

which was the case in our patient. Of the reported cases, almost one third of the patients continued to receive the drug after an initial allergic reaction to ceftriaxone as they were diagnosed retrospectively.

In conclusion, ceftriaxone can cause fatal hemolysis and should be used with caution especially in patients who are immunocompromised or have an underlying hematological condition. ARF may be the presenting manifestation of ceftriaxone-induced IHA and the prognosis may be favorable for recovery with early diagnosis and initiation of supportive therapy including dialysis.

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## Large Granular Lymphocyte Leukemia (LGL) in a Child With Hyper IgM Syndrome and Autoimmune Hemolytic Anemia

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We describe a female with a history of autosomal recessive hyper-IgM (HIGM) syndrome along with a history of autoimmune hemolytic anemia and intermittent lymphadenopathy. She subsequently developed neutropenia, lymphocytosis and mild thrombocytopenia. Flow cytometry of the peripheral blood revealed the

presence of a marked predominance of cytotoxic T lymphocytes, shown to be clonal, with concomitant natural killer (NK) antigen expression. She responded to weekly methotrexate therapy. *Pediatr Blood Cancer* 2008;50:142–145. © 2006 Wiley-Liss, Inc.

**Key words:** autoimmune hemolytic anemia; granular lymphocyte leukemia; hyper-IgM syndrome

## INTRODUCTION

Large granular lymphocyte leukemia (LGL) is a rare, indolent form of non-Hodgkin's lymphoma. This clonal lymphoproliferative disease arises most frequently from T-cells and less commonly from natural killer (NK) cells [1]. The median age at presentation is 60 years old with less than 10% of patients younger than 40 years of

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age. LGL is quite rare in children [2]. While a third of patients are asymptomatic at presentation, when present, symptoms are often related to infections secondary to neutropenia [3]. Several conditions have been associated with LGL, most commonly rheumatoid arthritis (RA) in approximately 25–30% of patients and anemia in up to 20% of patients including pure red cell aplasia and hemolytic anemia [4].

**CASE REPORT**

Our patient, an only child, first presented at 16 months of age with gastroenteritis and splenomegaly. At 23 months of age she developed hepatosplenomegaly and a compensated Coombs positive autoimmune hemolytic anemia. Her evaluation revealed a high IgM titer to CMV. Her serum IgM was mildly elevated at 177 mg/dl (NL range 48–168) with an IgG of 20 (NL range 553–971) and IgA < 7. The patient was maintained on monthly immunoglobulin infusions without significant infectious complications. It was felt that she had an autosomal recessive form of a hyper-IgM (HIGM) syndrome. At 6 years of age she developed diffuse lymphadenopathy. A lymph node biopsy revealed an atypical lymphoid hyperplasia. She was then treated with 6-mercaptopurine with near complete regression of the lymphadenopathy, but persistent hepatosplenomegaly. Her IgM level was 1750 at that time. She had a waxing and waning autoimmune hemolytic anemia over the next 4 years with relapses when attempts were made to taper off prednisone. Cyclosporine was later added in an effort to taper off steroids with limited success. She also was treated on two occasions with Rituximab with only transient success. At age 13 she underwent for splenectomy for this refractory hemolytic anemia and neutropenia. Her anemia and neutropenia remitted after the surgery. Two months later she developed massive ascites of uncertain etiology. Over the course of several months she required multiple paracentesis procedures. Further genetic studies revealed her to have activation-induced cytidine deaminase deficiency.

She next presented with a cough, muscle weakness and weight loss. A CBC at that time revealed a WBC 81,000/mm<sup>3</sup>, Hgb 9.2 g/dl, platelets 245,000/mm<sup>3</sup>. The peripheral blood smear revealed numerous large, granular lymphocytes along with neutropenia. Flow cytometry on the peripheral blood was consistent with large granular lymphocytic leukemia with the presence of cytotoxic lymphocytes (Table I). T-cell gene rearrangement studies by PCR detected a clonal rearrangement of the TCR  $\gamma$  (gamma) gene. Since her presentation with T-LGL 1 year ago, she has been maintained on weekly methotrexate (Table II). Her hepatomegaly has subsequently resolved along with resolution of her cytopenias and positive Coombs' test.

