CASE REPORT

Primary thymic extranodal marginal zone B cell lymphoma as an incidental finding in a Caucasian woman

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SUMMARY

Primary thymic extranodal marginal zone B cell lymphoma (TML) is an extremely rare lymphoma strongly associated with autoimmune disease. We report an exceedingly rare case of TML found in a non-Asian population. TML was found incidentally in a 60-year-old Caucasian woman with a short history of muscle and joint pain. An anterior mediastinal mass was detected by a positron emission tomography-CT (PET-CT) scan and thymectomy was performed. The mass was contained within the thymus with a homogeneous pale cut surface with solid areas. Histologically, the typical morphological and immunophenotypic features of TML were found, with a prominent lymphoid infiltrate comprising of small-to-medium-sized neoplastic lymphocytes, plasmacytic differentiation and a distorted thymic epithelial network. Postoperative follow-up has indicated an associated undifferentiated connective tissue disease (UCTD) with features of systemic lupus erythaematosus.

BACKGROUND

Primary thymic extranodal marginal zone B cell lymphoma (TML) is an extremely rare lymphoma with only 23 reported cases in the literature. Among the 23 patients reported to date, 18 were Asian.^{1 2} TML is often associated with autoimmune disease, especially Sjögren's syndrome. Most patients are in the fifth or sixth decade and there is a marked female predominance. The treatment is surgical excision and/or chemotherapy, and there is an excellent outcome with long-term survival.³ We report an exceedingly rare case of TML in a non-Asian population.

CASE PRESENTATION

A 60-year-old Caucasian woman presented with a 6-week history of muscle pain and arthralgia in the arms and legs. She reported constant pain at the shoulders, wrists and metacarpophalangeal, hip and knee joints, accompanied by swelling and morning stiffness. In addition, she had an involuntary weight loss of 1–2 kg. She had no symptoms of dry eyes or dry mouth, headache or jaw claudication, and no dermatological or heart and lung symptoms.

She had no relevant family history of rheumatological or autoimmune disease.

INVESTIGATIONS

The initial laboratory examination at admission revealed anaemia (11 g/dL), leucocytosis ($12.3 \times 10^9/L$) and thrombocytosis ($614 \times 10^9/L$), a significant increase in erythrocyte sedimentation rate (44 mm/h) and C reactive protein (108 mg/L). Lactate dehydrogenase was marginally increased (233 U/L) and thyroid-stimulating hormone was normal. Antinuclear antibody (ANA), anti-cyclic citrullinated peptides (anti-CCP) and rheumatoid factor were negative.

Positron emission tomography-CT (PET-CT) scan demonstrated increased fluorodeoxyglucose (18F) uptake symmetrically in the shoulders and hip joints, and also revealed a $62 \times 27 \times 10$ mm mass arising from the anterior mediastinum with relation to the thymus (figure 1). There was no sign of invasion or spread to surrounding structures or organs.

DIFFERENTIAL DIAGNOSIS

Initially, based on the clinical presentation and initial laboratory findings, polymyalgia rheumatica was suspected. However, after the PET-CT scan showed an anterior mediastinal mass with relation to the thymus, suspicion of a thymic neoplasm, including thymoma, was raised. The clinical presentation could then reflect a paraneoplastic syndrome. The case was discussed at a multidisciplinary conference and a plan for thymectomy was made. Thymectomy was performed through median

Figure 1 Positron emission tomography-CT (PET-CT) scan showing increased fluorodeoxyglucose uptake in an anterior mediastinal mass with relation to the thymus.

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Figure 2 Effaced architecture with diffuse lymphoid infiltration and interspaced reactive follicles (Giemsa, $\times 250$).

sternotomy and submitted for pathological examination. Resection specimen examination revealed a semilobulated mass with lobes measuring $7 \times 3 \times 0.8$ cm and $7 \times 2.5 \times 1$ cm, and weighing 17 g. The mediastinal mass was contained within the thymus and did not show invasion in the surrounding structures. The cut surface had a homogeneous pale appearance with no cystic spaces, but with solid areas without a well-defined tumour.

Histologically, the normal thymic lobular architecture was effaced by a dense lymphoid infiltrate with scattered reactive lymphoid follicles. Cortical areas and a few residual Hassall corpuscles could be identified. The lymphoid infiltrate consisted of small-to-medium-sized lymphocytes with pale cytoplasm. There was prominent plasmacytic differentiation. The thymic epithelial network was highlighted by cytokeratin marker AE1/AE3 and was found distorted due to the infiltrate. The neoplastic lymphoid cells were positive in B cell markers CD79a, CD20, PAX5 and BCL2, whereas CD3, CD5 and CD10 were negative. Plasma cells were highlighted by CD138 and showed clear λ -light chain restriction. Flow cytometry showed plasma cells and a population of B cells with λ -light chain restriction (figures 2–7). The findings were diagnostic of a TML.

TREATMENT

The patient went through radical surgical resection for both diagnosis and treatment as histology showed a completely encapsulated tumour, free margins and no lymphoma

Figure 3 Distorted thymic epithelial network due to the lymphoid infiltrate (CK AE1/3, $\times 250$).

Figure 4 Heavily infiltrated lymphoid consisting of small-to-medium-sized B lymphocytes with a pale cytoplasm positive for CD79a ($\times 400$).

involvement of regional lymph nodes, bone marrow or other mucosa-associated lymphoid tissue (MALT) sites. Thus, since it was histologically and clinically proven to be a low-grade lymphoma—WHO stage I—it was decided not to administer postoperative adjuvant chemotherapy or radiation therapy.

