CASE REPORT

Retroperitoneal amyloidosis as the presenting manifestation of Waldenstrom's macroglobulinaemia

Domingo Franco-Palacios,¹ Maher Tama,¹ Suprotim Samaddar,² Jay Yang³

¹Department of Internal Medicine, Wayne State University, Detroit, Michigan, USA

²Department of Internal Medicine, Huron Valley Sinai Hospital, Commerce Township, Michigan, USA

³Department of Oncology, Barbara Ann Karmanos Cancer Institute, Detroit, Michigan, USA

Correspondence to

Dr Domingo Franco-Palacios, dfrancopalacios@gmail.com

SUMMARY

Retroperitoneal amyloidosis has been described in a few case reports and is typically a secondary manifestation of inflammation or malignancy. We present the case of a 69-year-old man who presented with a large pleural effusion and an incidental retroperitoneal mass in the CT imaging. Further investigation confirmed the diagnosis of amyloid amyloidosis involving the retroperitoneum as well as a concurrent Waldenstrom's macroglobulinaemia. Chemotherapy consistent of drugs active against both the lymphoid and plasma cell components of the disease is the proposed therapy for Waldenstrom's macroglobulinaemia in those patients amenable to receive chemotherapy and can make a difference in the survival.

BACKGROUND

This case is challenging and constitutes a clinical dilemma. In this particular case, the incidental findings in the CT scan helped to elucidate the underlying pathology, and geared the diagnostic effort towards two different organs that a priori did not seem to be related to the initial presentation. Few reports have described primary amyloidosis with deposition of light chains immunoglobulins in the retroperitoneum. Furthermore, this is an interesting case because of the unusual clinical presentation with large visceral cavity deposits of amyloid: symptomatic large pleural effusion and incidental finding of retroperitoneal amyloidosis. It is important to emphasise the need of CT scans of the chest, abdomen and pelvis at time of diagnosis of Waldenstrom's macroglobulinaemia (WM) to properly stage the patient considering that up to 20% of WM patients may have extramedullary disease (adenopathy, splenomegaly and for other extramedullary disease sites). Retroperitoneal involvement by amyloid (AL) amyloidosis is exceeding rare.

CASE PRESENTATION

A 69-year-old white man with a history of hyperlipidaemia and adenocarcinoma of the prostate was admitted to the hospital with a 6 week history of worsening dyspnoea on exertion and non-productive cough. His medical history was notable for hyperlipidaemia, syncopal episodes, osteoarthritis, diverticulosis and atrial arrhythmia. Prostate cancer was diagnosed 2 years ago with transrectal ultrasound-guided biopsy (Gleason 3 + 3) after elevated prostate-specific antigen levels were found in routine blood test. His cancer was under surveillance. He had bilateral total knee arthroplasty, left eye cataract surgery, prostate biopsy and appendectomy in the past. He has an approximately 25 pack-year history of

smoking but quit over 30 years ago. He occasionally drinks alcohol. Family history is remarkable for lymphoma in his mother and premature ischaemic cardiomyopathy in his father.

Physical examination revealed normal vital signs, and decreased breath sounds at the right base extending to the tip of the scapulae, accompanied by dullness on percussion in the same area. There was no peripheral oedema. His cardiac examination was normal.

INVESTIGATIONS

A chest x-ray and CT scan of the thorax confirmed the presence of a large right-sided pleural effusion (figure 1), a mild left-sided pleural effusion, mediastinal and hilar lymphadenopathy and a small pericardial effusion. No obvious parenchymal lung lesions were identified (figure 2).

Three litres of cloudy red pleura fluid were removed by thoracentesis. Analysis of fluid revealed it to be exudate in nature. No malignant cells were detected and flow cytometry showed no immunophenotypic evidence of monoclonal B-cell population.

Fluid culture and blood cultures were negative. Routine lab tests showed a mild anaemia (haemoglobin (Hb) 13 mg/dl), normal white cell count (8,900/dl) and differentials, normal platelet counts and no abnormalities detected in the basic metabolic panel (creatinine 0.9, blood urea nitrogen 14). A random urine sample was negative for proteinuria. Thyroid stimulating hormone was 5.6 IU ml, slightly elevated from the normal reference ranges. The serological analysis included antinuclear antibody which was not detected, rheumatoid factor was 0.5 (not elevated) and hepatitis panel was negative.

Figure 1 CT of the chest showing large right pleural effusion.

To cite: Franco-Palacios D, Tama M, Samaddar S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009329

Figure 2 CT of the chest showing and hilar lymphadenopathies and pleural effusion.

A transthoracic echocardiogram showed normal systolic function and a Doppler study of diastolic function was normal; no significant valvular disease, normal E/A ratio and normal cardiac structure but with an interventricular septal diameter of 14 mm (normal 7–11 mm). EKG and B-type natriuretic peptide were normal and months later an exercise stress test was also normal.

The CT scan of the thorax also demonstrated the presence of an extensive infiltration of the retroperitoneum (figure 3). CT of the abdomen and pelvis to investigate possible malignancy was performed. Findings were consistent with an infiltrative mass with diffuse and symmetrical involvement of the retroperitoneum, predominantly the perirenal space. The mass encased the adrenals, kidneys, aorta and inferior vena cava. An enlarged prostate was also described.