**DISCUSSION**

Approximately 10–15% of peripheral blood mononuclear cells are large granular lymphocytes, the majority of which are NK cells (CD3<sup>-</sup> CD8<sup>+</sup>). In 1977 McKenna first reported a syndrome with neutropenia and increased numbers of granular lymphocytes and in 1985 Loughran proposed the term LGL leukemia based on tissue invasion of the bone marrow, spleen and liver [5,6]. The FAB recognized LGL as a subgroup of chronic T-cell leukemia in 1989 and by 1993 Loughran proposed further sub classification into T-LGL and NK-LGL leukemia [7]. In 1994 the International Lymphoma Study Group proposed a Revised European-American Classification of Lymphoid Neoplasms [8]. T-Cell LGL is an indolent form of non-Hodgkin's lymphoma characterized by a clonal lymphoproliferation. NK-cell LGL are germline and usually not clonal in nature. LGL most commonly is due to the proliferation of cytotoxic T-cells (85%) and less commonly to NK cells (15%). Even though T-LGL is the most common T-cell neoplasm it only accounts for 4% of all chronic lymphoproliferative disorders.

Normally activated cytotoxic T-cells are eliminated through Fas-mediated apoptosis. T-LGL cells however, are resistant to Fas-mediated apoptosis [9,10]. Studies have shown that LGL leukemia

**TABLE I. Patient's Clinical Data**

Date	WBC	ANC	HGB	PLT	RETIC	Clinical features	Therapy
February 1997	8.0	3360	12.4	119,000			IV IgG
July 1998	4.0	1120	10.3	99,000		Diffuse adenopathy	6-MP
December 1999	7.0		6.2	56,000	12.7	AIHA-Coombs' positive	Prednisone
January 2001	3.4		7.1	94,000		AIHA continued	CSA + Prednisone
January 2002	3.2	2100	13.1	149,000			PDN
April 2002	7.9		6.4		17.9	AIHA	Rituximab + prednisone
May 2002	2.9	800	10.7	157,000	4.0		CSA + Prednisone
November 2002	3.5	400	12.4	120,000			
June 2003	4.3	344	10.1	79,000		AIHA	Rituximab
September 2003	2.9	200	8.0	83,000	2.84	Massive splenomegaly	
October 2003	2.0	300	7.5	86,000	4.34		6-MP, then splenectomy
November 2003	6.6		10.2	144,000			
December 2003	10.6	4020	11.3	501,000		January → massive ascites	
December 2004	23.8	500	11.5	443,000			
February 2005	81.0		9.2	245,000		Weight loss, muscle aches	PB → T-LGL PDN, MTX
March 2005	18.4	2945	9.2	356,000			Weekly MTX
November 2005	11.6	1500	11.4	382,000		Negative Coombs' test	Weekly MTX
December 2005	10.7	2600	13.1	405,000	0.86		Weekly MTX

TABLE II. Flow Cytometry on Peripheral Blood

Marker description		% Positive	
		Patient	References
CD2	T-cell/NK cell	98.6 (H)	69–85
CD3	T-cell	98.6 (H)	59–79
CD4	T-Helper/Inducer	2.8 (L)	36–52
CD5	T-cell/B subset	98.5 (H)	59–72
CD7	T-cell/NK Cell	97.3 (H)	62–84
CD8	T-suppressor/Cytotoxic	95.7 (H)	19–29
CD10	B-Cell/Gran	0.2 (L)	0.3–1.7
CD11c	Mono/Gran/NK/T subset	79.1 (H)	3–15
CD14	Monocytes	0.0	
CD16, 56	NK cell	0.3	
CD19	B cell	0.9 (L)	3–13
CD20	B cell	1.9	6–12
CD22	B cell	1.4	
CD23	B cell subset	0.1	
FMC7	B cell subset	1.5	
KAPPA	Kappa light chain	0.5	4–16
LAMBDA	Lambda light chain	0.4	2–12

H, high; L, low.

These findings show a markedly abnormal elevation of cytotoxic T-cell and reduced number of B cells.

cells express high levels of Fas ligand and sera from patients with LGL leukemia contain high levels of soluble Fas. Overall the evidence suggests that at least some cases of LGL leukemia are caused by dysregulation of apoptosis due to abnormalities in the Fas/ Fas-ligand pathway.

