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Sustained response to erythropoietin for anemia in NK-cell large granular lymphocytosis: A brief case report

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ABSTRACT

Large granular lymphocytic leukemia (LGL) is a rare lymphoproliferative disorder that involves the T-cell lineage in around 85% of cases and NK-cell lineage in 15%. Most patients require treatment at some point of their disease trajectory to address clinical symptomatology largely pertaining to cytopenia. While immunosuppression represents the backbone of LGL therapy, there is no consensus on the best next line following failure of immunosuppression. Here we present a case of LGL-associated cytopenia in a 73-year-old male refractory to immunosuppression, treated with adjunct erythropoietin alpha (EPO) with a marked response. Our case suggests that EPO therapy may provide therapeutic benefit in refractory LGL cases when used in conjunction with immunosuppressive therapy.

1. Introduction

Large granular lymphocytic (LGL) leukemia is a rare chronic lymphoproliferative disorder that involves the T-cell lineage in around 85% of cases and NK-cell lineage in the rest. [1,2] Chronic lymphoproliferative disorder of NK cells (CLPD-NK) is an entity recognized by the World Health Organization as a subtype of LGL. [3,4] In most cases the disease follows an indolent course, with a median overall survival of up to 10 years. However, some cases are characterized by an aggressive clinical behavior and resistance to therapy, resulting in a shortened survival. [1]

Many patients are asymptomatic at the time of diagnosis with mild cytopenia, however most patients eventually develop symptomatic disease with worsening cytopenia, fatigue or autoimmune phenomena requiring therapy. [2] Anemia represents a common manifestation seen in 28–100% of cases of LGL. [5] The causes of anemia in lymphoproliferative disorders are variable and often multifactorial including marrow infiltration, anemia of chronic disease/inflammation, autoimmune disorders such as autoimmune hemolytic anemia or pure red cell aplasia, and suppressed erythropoiesis by chemotherapy. [6,7]

A variety of evidence-based immunosuppressive therapies such as methotrexate, cyclosporine, prednisone, and cyclophosphamide with dexamethasone have shown acceptable results as initial treatment options for LGL. However, resistance and short-lived responses to frontline therapy represent an ongoing challenge, particularly in those with refractory anemia.

Interest lies in exploring treatment options for LGL resistant to frontline therapies, such as utilizing growth factors to enhance autologous cell-line production. There is limited data supporting the use of growth factors, particularly EPO, in treating LGL-induced resistant cytopenia. In a small single cohort of seven patients with refractory LGL, treatment with EPO resulted in poor or transient improvement in anemia. However, in this study EPO was used as single agent rather than as an adjunct to immunosuppressive therapy. [5] In comparison, the adjunct administration of darbepoetin alfa concurrently with cyclosporine and prednisolone in a case of T-cell large granular lymphocyte disorder (T-LGL), effectively improved the anemia while successfully treating the malignancy. [8] Studies utilizing EPO as such an adjunct

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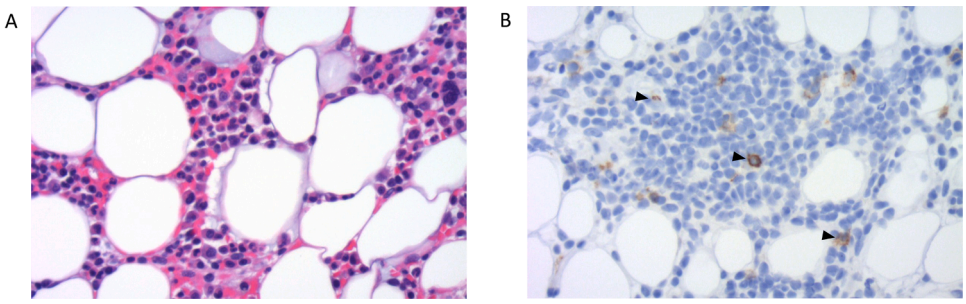

Fig. 1. Micrographs from the bone marrow biopsy of the patient. A. Wright staining (original magnification 200X) of the bone marrow core. B. Immunostain for CD56 showing rare cells that are positive in the membranous/cytoplasmic staining pattern (arrow).

therapy are vastly lacking. In this article we present a case that explores the utility of erythropoietin as an adjunct agent in a case of anemia in NK-cell LGL that was resistant to immunosuppressive therapy. To the best of our knowledge, this is the first reported use of EPO as adjunct therapy to immunosuppression in NK-cell LGL.

2. Case presentation

A 73-year-old man with a history of stage IVB diffuse large B cell lymphoma (DLBCL) of the neck was treated with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and dexamethasone (R-CHOP) in 2014 resulting in a complete remission. Five years later, in January 2019, he presented with fatigue, anorexia, 50 lbs. weight loss and dyspnea on exertion. Review of systems was pertinent for nausea and early satiety. The patient's past medical history was notable for aforementioned DLBCL. He was not on any chronic medications. The patient's body-mass-index was 19, and the rest of the physical exam was unrevealing.

