CASE REPORT

Adnexal mass secondary to extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with associated amyloid deposition

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SUMMARY

Systemic amyloid light chain amyloidosis (AL amyloidosis) is usually seen in association with a plasma cell disorder. Amyloid deposition associated with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is a rare phenomenon that is not typically associated with systemic AL amyloidosis. We describe the unusual case of a patient with an adnexal mass secondary to MALT lymphoma with associated amyloid deposition.

BACKGROUND

Systemic amyloidosis is a heterogeneous group of disorders characterised by abnormal tissue deposition of extracellular fibrillar proteins in a β -pleated sheet configuration.^{1 2} While there are over 28 types of amyloidogenic proteins, the β -pleated sheet structure allows binding of Congo red stain by all amyloid fibrils and demonstration of apple-green birefringence under polarised light.³ Immunoglobulin amyloid light chain (AL) amyloidosis (primary amyloidosis) is the most common type of systemic amyloidosis, and is typically associated with an underlying disorder of plasma cells or lymphoplasmacytoid cells that produce monotypic immunoglobulin light chains as a constituent of amyloid, the deposition of which results in severe cardiac and renal dysfunction. AL amyloidosis is by far most commonly seen in association with a plasma cell neoplasm such as plasma cell myeloma. However, in 2–4% of the cases amyloid deposition in tissue arise in the setting of a B-cell non-Hodgkin lymphoma,^{4–6} typically with plasmacytic differentiation that results in production of monoclonal light chain protein and AL amyloid formation/deposition. Amyloid deposition associated with an underlying B-cell non-Hodgkin lymphoma is best described in the setting of lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia), in which both systemic and localised amyloidosis can occur.^{4 6 7} Rarely, however, amyloid deposition may be seen as a localised deposit in association with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).⁸

MALT lymphoma is a mature B-cell neoplasm occurring in a variety of extranodal tissue sites, including the lung, gastrointestinal tract, oropharynx, salivary glands, skin and orbit; and often arise in the setting of autoimmune disorder or chronic

inflammation.⁶ First described in 1983 by Isaacson and Wright, MALT lymphoma was first recognised as a diagnostic category in 1994 in the Revised European-American Lymphoma (REAL) classification system, and more recently in the WHO classification system.^{9 10} MALT lymphomas generally have clinically indolent behaviour. Approximately one-third of cases present with disseminated disease. However, survival is similarly excellent for patients with localised versus disseminated disease; in a study of 156 patients, the 5 and 10-year overall survival rates were 86% and 80%, respectively.¹¹

Amyloid deposition associated with MALT lymphoma has only been infrequently described in literature, and appears to represent a localised rather than systemic disorder.⁸ Various sites of involvement, including the lung, gastrointestinal tract, and oral mucosa, have been reported. To date, amyloid deposition manifesting as an adnexal soft tissue mass in the setting of extranodal marginal zone lymphoma has not been described.

CASE PRESENTATION

A 55-year-old woman with a history of chronic sinusitis and upper respiratory tract infections presented with dry cough, and was diagnosed with a 'walking pneumonia.' Since her lung infiltrate did not improve with serial antibiotics, the patient underwent a chest CT that showed opacities in the right middle and lower lobes. A subsequent bronchoscopy with bronchial brushings provided no evidence for malignancy or infection. Given the persistence of her radiographic findings, a repeat bronchoscopy of the right middle lobe was performed and showed a lymphocytic infiltrate composed of admixed CD3 positive T-cells and CD20 positive B-cells. κ and λ Immunostains did not show light chain restriction. No amyloid deposits were noted. Although definitive diagnostic evidence of lymphoma was not demonstrated morphologically and/or immunophenotypically, molecular study subsequently detected the presence of clonal immunoglobulin heavy chain gene rearrangement. Of note, the patient had not had fevers, chills or weight loss, but had noted mild dyspnoea on exertion without limitation of her exercise tolerance.

Following the bronchoscopy, she underwent a positron emission tomography (PET/CT) which demonstrated a 3.2×2.3 cm right middle lobe

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Figure 1 CT (left) and positron emission tomography CT fusion (right) transaxial images of the pelvis showing a 4.4×2.1 cm hypermetabolic left adnexal mass with a standardised uptake value of 14.8. The activity anteriorly in the pelvis is due to partial volume effect from excreted radiotracer in the urinary bladder. The small focus of uptake posteriorly in the pelvis, anterior to the sacrum, is secondary to lymphoma infiltration.

infiltrate with a standardised uptake value (SUV) of 4.5, a 4.7×2.5 right middle lobe infiltrate with an SUV of 5.3, and a subcutaneous left medial thigh nodule measuring 0.8 cm with an SUV 7.5. Fine needle aspiration of the left thigh nodule was subsequently performed and sent for flow cytometric analysis, which showed a monotypic population of λ restricted B-cells positive for CD19, CD20 and CD22. Given this finding, the overall presentation was thought to be consistent with MALT lymphoma, stage IVA. Further evaluation demonstrated the following: IgG 522, IgA 53 and IgM 622; normal complete blood count; and normal total protein and albumin. Serum protein electrophoresis and immunofixation did not demonstrate a monoclonal spike. Serum κ and λ light chain levels were 880 and 413 mg/dL, respectively. Hepatitis B and hepatitis C serologies, HIV ELISA, and *Helicobacter pylori* stool antigen were also negative.

As she was asymptomatic from her indolent lymphoma, no treatment was initiated. A repeat PET scan 5 months later demonstrated a new hypermetabolic mass in the left hemipelvis measuring 4.4×2.1 cm with an SUV of 14.8 (figure 1). The next day, on pelvic ultrasound the mass was localised to the left adnexa showing moderate vascularity. A subsequent pelvic MRI completed 4 weeks after the PET scan demonstrated an increase in size of the left adnexal mass to 5.6×2.2 cm. The patient then underwent a laparoscopic bilateral salpingo-oophorectomy.

