

Hyperviscosity syndrome provoking heart failure in a patient with waldenström macroglobinemia

Summary

A 75-year-old woman with past medical history of anemia presented with progressive, worsening shortness of breath. Upon arrival to the hospital, a chest x-ray revealed a moderate right-sided pleural effusion with a possible superimposed pneumonia or atelectasis. Further evaluation identified heart failure arising from hyperviscosity syndrome resulting from her underlying Waldenström Macroglobinemia (WM).

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Background

In patients with WM, hyperviscosity syndrome is a well-documented phenomenon, which can trigger heart failure and its known sequelae, such as pleural effusions, which are oftentimes transudative. Despite its association with WM, patients with this underlying hematologic malignancy rarely present with transudative pleural effusions at the time of diagnosis.

Case presentation

We present a 75-year-old woman with no medical follow up for several years who developed progressively worsening shortness of breath with associated orthopnea and weight loss over the past year. Additionally, she reported leg heaviness, abdominal distention, subjective fevers, dry cough and a poor appetite. She denied any drenching night sweats. Her past medical history was notable solely for chronic anemia and alcohol dependence. She had not been taking any medications prior to admission. Her family history was significant for a mother with anemia. The patient was an active smoker, with a 35-40 pack-year smoking history.

On arrival to the emergency department, patient was hypoxic, prompting administration of supplemental oxygen via nasal cannula. She was afebrile and hemodynamically stable. On exam, she was cachectic and fatigued with hepatomegaly and without palpable lymphadenopathy. Labs were drawn, which showed a thrombocytopenia of 58th/mm³ and hemoglobin of 5g/dL. Chest x-ray showed a moderate right-sided pleural effusion with a possible pneumonia or atelectasis. An echocardiogram showed an ejection fraction of 55% with pulmonary artery pressure of 38mmHg suggestive of mild pulmonary hypertension. Brain natriuretic peptide (BNP) was elevated to 1840pg/mL. The patient was initially treated for community-acquired pneumonia and given intravenous (IV) furosemide. Computed tomography (CT) of the chest revealed a moderately-sized, partially loculated right pleural effusion with resulting complete middle lobe and multi segment right lower lobe atelectasis. Given these findings, the patient underwent a thoracentesis with removal of 1.2liters.

Investigation

Fluid analysis revealed a pH 7.52, albumin 1.3g/dL, glucose 112mg/dL, amylase 52IU/L, protein 3.7g/dL, lactate dehydrogenase (LDH) 107 U/L. Serum LDH 187 U/L, serum protein 8.8g/dL. Given these findings, the patient's effusion was characterized as transudative in nature with negative cytology. The patient underwent a CT of the abdomen and pelvis due to her worsening abdominal distention which revealed small-volume ascites, hepatomegaly, measuring 19cm in length, splenomegaly, measuring 15cm in length with a large confluent retroperitoneal mass at the root of the mesentery extending from the celiac access to at least the level of the aortic bifurcation with extension along the common iliac chains and external iliac chains. Much of the mass had enveloped the mesenteric arteries and solitary renal arteries bilaterally as well as the ureters. Her serum protein electrophoresis (SPEP) was notable for an M-spike of 4.3g/dL, an elevated kappa/lamda light chain ratio of 17.7 and serum viscosity was elevated at 3.9cP.

The degree of lymphadenopathy was concerning for a lymphomatous process. Fine needle aspiration (FNA) of the axillary lymph node was consistent with B-cell lymphoproliferative disorder, showing a monotonous population of small lymphocytes with round, ovoid nuclei, condensed chromatin and scant cytoplasm. Occasional plasmacytoid cells were identified. Flow cytometry revealed lymphoma cells that were CD 19+, CD 20+, CD5-, CD10-, CD23-, CD 103- and CD 116- and surface kappa +. These findings were suggestive of a lymphoplasmacytic lymphoma (LPL). Bone marrow biopsy showed 80% involvement with small cell B-lymphoma with plasmacytic differentiation.