OUTCOME AND FOLLOW-UP

On clinical review, now 8 months postsurgery, there is no evidence of recurrent lymphoma. Postoperative rheumatological

Figure 5 A dense lymphoid infiltrate consisting of prominent plasmacytic differentiation highlighted by immunostaining for immunoglobulin by CD138 ($\times 400$).

Figure 6 Clear λ -light chain restriction with λ positive and κ negative (Serial sections, $\times 400$).

follow-up has showed abnormalities suggestive of undifferentiated connective tissue disease (UCTD). Laboratory findings with anti-Smiths antibodies and anti-nuclear ribonucleoprotein (anti-nRNP) antibodies and accompanying inflammatory activity

are indicative of systemic lupus erythaematosus (SLE). Further tests are ongoing for the final categorisation. The patient continues to be treated with prednisolone 7.5 mg daily and has experienced convincing relief of symptoms.

DISCUSSION

TML is extremely rare and most often reported in Asians with autoimmune diseases, in particular Sjögren's syndrome. We have presented an exceedingly rare case of TML found in a non-Asian population, discovered incidentally in a middle-aged Caucasian woman. Based on the clinical presentation together with laboratory findings, a diagnosis of polymyalgia rheumatica was proposed, but after a mediastinal mass was detected by PET-CT scan, a thymic neoplasm was suspected. The resection specimen examination revealed a homogeneous pale cut surface with solid areas in the thymus. Inagaki *et al* describe several cases with similar pathological findings, in the largest reported series of TML (15 cases). In contrast to the findings of Inagaki *et al*,² of multiple variable cysts, we did not find any cysts in our specimen examination. Typical morphological and immunophenotypic features of TML were found, as microscopy showed a prominent lymphoid infiltrate comprising small-to-medium-sized neoplastic lymphocytes, plasmacytic differentiation and a distorted thymic epithelial network. Immunohistochemistry and flow cytometry confirmed a clonal B cell and plasma cell population with λ -light chain restriction.³

TML has been strongly associated with autoimmune disease, most commonly Sjögren's syndrome. Our patient has been admitted for postoperative rheumatological follow-up and has shown abnormalities suggestive of an associated UCTD with features of systemic lupus erythaematosus. To the best of our

Figure 7 Flow cytometry showing plasma cells and a population of B cells with λ -light chain restriction.

knowledge, only two other reported cases of TML have been associated with systemic lupus erythematosus.^{4 5} The detailed aetiological relation between systemic lupus erythematosus and TML is unclear. However, there is a well-documented association between autoimmune disease and lymphoid neoplasms, mostly marginal zone lymphomas. The lymphomas are thought to arise as a result of chronic antigen stimulation caused by the autoimmune disease.⁶

It is apparently a very rare lymphoma type in Caucasians as, to the best of our knowledge, only five cases have been reported in the non-Asian population.² Whether there is a genuine ethnic difference is not known. Epidemiological studies⁷ have suggested a possible relationship between lymphoma and environmental, toxic or lifestyle-related factors, which could account for the apparent predilection in Asians. On the other hand, there might be a possible difference in the incidence of autoimmune disease or in the diagnostic procedures performed regarding the clinical, radiological and pathological work up. From a clinical point of view, TML is a slow growing low-grade lymphoma remaining localised for a long time, with unclear clinical features, and patients are usually asymptomatic with incidental radiological findings. From a pathological point of view, a diagnosis of TML in a biopsy from an anterior mediastinal mass can be difficult, because the presence of the mixture of small-to-medium-sized lymphocytes and thymic epithelial cells may be sparse and mimic thymic lymphoid hyperplasia, or may be misinterpreted as tissue from a mediastinal lymph node with marginal zone B cell lymphoma. Parrens *et al*⁸ investigated 14 cases initially diagnosed as thymic lymphofollicular hyperplasia in patients with either myasthenia gravis or connective

tissue disease, and found three cases where the morphological, immunohistochemical and molecular findings showed development of early or focal TML associated with thymic lymphofollicular hyperplasia. Thus, TML might be an underdiagnosed lymphoma.

Appropriate tissue sampling and careful examination of the H&E-stained sections as well as application of appropriate immunohistochemical stains are fundamental in the histopathological work up. Cytokeratin staining is especially important in order to identify the alternation of the epithelial network, which is associated with TML. The objective of identifying TML is not only important from an academic point of view but also because of the reported risk of its transformation to aggressive large B cell lymphoma.^{3 5}

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Contributors JKP researched the literature and conceived the study. CS and TSL were involved in patient recruitment. MBM and CS made the histopathological diagnosis. JKP wrote the first draft of the manuscript. All the authors reviewed and edited the manuscript, and approved the final version.

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Learning points

- ▶ Thymic extranodal marginal zone B cell lymphoma (TML) is an extremely rare low-grade marginal zone B cell lymphoma strongly associated with autoimmune disease.
- ▶ TML is exceedingly rare in non-Asian populations.
- ▶ Patients are often asymptomatic and TML may be discovered incidentally by imaging diagnostics.
- ▶ Diagnosis of TML in a biopsy can be difficult, and appropriate tissue sample and careful examination with immunohistochemistry, including cytokeratin staining, is important, to permit identification of TML.

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