A CT-guided needle core biopsy of a left retroperitoneal mass was performed. There was deposition of acellular homogeneous pale pink material that surrounded the fat cells, also noted involving the soft tissue. Focally there was lymphoplasmacytic infiltrate and foreign body multinucleated giant cell reaction around amyloid deposition. The blood vessels also contained this amorphous acellular material in the blood vessel wall (figure 4). Diagnosis of amyloidosis was confirmed by the presence of apple-green birefringence on polarised light examination of a tissue biopsy stained with Congo red (figure 5).

Liquid chromatography tandem mass spectrometry of the retroperitoneal mass was done at Mayo Clinic (Rochester,

Figure 3 CT of the abdomen showing an infiltrative mass with mixed attenuation. Diffuse and symmetrical involvement of the retroperitoneum is seen predominantly in the perirenal space. The mass encases the adrenals, kidneys, aorta and inferior vena cava.

Figure 4 Low-power view of retroperitoneal mass demonstrating a connective tissue core with background chronic inflammation and multiple extracellular deposits of amorphous, glassy, eosinophilic material ($\times 100$ magnification, H&E stain).

Minnesota, USA). CD138 highlighted scattered plasma cells. Liquid chromatography-mass spectrometry (LC MS/MS) was performed on peptides extracted from Congo red positive/microdissected areas of the paraffin-embedded retroperitoneal mass biopsy specimen. LC MS/MS detected a peptide profile consistent with AL (κ)-type amyloid deposition. The findings supported the diagnosis of amyloidosis and indicated AL (κ)-type amyloid deposition.

Serum immunofixation showed IgM κ band present in γ zone at low concentration. Urine immunofixation showed weak Bence Jones-type κ band present. The κ : λ ratio was 4.01 (normal 0.26–1.65) after quantification of light chains immunoglobulins (κ 4.49 and λ 1.12).

A bone marrow biopsy was performed next and showed a nodular and interstitial infiltration of small lymphocytes, rare plasmacytoid lymphocytes and plasma cells. Immunohistochemistry showed the lymphoid aggregates to be CD20 positive B cells. CD3 highlighted a background T cells (figure 6). Plasma cells were identified by CD138 and MUM1 and were distributed singly and in small clusters and were predominantly κ -positive. Congo red stain was negative for amyloid protein in the bone marrow. There were no granulomas or metastatic malignancy. Analysis of 20 metaphase cells revealed a uniform pattern of a normal male karyotype.

Figure 5 Strong bright orange reaction of amorphous deposits on Congo Red stain that are birefringent with polarisation (inset) ($\times 400$ magnification, Congo Red stain).

Figure 6 High-power view of bone marrow biopsy demonstrating a paratrabecular collection of lymphocytes, plasma cells and rare plasmacytoid lymphocytes. Serum immunofixation confirmed a clonal IgM κ band ($\times 400$ magnification, H & E stain).

Final diagnosis was lymphoplasmacytic lymphoma with a background of normocellular marrow with trilineage haematopoiesis.

DIFFERENTIAL DIAGNOSIS

The clinical presentation of symptomatic pleural effusion and vague systemic symptoms in our patient represented a clear diagnostic challenge. Although he did have recurrent syncopal episodes and orthostasis suggestive of autonomic neuropathy, there was no evidence of cardiac or renal involvement.

Causes of exudative pleural effusion were investigated (including immunological causes, malignancy, infectious and non-infectious inflammation, iatrogenic causes and movement of fluid from below the diaphragm) but they did not yield to the diagnosis. The striking findings of soft tissue deposition in the retroperitoneum, although incidentally found, was determinant to the diagnosis. Only few reports have described primary amyloidosis with deposition of light chains immunoglobulins in the retroperitoneum.^{1 2} In a series of six patients with AL associated with lymphoplasmacytic lymphoma organ involvement was variable, with frequent bulky lymphadenopathy and visceral cavity deposits (two of them had retroperitoneal involvement).³ Effusions in systemic amyloidosis are rare. Large effusions, occupying over one-third of the hemithorax on chest radiograph (as seen in our patient), were reported in 6% of cases of AL amyloidosis in the largest single centre experience published.⁴ The diagnosis of retroperitoneal amyloidosis was confirmed by tissue biopsy. The type of AL was suggested by the serum and urine immunofixation results but only confirmed by the typing of amyloid fibrils by mass spectroscopy. Bone marrow biopsy showed a lymphoplasmacytic lymphoma. This in conjunction with the serum IgM paraprotein confirmed a diagnosis of WM.

TREATMENT

Chemotherapy was started consistent of drugs active against the lymphoid and plasma cell components of the disease. Cycle number one with fludarabine, rituximab and cyclophosphamide was started 1 month after WM with systemic amyloidosis was confirmed.

OUTCOME AND FOLLOW-UP

A repeat bone marrow biopsy performed 2 months after initiation of chemotherapy showed a normocellular bone marrow

with adequate trilineage haematopoiesis and did not show evidence of clonal population.