A complete blood count showed severe anemia with a hemoglobin (Hb) concentration of 5.7 g/dl, severe neutropenia with an absolute neutrophil count (ANC) of 400/µl, and a normal platelets count. A complete metabolic panel including folate, vitamin-B12, thyroid functions, and iron studies was performed, and the results were within normal limits. A Positron Emission Tomography-Computed Tomography (PET-CT) scan obtained to evaluate DLBCL relapse was unrevealing. He then underwent a bone marrow biopsy which showed a hypocellular bone marrow (BM) at 20% cellularity with a relative decrease in erythropoiesis, without any evidence of myelodysplasia; however there was an atypical NK-cell population that was CD45+, CD2+, CD3-, CD4-, CD5-, CD7+, CD8-/+, CD10-, CD11c+, CD16+, CD38+ by flow cytometry making up approximately 25% of the marrow cellularity, immunohistochemical studies performed on the bone marrow core revealed that the cells were CD56+ and CD57+ (in rare cells) (Fig. 1). Similar flow cytometric findings were seen in peripheral blood with a

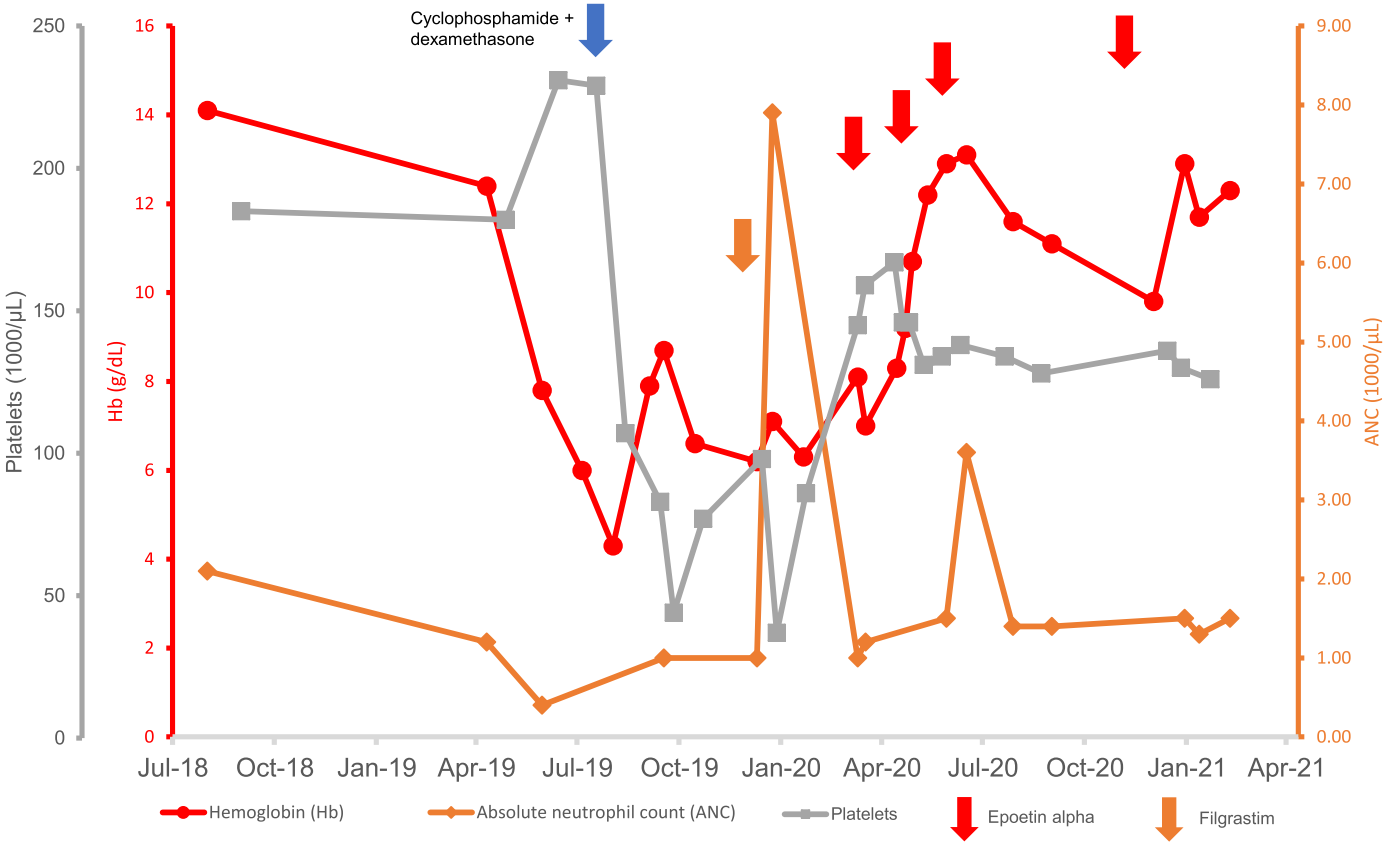

Fig. 2. Hemoglobin and absolute neutrophil count trends with erythropoietin (EPO) treatment. Data are tabulated as Hg in g/dL and ANC as 10^3\mm^3 (Y axis) and time between August 2018 and February 2021 (X axis). EPO treatments indicated with red arrows and filgrastim treatment indicated with blue arrow.