Histologically, both fallopian tubes showed diffuse intramural deposition by amorphous eosinophilic material (figure 2A–C), which was highlighted by a Congo red special stain and identified as amyloid based on the characteristic ‘apple-green’ birefringence under polarised microscopy (figure 2D). The amyloid deposits were invariably surrounded by an atypical lymphoid infiltrate composed of small lymphocytes with mature chromatin (figure 3A) admixed with a small number of plasma cells, some with intranuclear inclusions/Dutcher bodies (figure 3B); the infiltrate constitutes 10% of the entire mass volume, while 90% of the entire mass volume consisted of amyloid deposits. The ovaries were histologically unremarkable.

Immunohistochemical studies demonstrated that the atypical lymphoid infiltrate was composed of predominantly CD20 positive B-cells (figure 3B) that aberrantly express B-cell lymphoma 2 (BCL-2) (figure 3C) and CD43 (figure 3D); while negative for CD5, CD10, CD23, BCL-6, and cyclin D1. κ and λ Immunostains demonstrated the plasma cell component was λ light chain restricted, thereby establishing the clonal nature of

the infiltrate. The amyloid deposits were also positive for λ but not for κ (figure 3E, F). The proliferation index based on Ki-67 was less than 10%. Based on these findings, a diagnosis of extranodal marginal zone lymphoma/MALT lymphoma with associated amyloid deposition was rendered.

OUTCOME AND FOLLOW-UP

The patient has remained on observation without further complications of her disease. She continues not to have evidence of systemic amyloidosis.

DISCUSSION

A review of the literature revealed 26 prior reports of localised amyloid deposition in association with MALT lymphoma, with a total of 75 reported cases. Sites previously reported to be involved included lung (n=26), breast (n=17), stomach (n=5), bowel (n=4), orbit (n=4), central nervous system (n=3), salivary gland (n=3), oral mucosa (n=2), skin (n=2), larynx (n=2), retroperitoneum (n=2), thyroid (n=1), tonsil (n=1) and other soft tissue (n=5). Some patients were found to have multiple sites of involvement by MALT lymphoma with amyloid deposition.^{7 8 12–36} The largest case series (20 cases) of MALT lymphoma associated amyloid deposition was published by Ryan *et al.*⁸ However, in the majority of cases (n=16) the diagnosis of amyloid deposition was performed at the time of the diagnosis of lymphoma.

As the techniques available for the detection of amyloid deposits become more sophisticated, it is increasingly important to consider an underlying lymphoma, particularly MALT lymphoma, in the presence of a new diagnosis of amyloidosis. In some cases, localised amyloid deposition can be found after the initial diagnosis of MALT. Some have indicated that there is an association between nodular pulmonary amyloidosis, autoimmune disease such as Sjögren’s syndrome and MALT lymphoma as well.³⁰

In this case, the decision to pursue PET/CT for staging was based on data from Beal *et al.*³⁷ which has demonstrated that MALT lymphomas may be fluorodeoxyglucose (FDG)-avid in up to 80% of cases and may lead to upstaging of patients in up to 12% of cases.

Non-specific FDG uptake has been described in amyloidosis,^{38–40} and in particular pulmonary amyloidosis. The intensity of FDG uptake has been described as variable, with SUV

Figure 2 (A) The fallopian tubes show diffuse intramural involvement by eosinophilic deposits and patchy lymphocytic infiltrate; (B) higher magnification showing amorphous nature of the deposits; (C) the eosinophilic deposits are positive for Congo red histochemical stain, and (D) identified as amyloid based on the characteristic 'apple-green' birefringence under polarised microscopy.

Figure 3 (A) The amyloid deposits are intimately associated with an atypical lymphoid infiltrate composed of small lymphocytes with mature chromatin; admixed with a small number of plasma cells (arrows), some with intranuclear inclusions/Dutcher bodies (arrow head); the atypical lymphoid infiltrate is composed of predominantly (B) CD20 positive B-cells that aberrantly express (C) BCL-2 and (D) CD43. (E, F) κ and λ Immunostains demonstrated the plasma cell component was λ light chain restricted, thereby establishing the clonal nature of the infiltrate. The amyloid deposits were also positive for λ but not for κ .

numbers in the range of 4–15 (14.8 in our case) and is probably related to the number of inflammatory cells within the lesion.

In contrast to amyloid deposition associated with MALT lymphoma, systemic AL amyloidosis is considered to be a life-threatening disorder that is complicated by cardiac and renal failure. In these cases, amyloid deposition is most commonly demonstrated in biopsies of the kidneys, heart, nervous system, intestinal tract and muscle and lungs. Currently patients with systemic AL amyloidosis are treated with alkylator-based chemotherapy, and often consolidated with an autologous stem cell transplant. Nevertheless, the 6-month overall survival is only 65%, with a median overall survival of 13–24 months.^{2 4 41 42} However, these data and treatment recommendations do not apply to patients with MALT lymphoma and associated amyloid deposition, in whom liver, renal, nervous system or cardiac involvement do not occur. This suggests that MALT lymphoma associated amyloid deposition appears to carry a different natural history and clinical course.⁷ Accordingly, MALT lymphoma with amyloid deposition may be amenable to conservative management as in our patient.

Learning points

- ▶ Amyloid deposition may be seen rarely in association with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).
- ▶ Amyloid deposition associated with MALT lymphoma is seen within regions affected by lymphoma and as in this case may occur in the adnexa.
- ▶ Amyloid deposition associated with MALT lymphoma is not systemic amyloid light chain amyloidosis and carries an indolent course.

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