The patient has now received a total of four cycles out of six planned cycles of fludarabine, cyclophosphamide and rituximab. Although he has required multiple thoracentesis in the past, they have sequentially yielded lesser amounts of fluid and his last thoracentesis was 7 months ago. His last CT imaging studies of the chest, abdomen and pelvis 8 months after chemotherapy revealed reduction in his overall adenopathy but unchanged amyloid infiltration of the retroperitoneum.

His serum and urine protein electrophoresis still reveals the presence of an M-protein at low concentrations. He is doing generally well except for dyspnoea with ambulation.

DISCUSSION

This case is challenging and constitutes a clinical dilemma. In this particular case, the incidental findings in the CT scan helped to elucidate the underlying pathology, and geared the diagnostic effort towards two different organs that a priori did not seem to be related to the initial presentation. Rarely, AL amyloidosis can be associated with non-Hodgkin's lymphoma (NHL), in particular WM or lymphoplasmacytic lymphoma.¹

Few reports have described primary amyloidosis with deposition of light chains immunoglobulins in the retroperitoneum.^{1 2} Cohen *et al.* described a series of six patients with AL associated with NHL, primarily lymphoplasmacytic lymphoma. Organ involvement was variable, with frequent bulky lymphadenopathy and visceral cavity deposits, two of them had retroperitoneal involvement.³ Large effusions, occupying over one-third of the hemithorax on chest radiograph (as seen in our patient), were reported in 6% of cases of AL amyloidosis in the largest single centre experience published.⁴

Only few cases reported the presence of amyloidosis of any type in the retroperitoneum, some of them were associated with malignancies, renal cancer being the most common.⁵⁻¹⁰

Frontline treatment options for WM include oral alkylators (eg, chlorambucil), nucleoside analogues (cladribine or fludarabine), the monoclonal antibody rituximab, as well as combinations of these agents. Individual patient considerations, including the presence of cytopenias, need for more rapid disease control, age and candidacy for autologous transplantation therapy, should be taken into account in making the appropriate choice of a first-line agent.^{11 12}

Learning points

- ▶ Amyloidosis, although a rare condition, is a known cause of large pleural effusions and cavity deposits.
- ▶ Primary amyloidosis can be caused by deposition of light chain immunoglobulins as seen in patients with non-Hodgkin's lymphomas, specifically lymphoplasmacytic lymphoma or Waldenström's macroglobulinaemia.
- ▶ AL amyloidosis secondary to Waldenström's macroglobulinaemia is a rare complication of this already uncommon malignancy. Retroperitoneal involvement is also exceeding rare.
- ▶ CT scans of the chest, abdomen and pelvis should be obtained at time of diagnosis to properly stage the patient.
- ▶ Chemotherapy consistent of drugs active against the lymphoid and plasma cell components of the disease is the proposed therapy.

Contributors All the authors have contributed equally towards preparing the manuscript and have approved the final draft of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Gertz MA, Kyle RA, Noel P. Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenström's macroglobulinemia. *J Clin Orthod* 1993;11:914–20.
- 2 Gertz MA, Merlini G, Treon SP. Amyloidosis and Waldenström's macroglobulinemia. *ASH Educ Book* 2004;2004:257–82.
- 3 Cohen AD, Zhou P, Xiao Q, et al. Systemic AL amyloidosis due to non-Hodgkin's lymphoma: an unusual clinicopathologic association. *Br J Haematol* 2004;124:309–14.
- 4 Berk JL, Keane J, Seldin DC, et al. Persistent pleural effusions in primary systemic amyloidosis. *Chest* 2003;124:969–77.
- 5 Takebayashi S, Ono Y, Sakai F, et al. Computed tomography of amyloidosis involving retroperitoneal lymph nodes mimicking lymphoma. *J Comput Assist Tomogr* 1984;8:1025–7.
- 6 Allen HA, Vick CW, Messner JM, et al. Diffuse mesenteric amyloidosis. CT, sonographic and pathologic findings. *J Comput Assist Tomogr* 1985;9:196–8.
- 7 Glynn TP Jr, Kreipke DL, Irons JM. Amyloidosis: diffuse involvement of the retroperitoneum. *Radiology* 1989;170:726.
- 8 Halm U, Berr F, Tannopfel A, et al. Primary amyloidosis of the mesentery and the retroperitoneum presenting with lymphedema. *Am J Gastroenterol* 1998;93:2299–300.
- 9 Banerji JS, Gopalakrishnam G, Sriram K, et al. Localized retroperitoneal amyloidosis mimicking retroperitoneal fibrosis: a rare cause of obstructive uropathy. *Singapore Med J* 2009;50:e332.
- 10 Coakley FV, Hricak H, Presti JC Jr, et al. Diffuse retroperitoneal amyloidosis due to renal cell carcinoma. *Br J Radiol* 1999;72:412–3.
- 11 Comezo R. How I treat Amyloidosis. *J Am Soc Hematol Blood J* 2009;114:3147–57.
- 12 Treon SP. How I treat Waldenström macroglobulinemia. *J Am Soc Hematol Blood* 2009;114:2375–85.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow