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Original Article

Amyloid deposition in extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue: A clinicopathologic study of 5 cases

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ABSTRACT

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is the most common subtype of marginal zone lymphoma (MZL), with stomach being the most frequent primary site, followed by salivary gland, lung and ocular adnexa. Although clinically indolent, MALT lymphoma has the potential of local recurrence and systemic spread. Amyloid deposition is a very unusual complication of MALT lymphoma. In this study, we report clinicopathologic features of 5 cases of MALT lymphomas with associated amyloid deposits. One case showed amyloid deposits in the primary lesion; the other four cases showed amyloid deposits only in recurrences. Previous studies suggest that the amyloid deposits do not implicate worse prognosis. In our study, although amyloid deposits were focal and organ confined, one patient had extensive deposits of amyloid in the large bowel wall leading to bowel perforation and another patient developed significant peripheral neuropathy due to amyloid deposits in the brachial plexus. In conclusion, amyloid deposits in MALT lymphomas are rare and organ/tumour confined. However, complications can be critical and cause considerable morbidity. Therefore, pathologists should be aware of the association between MALT lymphoma and amyloid deposition, and clinical follow up is warranted.

1. Introduction

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) accounts for approximately 8% of all B-cell lymphomas. The most frequent primary site of involvement is the stomach, followed by the salivary gland, lung, ocular adnexa, skin, thyroid, and breast [1–3].

Regardless of the primary site, MALT lymphomas exhibit characteristic histological features. Typically, the neoplastic cells are distributed in expanded marginal zones and as diffuse sheets between residual normal follicles. Less commonly, germinal center/mantle zone colonization is present. The neoplastic cells themselves can be polymorphous, and in varying proportions, they appear as small mature lymphocytes, medium-sized monocytoid cells with pale cytoplasm, lymphoplasmacytic cells, plasma cells, and occasionally as scattered large centroblast-like cells [4].

In conjunction with morphology, immunohistochemistry (IHC), flow cytometry, and cytogenetics may be helpful in the diagnosis of MALT lymphoma. Usually, the neoplastic cells express CD20 and bcl-2, and most commonly do not stain with antibodies targeting CD23, CD10, bcl-6, and cyclinD1. Aberrant expression of CD43 is observed in 30–50% of cases. Only a minority (5–10%) of MALT lymphomas exhibits aberrant expression of CD5, and these cases may show a greater propensity for relapse and bone marrow involvement [5]. In instances of prominent plasmacytoid differentiation, detection of light chain restriction is facilitated by IHC. Another potentially useful diagnostic modality is cytogenetics [6].

Most patients with MALT lymphoma present at low clinical stage, and their disease is amenable to therapies that include surgical excision, radiation, anti-CD20 immunotherapy, and chemotherapy. *Helicobacter pylori* eradication is the standard management for gastric MALT lymphomas [7–9]. Although MALT lymphoma is generally considered to be clinically indolent, local

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Table 1
Immunohistochemical stains performed on initial diagnostic biopsies, and flow cytometry performed on four cases.

Patient	CD5	CD19	CD20	CD23	CD10	BCL2	BCL6	CyclinD1	Kappa	Lambda	Flow cytometry
1	–	+	–	–	–	–	NP*	–	–	+	M*
2	–	+	+	–	–	+	NP*	NP*	+	–	M*
3	+	+	+	±	–	–	NP*	–	+	–	M*
4	–	+	+	–	–	–	–	–	–	+	M*
5	–	NP*	+	–	–	–	–	NP*	+	–	NP*

M*: monoclonal B-cell population.
NP*: not performed.
Patient #3 showed some CD23 positive cells on the initial biopsy, but the relapsed lymphoma was completely CD23 negative.

recurrence and systemic spread are not uncommon, despite therapy [10,11].

Amyloid deposition has been reported as an unusual complication of MALT lymphoma. It has been postulated that immunoglobulin light chains, produced by the neoplastic plasmacytoid cells, are deposited as amyloid. Most reported cases of MALT lymphoma with associated amyloid have followed indolent clinical courses, and amyloid deposition has predominantly been peritumoural [12–14]. In this series, we describe the clinicopathological features of 5 cases of MALT lymphoma with associated amyloid deposition involving one or more organs. It is noteworthy that two cases presented with complicated clinical courses, causing morbidity in one case and demise in another.

2. Materials and methods

2.1. Patients

All cases were diagnosed at the Pathology Department, University Hospital, London, Ontario, Canada between 2004 and 2013. Clinical information on four cases was obtained from electronic consultation records and from the London Regional Cancer Centre Program. One referred case was submitted without clinical data.

2.2. Laboratory studies

All sections of primary and relapsed material were stained with Hematoxylin and Eosin (H&E), and Congo red stain. Selected slides of each case were stained with a battery of immunohistochemical stains. CD3, CD5, CD10, CD20, CD23, CD43, Bcl2, Bcl6, kappa, lambda and cyclinD1 immunostains (supplied by DAKO Denmark) were variably applied in each case. Antibody titers and antigen retrieval methods were based on the manufacture manual. All antibodies were polyclonal, with the exception of kappa, lambda and CD3 (monoclonal antibodies). Flow cytometry (Beckman Coulter FC500, 5 colour, CXP software) was available on 4 of the 5 cases and cytogenetic studies (chromosomal karyotype) were available on case #3. Please see Table 1 for the applied immunohistochemistry and flow cytometry results.

3. Results

Four of the five patients were males; the median age was 71 years (53–87 years). None had any autoimmune disease or chronic infection. All five patients were diagnosed with MZL lymphoma as described by the World Health Organization classification (2008). Two had primary orbital/adnexal lesions, one had primary pleural/lung lesion, one had a left arm subcutaneous lesion, and one presented as bone marrow involvement. All five patients had amyloid deposits identified at one or more anatomic sites during their disease course. The clinical and pathological features are described in detail below, and are summarized in Table 2.

Patient #1 presented with slowly progressive ptosis of left eye and a mass was found on his eyelid, and a small mass on the back. An excisional biopsy of the eye lesion and a fine needle aspiration biopsy of the back lesion revealed marginal zone lymphoma. An MRI of the head did not show extension of the mass beyond the orbit. The patient received 20 fractions of radiation therapy and he became asymptomatic. No further investigations or staging were performed. Four years later, the patient was incidentally found to

Table 2
Clinical presentation with initial and relapsed disease.

Patient	Age (years)	Sex	Time at diagnosis and relapse	Site of tumour	Amyloid/Congo stain	BM biopsy	Treatment	Outcome
1	66	M	2004 2008 2011	Left eye lid Abdominal Large bowel	Negative Positive positive	Negative Negative NP+	Radiation Chlorambucil CVP-R	Perforation
2	73	M	2004 2012 2014	Left orbit Jaw Right orbit and lung	Negative Positive Positive	Negative	Radiation Observation Observation	Alive with disease
3	53	M	2004 2012 2012	BM Gallbladder Peripheral nerves	Negative Positive Positive	Positive Positive	Observation Chemotherapy Chemotherapy	Alive with disease
4	87	M	2008 2012	Right lung Uvula	Negative Positive	Positive (minimal) NP+	Chemotherapy	Alive with disease
5	78	F	2013	Subcutaneous tissue, left forearm	Positive	NHA		

NP+: not performed.
NHA: no history available.
Patient #4 deceased a year later of unrelated diseases.