

A case report on the possible effects of large granular lymphocytic leukemia in limiting the concomitant acute myeloid leukemia expansion

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Abstract

Objective and Importance: The objective of our case report is to give a brief, but complete, description of an extremely rarely reported disease association: large granular lymphocyte (LGL) leukemia and acute myeloid leukemia (AML). The importance of our case report lies in the fact that further studies could be accomplished to reconsider and optimize the management of this disease overlapping.

Clinical Presentation and intervention: A 64 year-old male with leukopenia and neutropenia presented a concomitant diagnosis of large granular lymphocyte leukemia and acute myeloid leukemia. He was treated with two courses of standard chemotherapy fourteen months after diagnosis because of the progressive worsening of blood counts, and developing symptoms related to anemia and thrombocytopenia. During phases of cytopenia after chemotherapy, he presented multiple viral, bacterial and invasive fungal infections, showing a higher infective risk compared with other hematological patients.

Conclusion: Chemotherapy successfully treated both LGL and AML, and the patient is still in complete remission 27 months after the last chemotherapy cycle. Ultimately, we suggest: 1) chemotherapy optimized for AML could drive both malignancies to complete remission, 2) the coexistence of the AML and the LGL leukemia may place the patient at severe infective risk.

Keywords

LGL; acute myeloid leukemia; invasive fungal infection; concomitant presentation

Abbreviations

LGL: large granular lymphocytic; AML: acute myeloid leukemia; NK: natural killer; IFI: invasive fungal infection; G-CSF: granulocyte colony-stimulating factor; MDS: myelodysplastic syndrome; CTL: cytotoxic T-lymphocyte; CHOP: cyclophosphamide, hydroxydaunorubicin, oncovin®, prednisone; BMB: bone marrow biopsy; BMA: bone marrow aspirate; Npm: nucleophosmin

Introduction

Large granular lymphocytic (LGL) leukemia comprises a spectrum of rare lymphoproliferative chronic disorders caused by the clonal expansion of cytotoxic T cells or natural killer cells.

It is morphologically characterized by large granular lymphocytes named after their large azurophilic cytoplasmic granules [1,2].

Two-thirds of the patients present symptoms related to neutropenia, anemia or autoimmune diseases, such as rheumatoid arthritis, while the remaining one-third is asymptomatic [3,4]. The disease rarely has an aggressive course.

The possible anti-tumor activity of LGL against acute myeloid leukemia (AML) has been reported in literature before [5].

Specifically, both T-cell and Natural Killer (NK) cell-based immunotherapy is currently employed in the treatment of persistent AML [6,7].

We report here a case of concomitant diagnosis of AML and LGL leukemia, with AML progressing one year after its diagnosis.

Case Report

We report on a 64 year-old male who showed up at our outpatient facility with slight leukopenia and neutropenia (leukocytes 6280/mm³ with 24% neutrophils and 69% lymphocytes), without any clinical symptoms. After excluding an autoimmune pathogenesis of the cytopenia, a bone marrow biopsy was performed and resulted compatible with a simultaneous diagnosis of T-cell LGL leukemia and acute myeloid leukemia (NOS AML according to WHO classification 2008⁸, FAB classification "M1"). These diagnoses were concomitantly documented by a combination of morphological evaluation (cytological and histological examinations), immunophenotyping by flow cytometry, and T-cell gene rearrangement studies (table 1 A).

FISH study on bone marrow reported an abnormal karyotype in 6.2% of the analyzed metaphases: 45 X, -Y; however, this abnormality was considered a constitutional mutation, with no pathogenetic nor prognostic role in the development of hematological malignancies. We decided not to treat the patient as he was only slightly leukopenic and asymptomatic.

Fourteen months after diagnosis, the patient was admitted to our inpatient care unit, because of progressively worsening blood counts (Hemoglobin 7.7 g/dl; leukocytes 2.100/mm³; 24% neutrophils; platelets 49.000/mm³). He was in healthy clinical conditions with the exception of a well-controlled type 2 diabetes mellitus. Physical examination did not show any lymphadenopathy or splenomegaly. A mild hepatomegaly was palpable during inspiration.

The bone marrow biopsy was repeated and confirmed the diagnosis of AML while showing no sign of T-cell LGL (table 1 B).

In the absence of remarkable comorbidities, the patient was considered fit to receive conventional chemotherapy comprising Cytarabine 100mg/m² for 10 days, in continuous perfusion, Daunorubicin 50mg/m² (days 1, 3 and 5) and Etoposide 50mg/m² for 5 days. The following period, characterized by a

severe cytopenia, which lasted roughly 20 days, was complicated by a 12 days long fever, with positive blood culture for *Enterococcus Faecium*, which was successfully treated with Vancomycin and Meropenem. The patient presented also a severe HSV nasal infection successfully treated with high dose Valacyclovir.