39% atypical NK-cell population. T-cell gamma chain and beta chain gene rearrangement analysis assessing T-cell clonality was negative by PCR. Karyotyping of the bone marrow showed a 46, XY karyotype without any clonal abnormalities. These findings were consistent with a diagnosis of CLPD-NK. The patient was subsequently started on immunosuppressive therapy with cyclophosphamide 50 mg daily for 2 weeks in 3 week-cycles, in addition to weekly 40 mg of oral dexamethasone. The treatment resulted in improvement of symptoms and ANC to 1000/μl, along with a decrease in the BM NK-cell population to 9% by flow cytometry. Despite the pathologic response to treatment, anemia failed to improve, and the patient remained transfusion dependent, totaling 42 units over nine months, and resulting in a secondary hemochromatosis with an increase in ferritin levels to more than 1500 μg/l. The treatment also resulted in severe thrombocytopenia that appeared within 2 months of initiation of treatment, with a platelet count of 44,000/μl.

Given the refractoriness of the anemia, the patient was treated with a single dose of EPO 40,000 U in May 2020, as an adjunct therapy to the ongoing cyclophosphamide and dexamethasone, resulting in a marked improvement of his anemia, with an increase in Hb from 8 to 9.2 g/dl within one week. Treatment was continued for the three following weeks, with weekly EPO 20,000 U (reduced from the previous dose in order to reduce side effects, given the favorable response) resulting in a further improvement in Hb to 12.9 g/dl. Concomitantly, ANC and platelet count also improved to 1500/μl and 138,000/μl, respectively. This dramatic hematological response was associated with a concomitant improvement in the fatigue and dyspnea. With this remarkable response to the treatment, EPO was stopped for the following 4 months without a notable decrease in Hb, which remained stable for the following 6 months, while he was maintained on immunosuppressive therapy. Hb started to gradually decrease to 9.4 g/dl in December 2020 for which EPO 20,000 U was restarted resulting in an increase Hb concentration to 12.9 g/dl within 3 weeks (Fig. 2). The patient remains transfusion-independent at last follow-up, additionally cyclophosphamide was discontinued after 20 months of therapy without any further drop in Hb (Fig. 2).

3. Discussion

Here we present a case of refractory anemia and neutropenia secondary to CLPD-NKs, an LGL subtype, that was successfully treated with EPO. The dramatic improvement in blood counts spared the patient chronic transfusions and improved his symptoms, paving the road for a possible role for EPO in this disease category. The etiology of this patient's anemia was likely multifactorial but there was certainly evidence of marrow infiltration with hypoproliferation given the decreased erythropoiesis noted on bone marrow biopsy. Suppressed erythropoiesis by the immunosuppressive regimen cannot be ruled out as well, as there was evidence of platelet suppression after the treatment was started. However, the severe anemia and neutropenia preceded the immunosuppressive therapy, suggesting that his LGL is the most responsible for this cytopenia.

Surprisingly, in addition to correcting the anemia, EPO resulted in reversing the concomitant thrombocytopenia and neutropenia. The response was also durable and lasted for six months prior to requiring retreatment with EPO resulting in a subsequent response. Given this noted response to retreatment, a repeat bone marrow biopsy was not pursued. This case adds girth to a therapeutic avenue that is sparse in evidence, given that the role of EPO as adjunct therapy to immunosuppression in LGL is poorly studied, with none previously reported in CLPD-NK.

While immunosuppressive therapy remains the mainstay treatment of LGL, with its main indication being cytopenia and symptomatic disease, the role of hematopoietic growth factors such as EPO have yet to be proven as an adjunct therapy. Our patient's strong and long-lasting response to EPO contrasts with data reported in the medical literature with patients either having only partial or short-lived responses to EPO. [5, 8] Unfortunately the erythropoietin level was not measured prior to initiation of therapy in our case, it would however be recommended prior to administration of EPO. Further characterization of the described response in CLPD-NK is warranted as it may differ compared to T-LGL. However, given the largely indolent course and rarity of LGL leukemia, and CLPD-NK accounting for only 10–15% of this portion [1,2,5], larger cohorts or randomized controlled trials represent a very challenging task. Continuous reporting of successful therapeutic approaches will significantly inform treatment decisions in this rare disease.

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Declaration of Competing Interest

There is no conflict of interest to declare for this project.

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TK and FS summarized the case and conducted literature review. TK and FS wrote the manuscript. BR and BB provided the micrographs. FS, BL and NSS provided clinical data. NSS critically reviewed the manuscript. All authors read and approved the final manuscript.

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