T-cell large granular lymphocytic leukemia and plasma cell disorders

Although neutropenia is not common as an initial presentation in patients with multiple myeloma (MM), it is a common adverse effect of the therapy used for MM and a more frequent problem in relapsed or refractory disease.[1-3] In rare cases, neutropenia may accompany the diagnosis of monoclonal gammopathy of undetermined significance (MGUS).[4] T-cell large granular lymphocytic (T-LGL) leukemia is a chronic lymphoproliferative disorder characterized by a clonal expansion of T-LGLs with a cytotoxic phenotype (CD3, CD8, and CD57).[5] It is a relatively rare malignancy and accounts for 2-5% of chronic lymphoproliferative diseases in the US.[6] T-LGL leukemia typically presents in patients over 60 years of age, with neutropenia being the most common cytopenia at diagnosis.[5] The association between T-LGL leukemia and B-cell disorders has been reported in the setting of indolent and aggressive B-cell non-Hodgkin lymphomas.[7] There have been few reports of T-LGL leukemia co-existing with plasma cell disorders, and these generally consist of case reports or small case series.[8-11] Here we report the largest case series of patients published to date with a diagnosis of plasma cell disorder and co-existing T-LGL leukemia.

We conducted a retrospective review of all patients seen at the Mayo Clinic between January 1994 and June 2018 with a diagnosis of T-LGL leukemia and a plasma cell disorder (PCD). Patients were identified from a database search of bone marrow histopathology records and

Table 1. Baseline characteristics.

	Age *	Sex	PCD	Time between diagnoses	TCR	Bone marrow	ANC x10^9/L)	Neutro-penia	Hb (g/L)	Anemia	Splenomegaly	T-LGL leukemia therapy	Course of T-LGL leukemia
T-LGL leukemia pre-PCD													
1	47	M	MGRS	207	+ve	+ve	–	Y		N	Y	CD	Relapsing
2	44	F	MGUS	128	NA	+ve	5.83	N	12.5	N	N	None	Indolent
3	58	F	MGUS	81	NA	+ve	–	Y		Y	NA	GCSF, EPO, MTX, CsP, Anti IL-2/IL1-15 mAb, C, Splenectomy	Relapsing
4	57	M	MM	79	+ve	+ve	–	Y		NA	N	None	Indolent
Concurrent T-LGL leukemia and PCD													
5	67	F	MGUS/MM	0	+ve	-ve	2.16	N	13.2	N	N	None	Indolent
6	64	M	MGUS/MM	0	+ve	+ve	1.1	Y	14.4	N	N	CP	Responded
7	43	M	MGUS/LPL	0	+ve	+ve	0.95	Y	12.1	Y	N	C	Responded
8	79	F	MGUS	0	+ve	+ve	–	N		Y	N	EPO, P, D, MTX, Cs, C	Relapsing Relapsing
9	52	F	MGUS/MM	0	NA	+ve	–	Y		Y	Y	C, Cs, MTX, GCSF/EPO, Splenectomy	
10	68	F	SMM	0	NA	+ve	0.1	Y	12.2	N	Y	MTX	Responded
11	73	F	MGUS	0	+ve	NA	–	Y		N	N	None	Indolent
12	49	F	MGUS	0	+ve	+ve	0.96	Y	11.3	Y	N	None	Indolent
13	66	F	MGUS	0	+ve	+ve	–	NA	7	Y	Y	CsV, CMTX	Relapsing
14	73	M	MGUS	0	+ve	+ve	–	Y		NA	N	None	Indolent
15	56	M	MM	0	+ve	+ve	–	N	6.6	Y	Y	CP	Responded
T-LGL leukemia post PCD													
16	70	M	MM	10	+ve	+ve	1.63	Y	6.4	Y	N	CP	Responded
17	72	M	MM/AL	14	+ve	+ve	1.62	Y	10.8	Y	N	None	Indolent
18	77	M	MGUS	15	NA	+ve	2.85	N	7.5	Y	N	None	Indolent
19	74	F	SMM/MM	27	+ve	NA	0.96	Y	10.1	Y	N	None	Indolent
20	70	F	LPL	46	+ve	+ve	0.59	Y	6.9	Y	Y	MTXP	Responded
21	66	F	MM	63	+ve	+ve	0	Y	10.6	Y	N	None	Indolent
22	71	M	MGUS	90	+ve	+ve	0.6	Y	8.7	Y	N	MTX, C, Atzmb	Refractory

