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THE CASE OF T-CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA PRESENTED AS TRANSFUSION DEPENDENT ANEMIA WITH SUSTAINED RESPONSE TO CYCLOSPORINE A THERAPY: CASE REPORT

T-ČELIJSKA LEUKEMIJA VELIKIH GRANULISANIH LIMFOCITA SA KLINIČKOM SLIKOM TRANSFUZIONO ZAVISNE ANEMIJE I PROTRAHOVANIM TERAPIJSKIM ODGOVOROM NA CIKLOSPORIN A: PRIKAZ SLUČAJA

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Summary
Case report. A 41-year-old man presented with anemia, lymphocytosis and splenomegaly. T-cell large granular lymphocyte leukemia was diagnosed based on lymphocytosis of T-cell large granular lymphocytes, characteristic immunophenotype (CD3+, CD8+, CD16+, CD57+) of the lymphocytes and clonally rearranged T-cell receptor genes. Therapy indication was transfusion-dependent anemia. Initial cyclosporine therapy and low-dose oral methotrexate failed to control anemia and lymphocytosis. Yet, a complete clinical and hematological response (without molecular remission) was achieved and sustained when cyclosporine was reintroduced into the therapy. Conclusion. Our case confirms that cyclosporine therapy is effective in treating T-cell large granular lymphocyte leukemia and suggests that indefinite treatment may not be needed to maintain the response. Key words: Leukemia, Large Granular Lymphocytic; Diagnosis; Lymphocytosis; Anemia; Cyclosporine; Treatment Outcome

Sažetak
Prikaz slučaja. Bolesnik star 41 godinu inicijalno je predstavljeno anemijom, limfocitozom i splenomegalijom. Dijagnoza T-ćelijske leukemije velikih granulisanih limfocita postavljena je na osnovu prisustva limfocitoze velikih granulisanih limfocita (citomorfološki), karakterističnog imunofenotipa limfocita (CD3+, CD8+, CD16+, CD57+) i klonskog rearanžmana gena za T-ćelijski receptor. Glavna terapijska indikacija bila je transfuзионска анемија. Инцичалне лечење циклоспорином као и ниском дозом пероралног метотрексата није успело да контролише анемију и limfocitozu. Међутим, конвено увођењем циклоспорина у терапију постигнут је комплетни клинички и хематолошки odgovor bez molekularне re- misije. Zaključak. Naš slučaj potvrđuje da je ciklосporin delotворан u terapiji leucemije velikih granulisanih limfocita i ukazuje да doživotна терапија ради одржавања terapijsког odgovora ne mora бити неопходна. Ključne reči: T-LGL leukemija; dijagnoza; limfocitoza; anemija; ciklосporin; ishod lečenja

Introduction

T-large granular lymphocyte (T-LGL) leukemia is a rare lymphoproliferative disorder that comprises 2%–5% of all T-cell/natural killer (NK)-cell malignancies [1, 2]. The diagnosis is suggested by flow cytometry and demonstrates an expansion of CD3+CD8+CD57+ T-cells that is confirmed by T-cell receptor gene rearrangement studies [2–4]. In most patients, this is an indolent disorder with a median survival time >10 years [1, 2, 4]. Approximately two thirds of all patients with indolent T-LGL leukemia develop cytopenias, recurrent bacterial infections, autoimmune disorders, and/or splenomegaly over the course of their disease. Thus, more than half of these patients require treatment [3]. Immunosuppressive therapy, including single agent corticosteroids, methotrexate, cyclophosphamide and cyclosporine (CsA), is effective in controlling symptoms and cytopenia [3, 4]. In this report, we discuss our own experience and report a complete response to CsA.

Case Report

A previously healthy 41-year-old man was admitted to our department for the investigation of symptomatic anemia. He did not have palpable peripheral lymphadenopathy, splenomegaly or hepatomegaly. His complete blood count showed anemia (hemoglobin (Hgb) of 80 g/L, erythroid indices: MCV 109.7 fl, MCHC 33.73 g/dl, RDW 19.6%) and lymphocytosis (white blood count - WBC) of 12.2 x 10^9/L, with a differential count of 51% lymphocytes, total lymphocyte count:...
4.816 x 10^9/L). The lymphocytes were small to intermediate with discrete but visible granules in cytoplasm (Figure 1). Other laboratory test results were as follows: reticulocytes 1x10^3/L, negative direct and indirect Coombs’ test, liver enzymes, creatinine, blood urea nitrogen, and iron within the normal range. Hepatitis B surface antibody (HBsAg), anti hepatitis C virus (HCV), anti human immunodeficiency virus (HIV), Cytomegalovirus and Epstein-Barr virus were negative, whereas Mycoplasma pneumoniae and Adeno virus IgM were slightly positive. Bone marrow (BM) cytology showed moderate erythroid hypoplasia. The small to intermediate lymphocytic cells comprised 25% of the BM cells. Ultrasonography showed a slightly enlarged spleen. Treatment with corticosteroids was started (prednisone 20 mg/day). However, transfusions with erythrocytes were needed to address a persistent drop in Hgb to 67 g/L.

