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CASE IMAGE

T-cell large granular lymphocytic leukemia associated with inclusion body myositis

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A 58-year-old woman presented with a new onset of generalized weakness and a 6 months history of frequent falls. Her vitals were stable, and cardiovascular, pulmonary, and abdominal examinations were unremarkable. Her mentation was intact with apparently normal cognition. A neurological examination revealed normal cranial nerve function, bilateral quadriceps weakness (sitting-rising test), inability to grip, and muscle atrophy most prominent in the finger flexors and knee extensors. No focal or generalized tenderness, numbness, or paresthesias were noted.

A complete blood count showed normocytic anemia (hemoglobin 8.5 g/dL, reference range 11.5-15.5; mean corpuscular volume 91fL, range 80-100), inappropriate reticulocytes count (50×10^9/L, range 50-100), white blood cell count of 3.67×10^9/L (normal 3.7-11) with 16% neutrophils (range 40-70) and 80% lymphocytes (range 20-40), and a normal platelet count (194×10^9/L, range 150-400). Laboratory studies revealed elevated creatine phosphokinase (1614 U/L, range 30-220) and liver enzymes (AST 190 U/L, range 13-35; ALT 216 U/L, range 7-38) with slightly increased total bilirubin (2 mg/dL, range 0.2-1.5). Lactate dehydrogenase was 291 U/L (normal 135-214). Results of renal and thyroid function, autoimmune panel (extractable nuclear antigens and antinuclear antibodies, rheumatoid factor), vitamins, iron, and copper levels were all unremarkable. Furthermore, virological studies did not reveal any active infection.

A microscopic evaluation of a peripheral blood smear identified the presence of large granular lymphocytes (Figure 1A) prompting the order of a flow cytometry low-grade lymphoma panel, which showed a predominance (90%) of circulating lymphocytes expressing CD2+, CD3+, CD5+ (dim), CD7+ (dim), CD8+, CD16+, and CD57+. Further study of T-cell clonality detected a positive TCR-gamma rearrangement, while assessment of T-cell receptor Vβ family usage confirmed the overrepresentation of Vβ13.1 within CD3/CD8 lymphocytes consistent with a diagnosis of T-cell large granular lymphocytic leukemia (T-LGL). No *STAT3* mutations were detected. A bone marrow evaluation revealed involvement by T-LGL with a phenotype similar to that noted in the patient's peripheral blood. Additionally, a granzyme B stain demonstrated occasional positive cells whereas a TIA1 stain revealed several positive cells, including areas with a sinusoidal growth pattern.

An extensive electrodiagnostic examination (electromyography) showed abnormal spontaneous activity consistent with a generalized myopathy. These findings prompted a left deltoid muscle biopsy (Figure 1B) which revealed the presence of brisk endomysial lymphocytic inflammation, internalized nuclei, few rimmed vacuoles, and endomysial fibrosis (Figure 1C-D), consistent with a diagnosis of inclusion body myositis (IBM). Notably, immunohistochemistry showed that the infiltrate consisted of CD3+CD8+ cells (Figure 1E-F) with a pattern of granzyme B/TIA1 expression similar to the observed BM findings. The patient was started on methotrexate (15 mg/weekly), intravenous immunoglobulin (2 g/kg/monthly), and steroids (60 mg daily tapered) with partial control of IBM symptoms and resolution of cytopenias.

While routinely used first-line agents for T-LGL (methotrexate, cyclosporine, and cyclophosphamide) show overall response rates of 60%-70%, no effective therapies have been found for IBM, and the current management includes nonpharmacological interventions

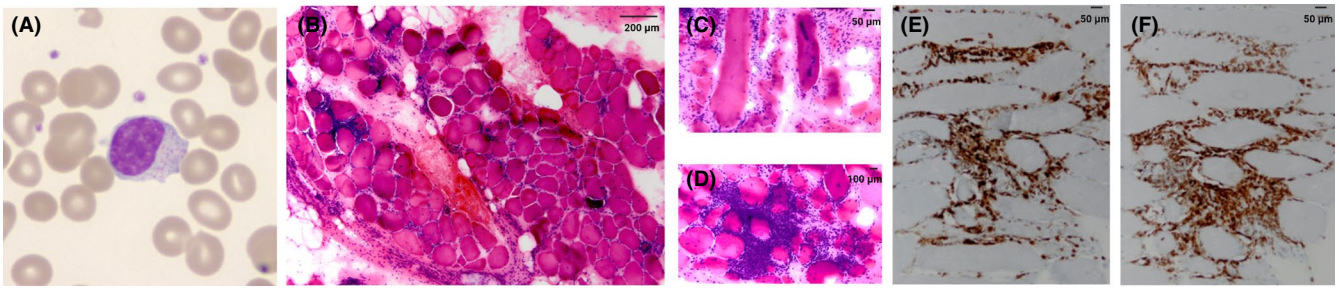

FIGURE 1 (A) Wright-Giemsa stain, 100× oil immersion objective showing large granular lymphocyte with azurophilic granules. Hematoxylin and eosin stain, left deltoid muscle biopsy (B) showing the presence of brisk endomysial lymphocytic inflammation, internalized nuclei, few rimmed vacuoles, and endomysial fibrosis (C-D), consistent with a diagnosis of inclusion body myositis (IBM). CD3 (E) and CD8 (F) immunostains showing cytotoxic T cells infiltrate of muscle fibers

(eg, physical therapy) and immunosuppression.[1,2] These measures are usually incapable of modifying the progressive and degenerative natural course of IBM, and thus, patients are often relegated to the use of a wheelchair at a median of 13-15 years from symptom onset. This stark difference with the aforementioned effectiveness of the immunosuppressive regimens for T-LGL implies, among other factors, that muscle fibers may be a "sanctuary" site less likely to be freed from neoplastic-like CD8+ reactions using conventional therapies. We encourage clinicians to judiciously investigate patients presenting with T-LGL, which in some instances may accompany distinct entities of autoimmune nature with invariant prognostic significance.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

C.G and JPM wrote the manuscript; GAY, KM, and CVC collected and analyzed pathology data and provided detailed morphologic information. All authors participated in critical review of the final paper and submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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