Differential diagnosis

The differential diagnosis of her pleural effusion included atelectasis, hepatothorax, urothorax, nephrotic syndrome, constrictive pericarditis, amyloidosis and malignancy. Though malignant pleural effusion warranted consideration, the transudative nature of her pleural fluid and her underlying heart failure initially suggested another underlying source of progressively worsening shortness of breath.

Treatment

Out of concern for lymphoma and in light of the patient's significant tumor burden, methylprednisolone 500mg IV daily was given until the diagnosis was made. Furthermore, surveillance for tumor lysis syndrome was initiated with daily monitoring of LDH, calcium, and uric acid. The patient ultimately developed tumor lysis syndrome, for which she was treated with IV fluids, sodium polystyrene sulfonate, furosemide, and allopurinol. The patient was initiated on CVP (cyclophosphamide, vincristine, high-dose prednisone) chemotherapy during her hospitalization. Rituximab was held given concerns of a flare in the setting of high viscosity levels.

Outcome and follow-up

Following discharge, the patient's chemotherapy regimen triggered worsening of her chronic anemia and blood transfusions were subsequently required. Two months after diagnosis, the patient unfortunately developed transfusion-associated circulatory overload (TACO) requiring intubation and admission to the intensive care unit (ICU). Her admission was also complicated by acute renal failure, thought to be secondary to a combination of acute tubular necrosis (ATN) from paraprotein deposition in the renal parenchyma, and to obstructive uropathy from tumor obstruction leading to bilateral hydronephrosis. During that hospitalization, the patient and her family decided against plasmapheresis, dialysis, and further chemotherapy, given the patient's declining functional status and the incurable nature of her Waldenström Macroglobinemia. The patient was transitioned to hospice care to focus on comfort and end of life care.

Discussion

Our patient had presented with a clinical picture that was concerning for heart failure, which was complicated by a pleural effusion. Additionally, her complaint of subjective fevers and the leukopenia suggested that her respiratory failure was secondary to a bacterial pneumonia, leading to the administration of antibiotics. She was initially given furosemide for diastolic heart failure, with improvement in her respiratory symptoms. The pleural effusion that was noted on chest x-ray warranted further work-up, with the chest CT revealing a partially loculated pleural effusion. A thoracentesis revealed a transudative effusion.

Transudative pleural effusions result from hydrostatic and oncotic pressure shifting in the chest. Light's Criteria is a method of discerning whether pleural fluid is transudative or exudative. The criteria take into account serum and pleural fluid protein and LDH. If one of the following three criteria is fulfilled, the fluid is defined as an exudate¹: pleural fluid protein/serum protein ratio greater than 0.5, or; pleural fluid LDH/serum LDH ratio greater than 0.6, or; pleural fluid LDH greater than two-thirds the upper limits of the laboratory's normal serum LDH.

Since our patient was discovered to have a right-sided pleural effusion, our investigation focused on the possible cause of her pleural effusion. Differential diagnosis included heart failure, constrictive pericarditis, nephrotic syndrome, urinothorax, hepatic hydrothorax, and atelectasis. The patient had no evidence of underlying liver disease, and urine was not identified in her pleural fluid. Furthermore, nephrotic syndrome typically presents with bilateral pleural effusions, which was not the case with our patient. Evidence of constrictive pericarditis on echocardiogram were lacking, as there was no biatrial enlargement,

dilatation of the inferior vena cava with reduced inspiratory collapse, a marked compromise in ventricular diastolic filling, enhanced mobility of atrioventricular valves, rightward movement of the interventricular septum, or abnormal contour in the posterior left ventricular and left atrial walls.^{2,3} Amyloidosis was also a consideration, given the signs of right-sided heart failure as evidenced by her hepatomegaly, ascites, diastolic dysfunction and increased left ventricular wall thickness on echocardiogram.⁴ Bone marrow biopsy is a required test in the initial work up of suspected amyloid-light chain (AL) amyloidosis, as it demonstrates a plasma cell dyscrasia as a cause of amyloid deposits.⁵ While the patient's bone marrow biopsy showed the former, there was no amyloid in the bone marrow. Furthermore, pleural effusions in patients with amyloid cardiomyopathy are typically exudative in appearance. Lastly, malignancy was also a consideration. Although malignant pleural effusions are usually exudative, 3% to 10% can be transudative, the etiology being possibly early lymphatic obstruction, obstructive atelectasis, or heart failure.