Subsequent diagnostic investigation excluded antinuclear, antimitochondrial, antinucleosuphosphate, antiparietal cell, antithyroid and anticardiac antibodies. Quantitative Igs were within the reference ranges. The Coombs direct (IgG and c3d) and indirect tests were positive. A 51Cr red cell survival study showed reduced survival times for erythrocytes (17 days). Flow cytometry of peripheral blood demonstrated a (CD3, TCR α/β, CD2, CD7, CD5, CD8, CD16, CD57, HLA DR) and (CD1a, CD2, CD7, CD5, CD8, CD16, CD57, HLA DR) lymphocyte immunophenotype. A BM biopsy showed a moderate interstitial infiltration with CD3+, CD8+, CD57+, Granzyme B+ T-lymphocytes (Figure 2). The T-cell receptor γ was positive for gene rearrangement and showed the presence of two rearranged clones. Therefore, T-LGL leukemia was diagnosed. The patient was started on CsA 250 mg/d, which was increased to 300 mg/d within two months. Due to the possible CsA side effects, the CsA blood level, blood pressure, kidney and liver function were monitored. All of the parameters were within the reference range, except the creatinine levels, which reached a maximum of 136 mmol/L. However, 10 months of CsA therapy resulted in only a partial response, for two and half years (30 mg/d weekly. He was on methotrexate therapy, exhibiting only a partial response, for two and half years (30 months). He was not transfusion dependent, but he was symptomatic due to anemia. Complete remission was not achieved, as demonstrated in the complete blood count values (WBC 13.7x 10^9/L, Hgb 96 g/L) and the dominant cell population in peripheral blood immunocytochemistry (90% CD3+, CD8+ lymphocytes). The CsA treatment was reintroduced. The initial and maintenance dose was 300 mg/d. Within only a few months, the patient achieved complete remission. After ≈ 3 years, the CsA was tapered down and excluded. The toxic effects of CsA were evident in the elevated creatinine levels (maximum 156 mmol/L). The patient was off CsA therapy for 4 years, and thus far he has been in complete hematological remission, and has repaired kidney function. A molecular response was missing. Although it was substantially decreased, an abnormal T-cell clone was detected by immunophenotyping and the presence of a T-cell receptor γ rearrangement in one clone.

Discussion

T-large granular lymphocyte leukemia is a rare lymphoproliferative disorder that is characterized by the clonal proliferation of CD3+ T-lytotoxic cells. It is an indolent disorder. However, its clinical course is quite uncertain. Its mortality may be as high as 20% in four years [5]. Most patients (50–82%) are asymptomatic at presentation [3]. Although neutropenia and recurrent bacterial infections are frequent and are considered to be a main cause of morbidity and mortality in patients with T-LGL leukemia, this was not the case with our patient. He had transfusion-dependent anemia, which is reported to occur in only 6% of patients [3, 4]. In addition to neutropenia (severe or moderate with recurrent infections) and associated autoimmune conditions that require therapy (most often rheumatoid arthritis), anemia (symptomatic or transfusion-dependent) is considered to be a therapy indication [3, 4, 6].

It is believed that sustained immune stimulation and a dysregulation of apoptosis underlies T-LGL leukemia pathogenesis, which is why immunosuppressive therapy remains the mainstay of treatment [4]. No standard therapy algorithm has been established, and
the current recommendations are based on small case studies and a recently published large French cohort study [3]. Lamy and Loughran [4] proposed methotrexate with/without prednisone and cyclophosphamide as a first-line therapy. However, they suggested that CsA could be used as an alternative first-line, particularly in patients with anemia, because in those cases, the overall response rate was 100%. It was first-line therapy in our patient. However, it initially led to only a partial response.

Methotrexate has been used with varying success with overall response rates of 44 to 87%, but generally it has obtained only a partial response [3, 4, 7]. Unfortunately, our patient only had a partial response. Few studies reported the use of purine analogs, polychemotherapy, antithymocyte globulin and other regimens in refractory or relapsed T-LGL leukemia [1, 2].

Because our patient did achieve a partial response during CsA therapy, we reintroduced the therapy; upon its reintroduction, it resulted in a favorable outcome. A complete clinical and hematological response was achieved. However, it did not result in an eradication of the leukemic LGL clone. The current opinion is that CsA should be given indefinitely to maintain a response [4]. However, after a 3-year CsA treatment in our patient, we excluded CsA due to slightly impaired kidney function. Osuji et al. [7] also reported that they were able to discontinue CsA treatment in three patients without any recurrence of cytopenias.

**Conclusion**

Our case confirms that cyclosporine therapy is effective in treating T-cell large granular lymphocyte leukemia but with a persistant underlying T-cell large granular lymphocyte clone. It also suggests that indefinite treatment may not be needed to maintain response.

**References**


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