LGL is commonly associated with various clinical disorders including autoimmune disorders, hematological diseases and malignancies. The most frequent association is with RA which occurs in up to 1/3 of patients [3]. Autoimmune thrombocytopenia, autoimmune hemolytic anemia and pure red cell aplasia have also been seen. Felty described five patients with RA, leukopenia and splenomegaly in 1924 and this triad is now known as Felty's syndrome (FS). Considerable clinical overlap has been observed between the LGL and FS. Both have been characterized by neutropenia, splenomegaly and arthritis. T-cells have also been implicated in the joint destruction associated with RA and approximately 1/3 of patients with FS have a clonal proliferation of T-cells [12]. Some experts in the field are of the opinion that these two disorders are on a continuum of a single disease process. Initially the diagnostic criteria for LGL included an absolute large granular lymphocytosis greater than  $2.0 \times 10^9/L$ . As the criteria for diagnosing LGL has changed over the years more patients with FS would now be classified as having LGL on the basis of flow cytometry and molecular analysis for TCR gene rearrangement. FS and LGL also share a common immunogenic link. Patients with these disorders have a similar frequency of the HLA-DR4 allele (80–90%) [13]. Interestingly patients with T-LGL without RA have a 33% frequency of this allele that is similar to racially matched, normal controls [14]. It appears that FS and T-LGL are related disorders where the presence of clonal TCR gene rearrangements is seen in T-LGL and not in patients with FS. Why some patients with RA are prone to develop a clonal expansion of T-LGL has not been elucidated. Our patient, like others with HIGM Syndrome, shares the feature of having chronic autoimmune disease which may be a harbinger of LGL. Others have linked the predisposition to autoimmune disease and LGL to specific HLA subtypes [1].

The causes of neutropenia seen in FS and T-LGL can be reduced to problems with production, distribution and destruction. Early studies of neutropenia in patients with FS discovered two distinct groups [15]. Evidence of humoral mediated neutrophil destruction was seen in 60% of patients. These patients had either non-complexed immunoglobulin (presumed to be anti-neutrophil antibodies) and/or immune complexes. The other 40% of patients lacked neutrophil-bound immunoglobulin but were reported to have decreased granulocyte colony growth in bone marrow cultures. Cell mediated mechanisms have also been implicated in the pathogenesis of neutropenia in T-LGL. The dysregulation of apoptosis via the Fas/ Fas-ligand pathway that is responsible for T-LGL cell survival is also related to the development of neutropenia in these patients [16]. T-LGL cells constitutively express Fas-ligand on their cell surface. The Fas-ligand receptor, Fas (CD95) is expressed on a variety of cells including normal granulocytes. In fact neutrophils express higher levels of Fas than eosinophils or monocytes. This would make neutrophils more susceptible to apoptosis in the presence of Fas-activating antibody [17]. Neutropenia may also result from increased margination due to precipitated immune complex activation of neutrophils [18]. Thus in any given patient with T-LGL any or all of these mechanisms might be involved in the pathogenesis of neutropenia.

While T-cell LGL is most often a chronic, indolent disease the majority of patients will require therapy at some point. In rare cases patients may go into a spontaneous remission. Indications to initiate therapy include severe neutropenia ( $ANC < 500$ ) or recurrent infections in those with less severe neutropenia and symptomatic or transfusion dependent anemia [1]. Therapeutic approaches have included methotrexate at  $10 \text{ mg/m}^2/\text{week}$  orally [19]. This regimen leads to complete remission in approximately 75% of patients though continued treatment is often required to sustain remission and several months of treatment are usually needed before counts improve. Cyclosporine A has also been used as an alternative to methotrexate [20] and in a small study of 25 patients, 50% had a response to therapy and 24% of patients achieved a complete

remission. Patients with T-LGL and myelodysplasia have a lower response rate to cyclosporine than those with T-LGL alone. Cyclophosphamide in combination with prednisone produces responses at a higher rate than prednisone alone with overall response rates of 66% and a median duration of 32 months. Growth factors such as GM-CSF or G-CSF have been used to more rapidly increase neutrophil counts in patients with severe neutropenia.

While T-LGL is very uncommon in children it should be considered in the appropriate clinical setting of a patient with chronic anemia, neutropenia and/or thrombocytopenia and increased large granular lymphocytes on peripheral blood smear. The diagnosis is made by demonstrating expansion of a T-cell or NK cell population on flow cytometry along with clonal TCR gene rearrangement by molecular studies.

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## Peripheral T-Cell Lymphoma in a Five Year Old

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We report a case presenting with persistent pyrexia that led to the diagnosis of peripheral T-cell lymphoma, a rare malignancy in childhood. The case illustrates diagnostic conundrums in a patient

who is not responding as expected to treatment. *Pediatr Blood Cancer* 2008;50:145–147. © 2006 Wiley-Liss, Inc.

**Key words:** panniculitis; peripheral T-cell lymphoma

## INTRODUCTION

Determining the diagnosis of a persistently pyrexial child with panniculitic rash and systemic upset requires extensive multi-system investigation.

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