CHEST

A 74-Year-Old Man With Waldenström Macroglobulinemia and Progressive Dyspnea

Vasilios Tzilas, MD, PhD; Andrew G. Nicholson, DM; Maria Gavriatopoulou, MD, PhD; Ioannis Ntanasis-Stathopoulos, MD, PhD; Meletios A. Dimopoulos, MD, PhD; and Demosthenes Bouros, MD, PhD

CASE PRESENTATION: A 74-year-old man presented to our department with progressive dyspnea on exertion over the last year. The patient did not report any other symptoms. He had previously smoked with a 60 pack-year history. He worked in an office and did not report any environmental, occupational, or domestic exposures. His history included asymptomatic Waldenström's macroglobulinemia that was diagnosed 18 months before respiratory symptoms. He was not receiving any treatment and was monitored regularly by the hematology department.

CHEST 2024; 165(2):e39-e43

Physical Examination Findings

On presentation, the patient was afebrile, with a heart rate of 88 beats/min, BP of 120/90 mm Hg, respiratory rate of 18 breaths/min, and oxygen saturation of 95% on ambient air. There was no peripheral edema or clubbing. Chest auscultation revealed the presence of bilateral symmetric crackles mainly at the lung bases.

Diagnostic Studies

Pulmonary function tests revealed a restrictive pattern with a moderate reduction of diffusion capacity of carbon monoxide (D_{LCO}) (FVC, 84% predicted; FEV_1/FVC, 0.75; TLC, 73% predicted; D_{LCO}, 56% predicted). Chest radiograph revealed reticulation mainly at the bases. High-resolution CT scan exhibited peripheral ground glass opacities with superimposed irregular reticulation and subtle traction bronchiectasis with relative subpleural sparing (Fig 1). Complete blood count and biochemistry panel were within normal limits. Immunoglobulin M (IgM) level was elevated (1440 mg/dL; normal range, 40 to 250 mg/dL). The last IgM value 1 year earlier was 1,230 mg/dL. Serology testing results for collagen tissue diseases, which included antinuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide, extractable nuclear antigen panel, and antineutrophil cytoplasmic antibodies, were all negative. A surgical lung biopsy showed a moderate-to-marked lymphoid infiltrate that included focal germinal centers that showed mild hyperplasia. There was mild associated interstitial fibrosis. Occasional foci of organizing pneumonia were present. No honeycomb changes were observed. Immunohistochemistry showed B cells mainly limited to follicles; however, although plasma cells were not particularly numerous, there was lambda light chain restriction, and focal Dutcher bodies were seen (Fig 2).

AFFILIATIONS: From the 5th Respiratory Department (V. T.), Hospital for Diseases of the Chest, "Sotiria," Athens, Greece; the Department of Histopathology (A. G. N.), Royal Brompton and Harefield Hospitals, Guy's and St Thomas NHS Foundation Trust and National Heart and Lung Institute, Imperial College, London, England; the Department of Clinical Therapeutics (M. G., I. N. S., and M. A. D.) and Medical School (D. B.), National and Kapodistrian University of Athens, and the Athens Medical Center (D. B.), Athens, Greece.