In June 2014, at the admission for the first consolidation cycle, comprising Daunorubicin 50mg/m² and Cytarabine 100mg/m² for seven days, the patient was in healthy clinical conditions and negative for a physical exam. However, during the leukopenic period, the patient had fever (39.3 C°) and the blood cultures were positive for *Blastoschyzomices Capitatum*. This invasive fungal infection (IFI) was localized also in the lung, liver and spleen; it was successfully treated with Voriconazole, Amphotericine B (5mg/kg/die) and granulocyte colony-stimulating factor (G-CSF) to improve granulocyte recovery.

At hematological recovery, bone marrow aspirate and bone biopsy were repeated and showed full remission of both leukemias as documented by morphologic and molecular exams (table 1 C). By November 2015 a checkup blood count documented: leukocytes 7110/mmc with 34.6% neutrophils and 53.5% lymphocytes.

Today our patient is in complete remission and healthy clinical conditions.

Discussion

This case report describes the rare condition represented by the simultaneous diagnosis of AML and a lymphoproliferative disorder such as LGL leukemia. Only once had this association been described before in literature [9].

The possible pathogenetic mechanisms that could justify this condition include a divergent differentiation of the same stem cell clone; a concomitant evolution of separate processes or the result of a pre-existing immune deficiency state[9-11].

The pathogenetic hypothesis of a common progenitor to both myeloid and NK cells is supported by the existence of a specific subtype of early leukemia, the myeloid/Nk cell precursor acute leukemia, which is characterized by chemoresistance and bad prognosis [12].

However, the present case may be the result of the prolonged coexistence of T-LGL with myelodysplastic syndrome (MDS), possibly evolving to AML in its final stage.

Although rare, it seems likely that the simultaneous occurrence of T-LGL and MDS may be somehow related rather than a chance event. *Saunthararajah et al.* [12] suggested two possible explanations [13]:

1: T-LGL might arise from a clonal MDS stem cell. Indeed, also *Jerez A. et al.* in their recent study sustain that a clonal cytotoxic T-lymphocyte (CTL) population can arise in the context of AA and MDS [14].

2: T-LGL could represent an autoimmune response to an antigen expressed by normal or MDS bone marrow cells. In both of these scenarios, one would hypothesize that the MDS arose first, followed by T-LGL.

As a last pathogenetic hypothesis we may not exclude that a minor LGL clonal line developed in the bone marrow thus favoring the development of the AML through a myelodysplastic period.

In our patient, the LGL leukemia was overwhelmed when the AML clearly progressed in the peripheral blood.

The disappearance of the LGL leukemia documented after the complete remission from the AML, may suggest that both the AML's cells and the LGL's clone were sensitive to the chemotherapy scheduled for the AML. This observation could give credit to the hypothesis, which states the existence of a common progenitor for both the malignant clones.

However, there is only one report of the administration of anthracyclines, in CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin®, prednisone) chemotherapy regimen, in LGL leukemia with evidence of response in one patient [15-17].

Another relevant fact is worth mentioning: our patient demonstrated a peculiar susceptibility to opportunistic infections including uncommon fungi such as *Blastoschyzomices Capitatum*, *Candida Norvegensis* and *Saccaromyces Cerevisiae*. Although complex to prove, this predisposition could be related to a further impairment of the cell-mediated immunity, induced by the preexisting LGL leukemia.

In conclusion, this peculiar concomitant presentation of AML and LGL shows that a chemotherapy optimized for AML could drive both malignancies to complete remission. Moreover, the coexistence of the AML and the LGL leukemia may place the patient at severe infective risk.

Table

EXAM TYPE	Diagnosis of LGL leukemia and AML (Table 1 A)		AML Progression (Table 1 B)		Complete remission (Table 1 C)	
	LGL leukemia	AML	LGL leukemia	AML		
BMB	CD3+/CD8+/CD57+ → 10% of lymphoid interstitial component.	50% of blasts cells in the lymphoid interstitial component. Cd34+ → 25% of the overall cellularity	Cd3+ / CD8+ / CD57+ → N.D.	Cd34+, CD68/PGM1-, MPO-	T lymphocytes CD3+/CD8+ (<5%)	No evidence of CD34+
Immunophenotype	Evaluated on peripheral blood (28/12/2012): → A 17% overall quantity of CD3+, CD4-, CD8-, gamma-delta receptor(TCR) +, and cytotoxic activity was documented	Evaluated on bone marrow -CD34+ CD117+ → 20% of the overall cellularity -Cd34+ CD13+ → 20% of the overall cellularity -Cd34+ CD33+ → 5% of the overall cellularity	Evaluated on peripheral blood: not detected CD3+, CD4-, CD8-, gamma-delta receptor(TCR)+	Evaluated on bone marrow -CD34+ CD117+ → 24% of the overall cellularity -CD34+ CD13+ → 24% of the overall cellularity -CD34+ CD33+ → 9% of the overall cellularity -CD 13+ → 24% of the overall cellularity	Evaluated on peripheral blood: CD3+ → 67% CD4+ → 33% CD 8+ → 41% CD3+ CD8- → 0% Cd3+ CD4- → 0%	Evaluated on bone marrow: Cd34+ → 0%
PCR	Biclonal Biallelic rearrangement of T cell Receptor Gamma	/	Not Performed	/	Negative	/
BMA	/	/	No excess of lymphoid cells	40-50% myeloid blast cells among overall cellularity	No excess lymphocytes	No excess blast cells
WT1/ABL *10⁴	/	/	/	342,65	/	30
Karyotype	/	45, X0 → 6,2% of the analyzed cells	/	45, X0 → 6,2% of the analyzed cells	/	/
Point mutation D835/I836 in TKD	/	Negative	/	Negative	/	/
ITD presence in JM fragment	/	Negative	/	Negative	/	/
Npm	/	Wild type	/	Wild type	/	/