PCD: plasma cell disorder; TCR: T-cell receptor gene rearrangement studies; ANC: absolute neutrophil count; T-LGL: T-cell large granular lymphocytic; Hb: hemoglobin; M: male; F: female; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; SMM: smoldering multiple myeloma; LPL: lymphoplasmacytic lymphoma; MGRS: monoclonal gammopathy of renal significance; AL: immunoglobulin light chain amyloidosis; C: cyclophosphamide; P: prednisone; D: dexamethasone; Cs: cyclosporine; MTX: methotrexate; V: vincristine; Atzmb: alemtuzumab; EPO: erythropoietin; GCSF: granulocyte colony stimulating factor; mAb: monoclonal antibody; Y: yes; N: no; NA: not available. *Age at T-LGL diagnosis.

were included if a diagnosis of both disorders was confirmed. All patients in the study met the 2016 World Health Organization diagnostic criteria for T-LGL leukemia and their respective PCD.[12] The study was approved by the Mayo Clinic Institutional Review Board.

Twenty-two patients were identified with a diagnosis of T-LGL leukemia and PCD. Patients' and disease characteristics are summarized in Table 1. The T-LGL leukemia diagnosis preceded the PCD in 4 patients (range of time interval between diagnoses, 79-207 months). The T-LGL leukemia was concurrent with the PCD in 11 patients, and was diagnosed after the PCD in 7 patients (range of time interval between diagnoses, 10-90 months). Median age at diagnosis of T-LGL leukemia was 66 years (range, 43-79); 55% of patients were female. The PCD diagnosis varied and included MGUS (n=13), MM (n=5), smoldering multiple myeloma (SMM) (n=2), lymphoplasmacytic lymphoma (LPL) (n=1), and one case of monoclonal gammopathy of renal significance (MGRS). One patient had myeloma with AL amyloidosis. Four patients with MGUS progressed to a more aggressive disease: 3 to MM and 1 to LPL. One patient with SMM progressed to symptomatic MM.

T-cell receptor (TCR) gene rearrangement studies were available and positive for clonal TCR gene rearrangement in 17 patients. Data on TCR gene rearrangement studies in the remaining 5 patients were not available. The immunophenotype of the aberrant T-cell population was available in 18 patients and was typical for T-LGL leukemia; the majority were CD2, CD3, CD7, CD8, CD16 and CD57 positive (Table 2). CD5 expression was variable and only a small proportion of patients (22%) expressed CD56. Anemia was present in 70% and neutropenia in 76% of patients at the time of T-LGL leukemia diagnosis. The median hemoglobin and neutrophil count, in patients with available data at the time of diagnosis, were 10.6 g/dL (range, 6.4-14.4 10.6 g/dL) and 0.96x10^9/L (range, 0-5.83x10^9/L), respectively. Splenomegaly was present in 29% of patients. None of the patients had a confirmed diagnosis of rheumatoid arthritis. Treatment for the T-LGL leukemia was variable with a number of different agents used, as listed in Table 1. Forty-five percent (n=10) of patients had an indolent disease course and did not receive specific therapy for T-LGL leukemia. Six patients responded to a single line of therapy; all of them received either cyclophosphamide or methotrexate-based regimens. The remainder had a relapsing course with multiple lines of therapy, including 2 patients who underwent splenectomy.

Table 2. Flow cytometry features.

	n=18
CD2	89%
CD3	94%
CD5	56%
CD7	72%
CD8	100%
CD16	67%
CD56	22%
CD57	89%
Clone %, median (range)	67% (22-100)

n: number.

Nine patients were identified as having symptomatic MM and T-LGL leukemia. The characteristics of these patients are presented in Table 3. Four patients had progressed from a pre-existing PCD, 3 from MGUS, and 1 from SMM. The diagnosis of T-LGL leukemia preceded myeloma in 1 patient, was concurrent in 4 patients, and post myeloma diagnosis in 4 patients. The time to diagnosis of T-LGL leukemia post myeloma ranged from 10 to 63 months. At the time of T-LGL leukemia diagnosis, neutropenia was present in 7 out of 9 patients and anemia in 6 out of 8; data were unavailable for 1 patient. The majority of patients were treated using novel agents, 7 receiving bortezomib-based therapy. Three patients underwent autologous stem cell transplantation. Therapy directed at the T-LGL leukemia was given to 4 out of 9 patients and consisted of cyclophosphamide and prednisone in 3 patients, all of whom responded to therapy with resolution of the cytopenias. One patient had T-LGL leukemia with multiple relapses which required several lines of therapy; he eventually underwent splenectomy. Three patients who developed T-LGL leukemia

Table 3. Multiple myeloma cohort.