CORRESPONDENCE TO: Vasilios Tzilas MD, PhD; email: tzilasvasilios@gmail.com

DOI: https://doi.org/10.1016/j.chest.2023.08.004

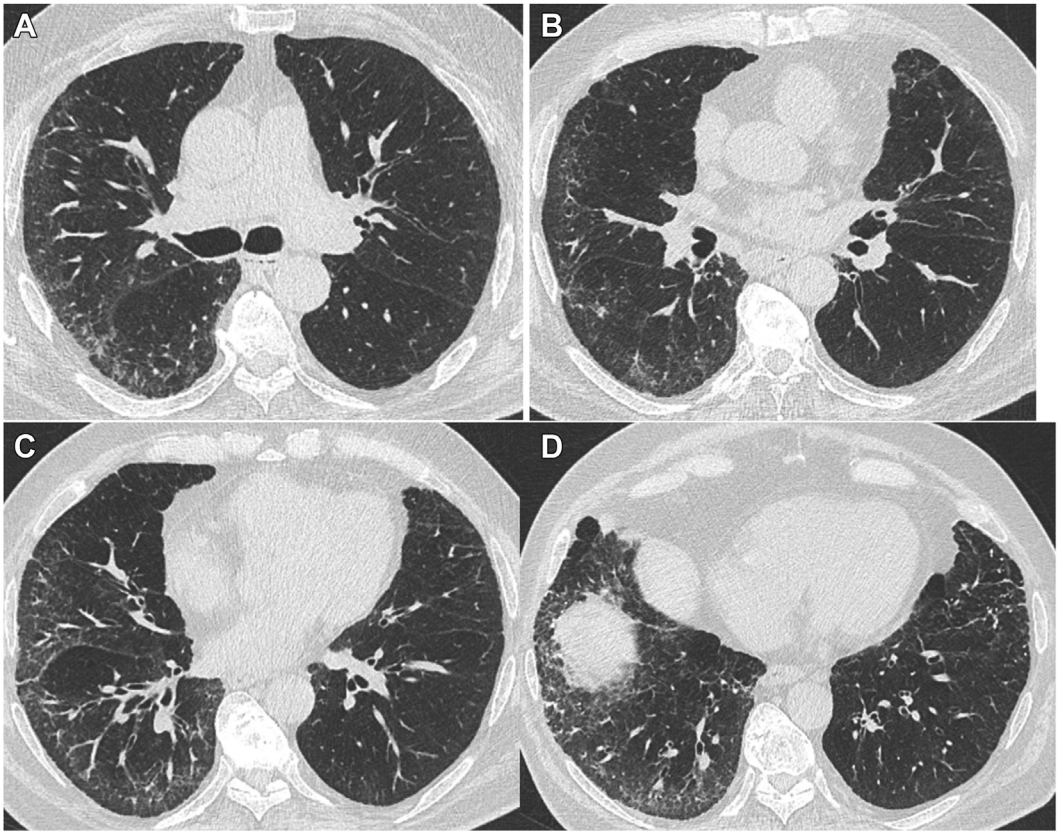

Figure 1 – *A-D, High-resolution CT scan. There are peripheral ground-glass opacities with superimposed irregular reticulation and subtle traction bronchiectasis with relative subpleural sparing (non-specific interstitial pneumonia pattern).*