The patient's pleural effusion resulted from a concomitant condition that is typically found in patients with WM and is known to trigger heart failure. The patient's thrombocytopenia, anemia, hypervolemia, hepatomegaly, hyperviscosity and B-symptoms were highly suspicious for monoclonal gammopathy. IgM monoclonal protein in the blood can lead to the development of hyperviscosity and peripheral neuropathy.^{6,7} Her SPEP was notable for an M-spike of 4.3g/dL, raising concerns for hyperviscosity syndrome. When accompanied by anemia, hyperviscosity and the associated plasma volume expansion may precipitate or aggravate heart failure,⁸ which was shown to be the case in our patient. Symptoms of hyperviscosity are present in up to 30% of patients with WM. The patient in our case did not have neurologic symptoms such as blurring, loss of vision, headache, vertigo nystagmus, dizziness, tinnitus, sudden deafness, diplopia or ataxia, thus not making her a candidate for plasmapheresis on her initial admission. Although the correlation between serum viscosity and clinical manifestations is not precise, symptoms often begin when serum viscosity is greater than 4cP, and most patients are symptomatic when serum viscosity is greater than 6cP. In one series, 0%, 67%, and 75% of patients had symptoms of hyperviscosity when the serum viscosity was less than 3, greater than 4, and greater than 5cP, respectively.⁹

While hyperviscosity syndrome provided a valuable clue to our patient's underlying diagnosis, other aspects of her presentation aligned closely with WM. Infiltration of hemopoietic tissues is the hallmark of WM (e.g., anemia, lymphadenopathy, hepatosplenomegaly), as was the case with this patient. Most patients with WM present with non-specific constitutional symptoms, and in fact, up to a quarter of patients with WM can be asymptomatic at the time of diagnosis. Weakness, fatigue, weight loss, and chronic oozing of blood from the nose or gums are among the most common of presenting symptoms at the time of diagnosis. In a group of 217 patients with WM, the following findings were identified at presentation¹⁰: constitutional B-symptoms-23%, bleeding-23% and neurologic symptoms 22%, symptoms secondary to hyperviscosity 31%, lymphadenopathy-25%, hepatomegaly-24% and splenomegaly-19%. In our case, the presenting symptoms were fatigue, weight changes, and hyperviscosity-related symptoms, particularly her dyspnea.

The diagnosis of WM is made following analysis of a bone marrow biopsy specimen, measurement and identification of the serum protein components, and clinical presentation.¹¹⁻¹³ The diagnosis is based on

the fulfillment of the following criteria presence of IgM monoclonal gammopathy (of any size) in the serum; greater than 10% infiltration by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation (lymphoplasmacytic features or lymphoplasmacytic lymphoma) with an intertrabecular pattern, on bone marrow biopsy; expression of typical immunophenotypes on bone marrow biopsy (e.g., surface IgM+, CD5-, CD10-, CD11c-, CD19+, CD20+, CD22+, CD23-, CD25+, CD27+, FMC7+, CD103-, CD138-). The plasmacytic component will be CD138+, CD38+ and CD45- or dim.^{14,15}

Our patient's SPEP showed an IgM kappa spike of 4.3gm/dl, and an elevated kappa/lambda light chain ratio of 17.7. Given these results, the patient underwent a bone marrow biopsy which revealed findings consistent with small B-cell lymphoma with plasmacytic differentiation, containing kappa-restricted plasma cell population that was CD38+, CD138+, kappa+, CD56-, CD19+, CD200-, and CD117-. In addition to fulfilling all three of the criteria described above, the patient harbored the PL 265 p mutation identified at exon 5 of the MYD88 gene found in 91% of patients with lymphoplasmacytic lymphoma or Waldenström's macroglobinemia.¹⁶ This gene leads to NF-κB activation leading to the promotion of LPL/WM cell growth and survival.¹⁷ With the findings of lymphoplasmacytic lymphoma with an IgM paraprotein, the diagnosis of Waldenström macroglobulinemia was made.

