature, 2009).

lymphoma.[12] T-cell lymphomas are less common. We report three patients with HSTCL, seen over a three year period – January 2011–December 2013 at CHBAH.

CLINICAL PRESENTATION

Three patients with HSTCL were identified over a three-year period (1 January 2011–31 December

2013) at the adult Clinical Haematology unit, Department of Medicine, Chris Hani Baragwanath Academic Hospital. All three of these patients were male, of black ethnicity, and presented at a mean age of 29 years (range: 21–42 years). All were HIV seronegative, with no other history or evidence of immunosuppression. A summary of the clinical features of these patients at presentation is depicted in Table 1. Of note is that all the patients had constitutional symptoms, hepatosplenomegaly and cytopaenias, but no significant lymphadenopathy.

The laboratory features at presentation for the patients are summarised in Table 2 and depicted in Figs. 1–4. All the patients showed abnormalities of their blood counts, with patient 3 presenting in a leukaemic phase of the disease. All the patients had malignant infiltration of their bone marrow. In addition, patient 1 had confirmed hepatic infiltration on liver biopsy with CD3+ tumour cells (liver biopsy was performed as his first bone marrow investigation did not yield a diagnosis, due to subtle infiltration).

DISCUSSION AND CONCLUSIONS

HSTCL is a rare subset of NHL. There are no reports in the literature of this entity being described in South Africa, despite lymphoma being the most common haematological malignancy in adults (the possibility of under-reporting of this entity cannot be excluded). The clinical presentation in the three patients seen at CHBAH is similar to that reported in the literature, with hepatosplenomegaly, minimal lymphadenopathy, constitutional symptoms, and cytopaenias. All patients had infiltration of bone marrow, spleen, and liver at presentation, although the degree of infiltration varied. Patient 3 presented in the leukaemic phase of the disease with evidence of disease in the peripheral blood, more profound cytopaenias, and a very poor performance status (PS = 4).

In addition to supportive care, the patients received combination chemotherapy, as indicated in Table 1. Despite the use of a number of different combination chemotherapy regimens in patients 1 and 2, neither of the patients achieved a complete remission and both died of refractory disease, with a mean survival of 7.5 months. Patient 3 presented in the leukaemic phase of the disease and demised shortly after initiating chemotherapy and was thus inevaluable. None of the three patients were considered for or were candidates for SCT.

Prior to the use of allogeneic SCT, the literature shows the limited efficacy and uniformly poor outcome of patients treated with a variety of chemotherapeutic interventions.[10] However, recent reports suggest a better outcome with SCT,[5,10,11] particularly with the use of intensive induction chemotherapy followed by early high-dose therapy and hematopoietic SCT.[5]

Clinicians, including haematologists, oncologists and pathologists need to be aware of this rare, aggressive form of NHL, so that a diagnosis can be readily established and the patient managed aggressively, with early consideration of SCT – the only potentially curative intervention in patients with HSTCL. Additionally, a multi-centred approach is advised, with pooling of patient data and the use of a uniform therapeutic approach, in order to explore and optimise the management of patients with this rare form of T-cell lymphoma.

ETHICS APPROVAL

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

CONFLICTS OF INTEREST

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

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