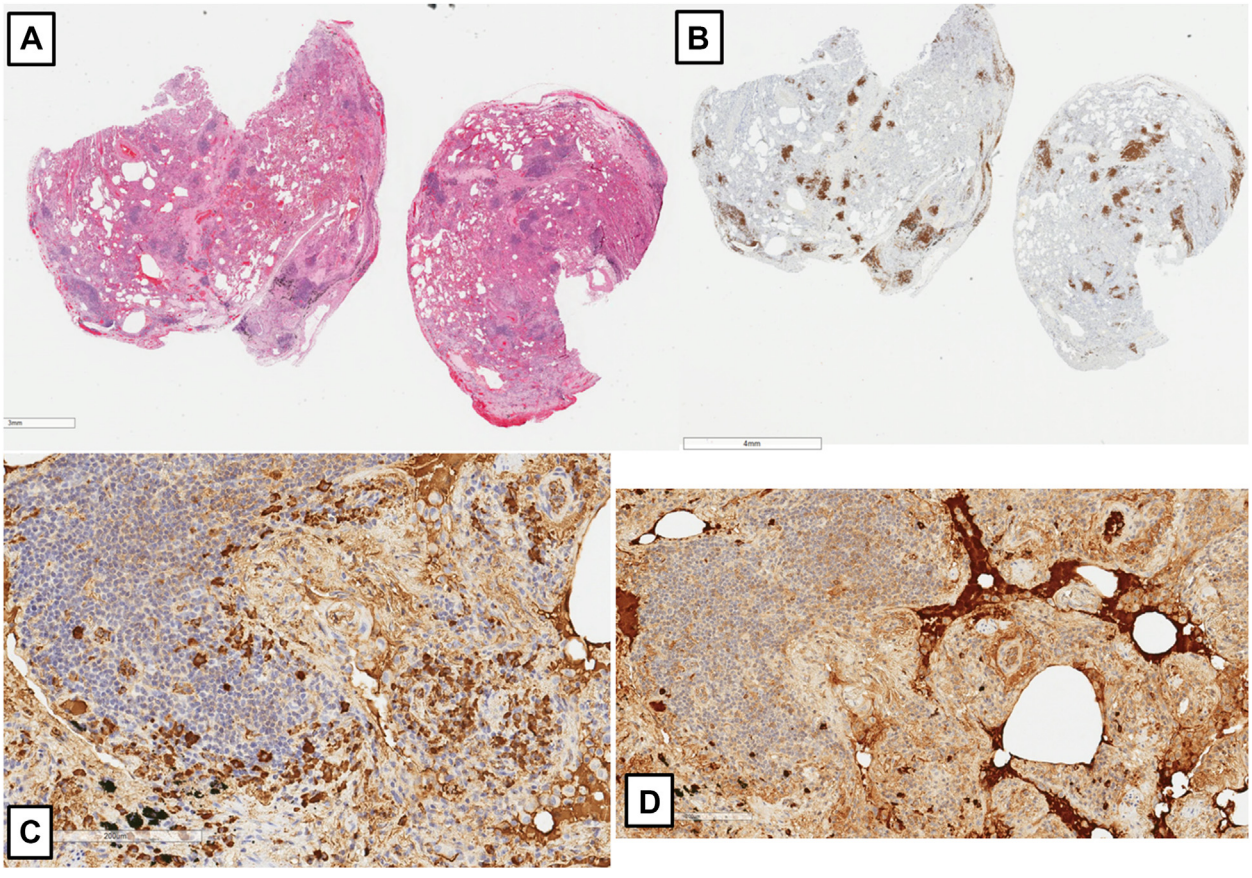

Figure 2 – *Lung biopsy specimens. A, The lung is diffusely involved by a moderate-to-marked lymphoplasmacytoid infiltrate. B, B-cells are limited mainly to germinal centers, C and D, but there is an excess of lambda positive plasma cells compared with kappa staining that indicates light chain restriction.*

What is the diagnosis?

Diagnosis: Lung involvement in the context of Waldenström macroglobulinemia (WM)

Discussion

WM is a rare B-cell lymphoproliferative disorder with an incidence of approximately three per million people and is characterized by bone marrow infiltration of B-lymphocytes, lymphoplasmacytoid cells, and plasma cells along with production of a serum monoclonal IgM. The clinical manifestations show great variability and are related to both paraprotein production and tumor cell infiltration. IgM paraprotein production may lead to hyperviscosity syndrome that manifests as dizziness, visual disturbances, rhinorrhagia, and aggravation of heart failure. In some patients, IgM paraproteinemia behaves as cryoglobulin that leads to cryoglobulinemia and cold agglutinin hemolytic anemia; although in other patients, it can cause IgM-related neuropathy.

Extramedullary involvement is rare in WM, occurring in approximately 5% of cases. Thus, clinical experience is extremely limited and is based mostly on small case series and case reports. Extramedullary involvement is defined by the presence of a clonal lymphoplasmacytic infiltrate at anatomic sites distant from the bone marrow, excluding circulating tumor cells. Most frequent sites of extramedullary disease are the lungs, soft tissue, cerebrospinal fluid, renal, and bone.

Lung involvement is a very rare extramedullary manifestation of WM that occurs in 3% to 5% of cases. Usually, it presents after the diagnosis of WM. In extremely rare cases, lung involvement can be the primary manifestation without bone marrow involvement and with IgM paraproteinemia. Symptoms include dyspnea, cough, and chest pain; some patients are asymptomatic. Dyspnea in patients with WM is multifactorial; thus, in these patients, it is important to include lung involvement in the differential diagnosis, to perform a thorough clinical examination of the respiratory system, and to obtain a chest radiograph. Furthermore, lung involvement can take several forms that make accurate diagnosis even more difficult. Infiltration of the pleura can lead to malignant pleural effusion. The median time from the diagnosis of WM to the development of pleural effusion onset is approximately 9 years. Identification of the MYD88 L265P mutation in pleural fluid with allele-specific polymerase chain reaction can be supportive of the diagnosis. The deposition of monoclonal IgM paraprotein in the lungs can lead to light chain deposition disease or amyloid, often characterized by the development of diffuse cystic lung disease. Infiltration of the lung by the lymphoplasmacytoid clonal cells can manifest as focal or multiple masses or consolidative areas. A rare case of endobronchial involvement has been described. In rare cases, lung involvement can mimic interstitial lung disease. In patients with WM and lung involvement, it is important to meticulously rule out infection, because it represents a major cause of morbidity and death in hematologic malignancies.

