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Case Report

Accidental finding of T-LGL in a Young Man

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Background

Large granular lymphocyte leukemia (LGL) is a rare chronic mature lymphoproliferative disorder originating from the T/natural killer (NK) lineage. The prevalence and statistical data regarding T-LGL cases in Ukraine are obscure. One significant challenge in diagnosing and reporting cases stems from the unavailability of clonal T cell receptor (TCR) rearrangement analysis, a pivotal confirmatory test, in Ukraine at present.

A study titled "The Ukrainian-American Study of Leukemia and Related Disorders Among Chornobyl Cleanup Workers from Ukraine" examined 110,645 male cleanup workers between 1986 and 2000. Only 4 cases of large granular leukemia were identified; however, this study faced limitations such as ineligibility, loss to follow-up, and refusals. In Europe, LGL accounts for approximately 5% of chronic lymphoproliferative disorders. The prevalent form of the disease is indolent T-LGL, constituting roughly 85% of all cases. The clinical presentations and symptoms lack specificity and can often be mistaken for other diagnoses.

Case Presentation

A male patient was admitted to the hospital, reporting bloody diarrhea occurring 3-4 times a day and occasional painful defecation with blood in the stool. His family doctor initially diagnosed him with internal hemorrhoids in remission following a diagnostic colonoscopy. Post-procedure, he developed a subfebrile temperature, prompting prophylactic antibiotic treatment with CIPROFLOXACIN 500 mg twice daily. However, the antibiotic regimen led to uncontrollable diarrhea, necessitating the use of activated charcoal and antispasmodics. The patient had no significant medical history, a non-smoker, and occasional alcohol consumer.

Upon hospitalization, an abdominal ultrasound showed no abnormalities except for an enlarged spleen measuring 123*55 mm. Blood tests revealed elevated erythrocyte sedimentation rate (ESR) at 60 mm/h, an increased lymphocyte count (2.53 g/l), and mild normocytic anemia (HGB – 91.3 g/l). Blood smear microscopy showed no pathological changes. Biochemical tests indicated normal liver function, creatinine clearance, and coagulation parameters. Viral infections, including hepatitis B, C, and HIV, were ruled out. However, increased serum protein levels and proteinuria were detected. Electrophoresis with immunofixation revealed Bence Jones proteinuria type kappa and monoclonal gammopathy of unclear significance (MGUS) - IgG type kappa paraprotein in the blood serum.

A CT scan indicated diffuse splenomegaly (125*112*56 mm) with a spleen index of 784 (normal not exceeding 470). Multiple para-aortic, aortocaval, and pericaval lymph nodes measuring 5 to 11 mm in diameter were observed. Subsequent bone marrow biopsy revealed a hypocellular specimen with an increased lymphocyte count of 36.6%. Neoplastic plasma cells (PCs) within the CD138/SSC gate in the CD19-negative cell population were not found. Based on no evidence of MM in the bone marrow re-analyses of immunophenotyping suggested, an association with T-LGLL atypical phenotype was found: CD16-/CD56-/CD5+/CD7+(Defined phenotype: CD45+/CD8+/CD3+/CD38+/CD5+/CD2+/CD7+/cyGranz+/HLA-DR+/CD57+/cyTcl1-/CD16-/CD56-/CD4-/CD11c with the presence of signs of cytotoxicity (Granzyme+57+), antigens associated with activation: CD38, HLA-DR.). The patient was advised to undergo T cell receptor rearrangement tests, unavailable in Ukraine.

Amidst the war, European countries extended assistance, enabling the patient's blood sample to be sent to Germany (MLL) for molecular genetic analysis. Clonality analysis for T cell receptor arrangements beta, delta, and gamma was conducted. Molecular changes were explored for diagnostic and prognostic relevance in Large granular lymphocytic leukemia, revealing aberrations in TCRB and TCRG. Based on these results, the diagnosis was compatible with LGL leukemia.

Follow-up and outcomes

At the twelve-month follow-up after diagnosis, the patient's complete blood count (CBC) continued to reveal a slight increase in lymphocyte count, elevated ESR, and occasional mild neutropenia without experiencing frequent infections. Anemia, previously observed, was no longer present. Biochemical results remained within normal ranges, except for persistently elevated total protein levels.