Hematological evaluation of LGL and AML at three chronological checkpoints

Legend: BMB: bone marrow biopsy, BMA: bone marrow aspirate, Npm: nucleophosmin. *this karyotype was considered as constitutional, and thus it was not further performed.

References

1. Loughran TP Jr. Clonal diseases of large granular lymphocytes. *Blood*. 1993; 82: 1-14.
2. Chan WC, Foucar K, Montserrat E. T-cell large granular lymphocyte leukemia. In: Jaffe ES, Harris NL, Stein H, et al, eds. *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001:197-198. *World Health Organization Classification of Tumours*.
3. Liu X, Loughran TP, Jr. The spectrum of large granular lymphocyte leukemia and Felty's syndrome. *Curr Opin Hematol*. 2011; 18: 254-9.
4. Lamy T, Loughran TP. Clinical features of large granular lymphocyte leukemia. *Semin Hematol*. 2003; 40: 185-95.
5. Costello RT, Sivori S, Mallet F, Sainty D, Arnoulet C, Reviron D, Gastaut JA, Moretta A, Olive D. A novel mechanism of antitumor response involving the expansion of CD3+/CD56+ large granular lymphocytes triggered by a tumor-expressed activating ligand. *Leukemia*. 2002; 16(5): 855-60.
6. Arpinati M and Curti A. Immunotherapy of acute myeloid leukemia. *Immunotherapy*. 2014; 6(1): 95-106.
7. Tolomelli G, Arpinati M, Brandi G. Cell Therapy Strategies are also Promising to the Future of Immunotherapy, *Journal of Hematology and Thromboembolic Diseases*. 2014; Dis 2: 138.
8. Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, et al. (2008) *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC; 25506952.
9. Malani AK, Gupta C, Rangineni R, Singh J, Ammar H. Concomitant presentation of acute myeloid leukemia with T-cell large granular lymphocytic leukemia. *Acta Oncol*. 2007; 46(2): 247-9.
10. Robak T. Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukemia. *Hematology*. 2004; 9: 387-400.
11. Lai R, Arber DA, Brynes RK, Chan O, Chang KL. Untreated chronic lymphocytic leukemia concurrent with or followed by acute myelogenous leukemia or myelodysplastic syndrome. A report of five cases and review of the literature. *Am J Clin Pathol*. 1999; 111(3): 373-8.
12. Imashuku S, Kudo N, Sungkyu P, Shinbo M, Furukawa T, Iwae S.. Myeloid/NK cell acute leukemia with unique blast morphology: de novo or secondary leukemia? *Int J Hematol*. 2013 Oct; 98(4):509-11.
13. Sauntharajah Y, Molldrem JL, Rivera M, et al. Coincident myelodysplastic syndrome and T-cell large granular lymphocytic disease: clinical and pathophysiological features. *Br J Haematol*. 2001; 112(1): 195-200.
14. Jerez A, et al. STAT3 mutations indicate the presence of subclinical T-cell clones in a subset of aplastic anemia and myelodysplastic syndrome patients. *Blood*. 2013; 122(14): 2453-9.
15. Huh YO, Medeiros LJ, Ravandi F, Konoplev S, Jorgensen JL, Miranda RN. T-cell large granular lymphocyte leukemia associated with myelodysplastic syndrome: a clinicopathologic study of nine cases. *Am J Clin Pathol*. 2009; 131(3): 347-56.
16. Ruskova A, Thula R, Chan G. Aggressive natural killer-cell leukemia: report of five cases and review of the literature. *Leuk Lymphoma*. 2004; 45(12): 2427-38.
17. Sretenovic A, et al. T-cell large granular lymphocytic (T-LGL) leukemia: a single institution experience. *Med Oncol*. 2010; 27(2): 286-90.

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