Treatment in cases of lung involvement is based on current guidelines for WM. First-line therapy options for symptomatic patients consists of alkylating drugs (bendamustine, cyclophosphamide) and proteasome inhibitors (bortezomib, carfilzomib, ixazomib), both in combination with rituximab, and Bruton's tyrosine kinase inhibitors (ibrutinib), alone or in combination with rituximab.

Clinical Course

Because of the history of WM and in the absence of signs and symptoms in favor of infection or other obvious diagnoses, we elected to perform a surgical lung biopsy. The results of the biopsy confirmed lung involvement in the context of his lymphoproliferative disease. The Hematology Department was informed about the results, and therapy was initiated that included six cycles of rituximab, cyclophosphamide, and dexamethasone (DRC regimen). Treatment was well-tolerated, whereas IgM levels fell to 821 mg/dL from 1650 at the time of treatment initiation (partial response). The patient remains stable after 1 year of treatment and reports improvement of his dyspnea. Imaging is stable while there is functional improvement (pulmonary function tests after 1 year: FVC, 91% predicted; FEV_1/FVC, 0.74; TLC, 76% predicted; D_{LCO}, 60% predicted).

Clinical Pearls

1. *In patients with respiratory manifestations, elevated levels of IgM should raise suspicion of an underlying lymphoproliferative disease that could provide a unifying diagnosis.*
2. *In patients with WM and respiratory manifestations, include lung involvement by the lymphoproliferative disease in your differential diagnosis. It can mimic interstitial lung disease.*

3. *In these cases biopsy-proven diagnosis by a specialized hemopathologist is essential because it secures diagnosis and guides appropriate treatment according to current guidelines for treatment of WM.*
4. *In patients with WM and lung involvement, it is important to rule out infection meticulously because it represents a major cause of morbidity and death in hematologic malignancies.*

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Other contributions: *CHEST* worked with the authors to ensure that the Journal policies on patient consent to report information were met.

Suggested Readings

Dimopoulos MA, Panayiotidis P, Moulopoulos LA, Sfikakis P, Dalakas M. Waldenström's macroglobulinemia: clinical features, complications, and management. *J Clin Oncol*. 2000;18(1):214-226.

Kyrtsonis MC, Angelopoulou MK, Kontopidou FN, et al. Primary lung involvement in Waldenström's macroglobulinaemia: report of two cases and review of the literature. *Acta Haematol*. 2001;105(2):92-96.

Girard N, Vasiljevic A, Cottin V, et al. Respiratory failure with diffuse bronchiectases and cryoglobulinaemia. *Eur Respir J*. 2008;31(6):1374-1378.

Consuegra A, Marcos PJ, Vázquez R, Pombo J, Debén G, Verea-Hernando H. Diffuse interstitial lung disease as a first manifestation of Waldenström's macroglobulinemia: case report and review of the literature. *Arch Bronconeumol*. 2014;50(4):151-153.

Banwait R, Aljawai Y, Cappuccio J, et al. Extramedullary Waldenström macroglobulinemia. *Am J Hematol*. 2015;90(2):100-104.

Gustine JN, Meid K, Hunter ZR, Xu L, Treon SP, Castillo JJ. MYD88 mutations can be used to identify malignant pleural effusions in Waldenström macroglobulinaemia. *Br J Haematol*. 2018;180(4):578-581.

Jensen L, Mann H. Cystic lung disease from protein deposition: pathogenesis and associated conditions. *Curr Radiol Rep*. 2018;6(3):12.

Thomas R, Braschi-Amirfarzan M, Laferriere SL, Jagannathan JP. Imaging of Waldenström macroglobulinemia: a comprehensive review for the radiologist in the era of personalized medicine. *Am J Roentgenol*. 2019;213(6):W248-W256.

Castillo JJ, Advani RH, Branagan AR, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. *Lancet Haematol*. 2020;7(11):e827-e837.