Remarkably, the patient remained asymptomatic, reporting no complaints or adverse symptoms. This stable condition, despite the persistent hematological findings, reaffirms the decision for vigilant observation and careful monitoring. Further follow-ups will be crucial to track the progression of the disease and any potential changes in the patient's health status.

Discussion

T-cell Large Granular Lymphocyte leukemia is a complex and rare neoplasm originating from mature T cells and natural killer cells. Its association with rheumatic diseases, chronic inflammation, and autoimmunity is

documented. However, the underreporting of T-LGL leukemia in patients with rheumatic disorders, such as vasculitis, systemic lupus erythematosus (SLE), Behcet's Disease (BD), and Sjogren's Syndrome (SS), is common due to limited awareness and the absence of routine T-cell receptor rearrangement testing in rheumatic patients.

The JAK-STAT pathway, crucial in rheumatic diseases, also plays a significant role in T-LGL leukemia. While JAK inhibitors (JAKi) are widely used for rheumatic conditions, their application in T-LGL leukemia is under investigation. Encouraging data regarding ruxolitinib and tofacitinib in refractory large granular lymphocyte leukemia have emerged, suggesting potential therapeutic avenues.

In our patient, rheumatologic diseases were diligently ruled out. Notably, rheumatoid arthritis, the most prevalent autoimmune condition in T-LGL leukemia, was excluded from the diagnosis. Cytopenias, a common manifestation in T-LGL, can stem from cytotoxic clone expansions, lineage restriction, or splenic sequestration. Chronic neutropenia, followed by anemia and thrombocytopenia, is the most frequent cytopenia observed. Immune-mediated mechanisms in co-existing autoimmune diseases can contribute to cytopenia pathogenesis.

During the evaluation, our patient initially presented with anemia, promptly resolved through iron supplementation and addressing the underlying cause—concurrent blood loss due to hemorrhoids. Subsequent follow-ups indicated no recurrence of anemia, yet occasional mild neutropenia persisted. Additionally, elevated erythrocyte sedimentation rate (ESR) endured in routine complete blood counts (CBCs).

Moreover, T-LGL leukemia has been associated with plasma cell disorders (PCD). Our patient was confirmed to have monoclonal gammopathy of undetermined significance (MGUS), a common B-cell dyscrasia. Coexistence of T-LGL leukemia with various PCD, including smoldering multiple myeloma, MGUS, and other forms, has been reported. The presence of MGUS in our patient aligns with these observations, underscoring the complexity of T-LGL leukemia and its potential associations with diverse hematologic disorders.

The discussion highlights the intricate interplay between T-LGL leukemia, rheumatic diseases, cytopenias, and plasma cell disorders, emphasizing the necessity for comprehensive assessments and vigilant follow-ups

to unravel the complexities of this rare hematologic condition. Continued research and clinical observation are imperative to enhance our understanding and management of T-LGL leukemia and its intricate associations.

Conclusion

It is crucial to differentiate T-cell Large Granular Lymphocyte (T-LGL) leukemia from other Large Granular Lymphocyte (LGL) proliferative disorders, T-cell leukemias, and lymphomas for accurate diagnosis and tailored treatment. Notably, patients with T-LGL can remain asymptomatic for extended periods, although follow-up and therapy initiation may become necessary as the disease progresses and symptoms emerge.

In developing countries, diagnosing LGL and monitoring disease progression pose significant challenges. In our patient, occasional neutropenia, the most common hematological abnormality associated with T-LGL, was noted. Additionally, splenomegaly and the presence of Monoclonal Gammopathy of Undetermined Significance (MGUS) were key diagnostic features.

Collaborative efforts with colleagues from Europe played a pivotal role, enabling access to advanced, specific diagnostic analyses. This collaboration facilitated the interpretation and discussion of complex clinical cases, highlighting the importance of international cooperation in advancing the understanding and management of rare hematologic disorders like T-LGL leukemia. Continued global collaboration and research are imperative to enhance diagnostic capabilities, refine therapeutic strategies, and improve patient outcomes, especially in the context of hematologic malignancies in developing nations.

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