Characteristics	Myeloma cohort (n=9)
Age	69 (56-77)
Male	56%
Preceding MGUS	3
Preceding SMM	1
Monoclonal protein	
IgG	4
IgA	3
IgD	2
Light chain type	
Kappa	5
Lambda	3
Hemoglobin, g/dL, median (range)	10.6 (6.4-14.4)
Neutrophils, x10^9/L, median (range)	1.36 (0-2.16-6.91)
ISS	
I	1
II	1
III	4
Missing	3
Cytogenetics	
Normal	1
Hyperdiploid	3
Del 13q	2
t(14;16)	1
1q amp	1
Missing	2
Therapy received	
ASCT	3
Bortezomib	7
Lenalidomide	3
Thalidomide	1
Radiotherapy	1

MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; ISS: International Staging System; ASCT: autologous stem cell transplantation; n: number.

after the diagnosis of myeloma did not receive specific therapy directed at the T-LGL leukemia. The clinical course of the T-LGL leukemia in these 3 patients was indolent and did not appear to be affected by therapy for MM.

At last follow up, 5 patients have died. With a median follow up of 76 months post T-LGL leukemia diagnosis, the median overall survival (OS) post T-LGL leukemia diagnosis was not reached for the entire cohort. In the cohort of patients with MM, median OS from time of myeloma diagnosis was 71 months.

Our study reports on the largest case series of patients with PCDs and co-existing T-LGL leukemia. The majority of patients (59%) had MGUS; however, rare disorders such as AL amyloidosis and MGRS were also seen. MM was the second most common PCD, and this included patients with *de novo* myeloma as well as those progressing from MGUS or SMM. This highlights the need for vigilance when monitoring patients with MGUS or SMM, particularly in those who develop unexplained neutropenia.

The T-LGL leukemia was diagnosed at the same time or after the diagnosis of the PCD in the majority of cases, and this is consistent with other case series of co-existent T-LGL leukemia and B-cell disorders.[7] The likelihood of developing a plasma cell neoplasm after diagnosis of T-LGL leukemia has previously been reported to be low. In one study, none of the 12 patients diagnosed with T-LGL leukemia and MGUS progressed to MM.[13] This has raised the possibility that the T-LGL clonal expansion represents an immune response to the monoclonal gammopathy and a potential role in tumor surveillance.[7] In our study, 2 patients with MGUS diagnosed after T-LGL leukemia have not progressed to myeloma at last follow up. However, one patient presented with MM several years after a diagnosis of T-LGL leukemia, and 4 patients diagnosed at the same time with T-LGL leukemia and MGUS progressed to myeloma or lymphoplasmacytic lymphoma. Our observations question the potential protective role of the T-LGL leukemia against development of MM. Furthermore, the course of the T-LGL was variable irrespective of the type of PCD or timing of diagnosis in relation to the PCD. Relapsing or indolent T-LGL leukemia was seen in all three groups of time intervals between the different diagnoses. This suggests the link between the PCD and T-LGL leukemia goes beyond an immune surveillance response, and that these patients need ongoing monitoring for progression of either disease. The development of T-LGL leukemia after diagnosis of a PCD is most poignantly highlighted by Case n. 16: a 70-year old man who was diagnosed with MM and received six cycles of bortezomib, cyclophosphamide and dexamethasone (CyBorD) followed by an autologous stem cell transplant. When the patient was reassessed 100 days after transplant, he was severely anemic (hemoglobin 6.4 g/dL) and remained transfusion dependent. Bone marrow revealed no evidence of a PCD but showed severe erythroid hypoplasia and 10-15% marrow involvement by T-LGL leukemia. His bone marrow biopsy at time of myeloma diagnosis and immediately prior to stem cell mobilization for transplant had shown no evidence of T-LGL leukemia. For the T-LGL leukemia to develop so quickly after treatment with high-dose melphalan raises questions about its presence at low levels throughout his disease, and indeed whether the plasma cell clone may have been suppressing expansion of the T-LGL clone. This observation also highlights the potential for the T-LGL clone to expand rapidly.

This study has some limitations represented by its retrospective nature and long study period. It does, however, report on the largest cohort of patients with T-LGL leukemia and PCDs. We recognize that our analysis likely underestimated the co-existence of these two conditions. Many patients with a PCD presenting with neutropenia may not be investigated for T-LGL leukemia and remain undiagnosed. Thirty-two percent (n=7) of the patients in our cohort developed T-LGL leukemia after the diagnosis of a PCD, the majority (71%, n=5) of whom had an active disorder receiving therapy (MM or LPL). This highlights the importance of monitoring these patients and considering T-LGL leukemia as a differential in the setting of unexplained cytopenias, especially when the plasma cell disorder is well controlled.

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