Conclusion

This case illustrates the need to consider heart failure secondary to hyperviscosity syndrome as the underlying etiology of transudative pleural effusions, in patients with suspected hematologic malignancy.

Learning points

- i. Heart failure is a typical cause of transudative pleural effusions; however, 30% of patients with WM develop heart failure secondary to hyperviscosity syndrome.
- ii. Consider concomitant illnesses (e.g., heart failure) associated with malignancy, in patients presenting with transudative pleural effusions.
- iii. Hyperviscosity syndrome is a cause of heart failure in patients with Waldenström Macroglobulinemia.

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None.

Conflict of interest

The author declares no conflict of interest.

References

1. Light RW, Macgregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med.* 1972;77(4):507–513.

2. Hoit BD. Imaging the pericardium. *Cardiol Clin.* 1990;8:587.
3. D'Cruz IA, Dick A, Gross CM, et al. Abnormal left ventricular–left atrial posterior wall contour: a new two-dimensional echocardiographic sign in constrictive pericarditis. *Am Heart J.* 1989;118(1):128–132.
4. Klein AL, Hatle LK, Burstow DJ, et al. Comprehensive Doppler assessment of right ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol.* 1990;15(1):99–108.
5. Swan N, Skinner M, O'Hara CJ. Bone marrow core biopsy specimens in AL (primary) amyloidosis. A morphologic and immunohistochemical study of 100 cases. *Am J Clin Pathol.* 2003;120(4):610–616.
6. MacKenzie RM. Macroglobulinemia. In: *Neoplastic Diseases of the Blood.* Wiernick PH, et al. editors. USA: Churchill–Livingstone; 1996;3:601.
7. Dimopoulos MA, Panayiotidis P, Mouloupoulos LA, et al. Waldenström's macroglobulinemia: clinical features, complications, and management. *J Clin Oncol.* 2000;18(1):214–216.
8. Bloch KJ, Maki DG. Hyperviscosity syndromes associated with immunoglobulin abnormalities. *Semin Hematol.* 1973;10(2):113–124.
9. Crawford J, Cox EB, Cohen HJ. Evaluation of hyperviscosity in monoclonal gammopathies. *Am J Med.* 1985;79(1):13–22.
10. García-Sanz R, Montoto S, Torrequera A, et al. Waldenström macroglobulinemia: presenting features and outcome in a series with 217 cases. *Br J Haematol.* 2001;115(3):575–582.
11. Swerdlow SH, Campo E, Harris NL, et al. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.* France: IARC Press; 2008.
12. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. *Semin Oncol.* 2003;30(2):110–115.
13. Dimopoulos MA, Kyle RA, Anagnostopoulos A, et al. Diagnosis and management of Waldenström's macroglobulinemia. *J Clin Oncol.* 2005;23:1564.
14. Fonseca R, Hayman S. Waldenström macroglobulinemia. *Br J Haematol.* 2007;138:700.
15. Groves FD, Travis LB, Devesa SS, et al. Waldenström's macroglobulinemia: incidence patterns in the United States, 1988–1994. *Cancer.* 1998;82:1078.
16. Treon SP, XU L, Yang G, et al. "MyD88 L265P somatic mutation in Waldenström's Macroglobulinemia." *NEJM.* 2012;367:826–833.
17. Gachard NI, Parrens M, Soubeyran I, et al. "IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenström macroglobulinemia/lymphoplasmacytic lymphomas." *Leukemia.* 2013;27(1):183–189.