ORBITAL MALT (Mucous Associated Lymphoid Tissue) LYMPHOMA

ESSAY

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Conclusion

Mucosa-associated lymphoid tissue (MALT) type lymphoma is now incorporated into the REAL and the WHO classification systems as extranodal marginal zone B-cell lymphoma (EMZL), MALT type [89].

EMZL (MALT) type is the most frequent lymphoma subtype found in the orbit and ocular adnexa, accounting for 35% to 80% of cases [4].

MALT lymphomas typically arise in tissues or organs that are normally devoid of any organized lymphoid tissue, such as the orbital region, but acquire reactive lymphoid tissue in response to persistent antigenic stimulation, as a result of chronic inflammatory or autoimmune disorders [4].

Chlamydia psittaci was identified as the causative infectious agent of ocular adnexal lymphomas. The presence of C. psittaci in ocular adnexal MALT lymphoma showed marked variation among different geographical regions, being most frequent in Germany, followed by the USA, and the Netherlands, but relatively low in Italy, the UK and southern China [1].

The association between HCV infection and B-cell NHL has been also demonstrated, especially in highly endemic

List of Contents

List of Abbreviations

AJCC	American Joint Committee on Cancer.
CEB	chlamydial elementary body.
Cp	Chlamydia psittaci.
CRB	chlamydial reticulate body.
CT	computed tomography.
EB	elementary body.
EBRT	External beam radiotheraby.
EMZL	extranodular marginal zone lymphoma.
GML	gastric MALT lymphoma.
HCV	hepatitis C virus.
H&E	hematoxylin and eosin.
HP	Helicobacter pylori.
IB	intermediate body
IgH	immunoglobulin heavy chain.
LDH	lactate dehydrogenase.
MALT	mucosa-associated lymphoid tissue.
MRI	magntic resonance imaging
NF-κB	nuclear factor kappa-B complex.
NHLs	non-Hodgkin lymphomas.
OAL	ocular adnexal lymphoma.
OAML	ocular adnexal MALT lymphoma.
OAMZL	ocular adnexal marginal zone lymphoma

PBMC	peripheral blood mononuclear cells.
PCR	polymerase chain reaction.
PET	Positron emission tomography.
RB	reticulate body.
REAL	Revised European–American Lymphoma.
RLH	reactive lymphoid hyperplasia
RT	Radiotherapy.
TNM	tumor, node, metastasis.
US	Ultrasonography.
WHO	World Health Organization.

List of Figures

List of Tables

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Introduction

The eye and ocular adnexal region, affected by hundreds of histologically different types of neoplasms, has the greatest variety of malignancies in the human body [(1)].

Lymphoma is the most frequent malignant tumor in the ocular region, composing approxmately 1% to 2% of non-Hodgkin lymphomas (NHLs) and 8% of extranodal lymphomas [(2)] .

The majority of ocular adnexal lymphomas (OALs) are primary extranodal neoplasms; however, 10% to 32% are secondary tumors in patients with disseminated lymphoma [(3)] .

More than 95% are of B-cell origin, and 80% are low-grade lymphomas. The most common subtype of primary OAL, accounting for 35% to 80% of cases, is extranodular marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) type, followed by follicular lymphoma (20%), diffuse large B-cell lymphoma (8%), and less commonly mantle cell lymphoma, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma [(4)].

Mucosa-associated lymphoid tissue (MALT) lymphomas typically arise in tissues or organs that are

normally devoid of any organized lymphoid tissue, such as the orbital region, but acquire reactive lymphoid tissue in response to persistent antigenic stimulation, as a result of chronic inflammatory or autoimmune disorders. Analyses of somatic mutations in the variable (V) region of the immunoglobulin (Ig) and heavy (H) chain gene segment have suggested a role of chronic antigen stimulation in the pathogenesis of ocular adnexal MALT lymphoma (OAML) [(4)].

Recently, Chlamydia psittaci was identified as the causative infectious agent of OALs. C. psittaci was detected in 80% of OAL specimens. There are several reports about the association of hepatitis C virus infection and non-Hodgkin lymphomas [(5)].

MALT lymphoma of ocular adnexa arises in the orbit, conjunctiva, eyelids, and lacrimal gland. Preliminary diagnosis of NHL of the orbit on the basis of clinical–radiological examinations still constitutes a significant clinical problem, as NHLs do not have characteristic symptoms differentiating them from other tumours of the orbit [(6)].

The histologic characteristics of MALT lymphoma include the presence of centrocyte-like cells that infiltrate the epithelium and that resemble centrocytes (small-cleaved cells)

of the normal germinal center. However, MALT lymphoma cells may exhibit a wide range of cytological appearances, from monocytoid B cells, small lymphocytes or small cleaved cells to large lymphoid cells. Transformation to large B-cell lymphoma has been observed occasionally in tumors with high mitosis rates and an increase in the number of large cells (>10%) [(7)].

Mucosa-associated lymphoid tissue lymphoma can be diagnosed immunohistologically, by the presence of immunoglobulin light chain, pan-B-cell antigens, and Bcl-2 and the absence of CD5, CD10, and CD23, and molecularly, by the presence of immunoglobulin or Bcl-2 gene rearrangements [(7)].

Mucosa-associated lymphoid tissue lymphomas usually follow a relatively indolent course and remain localized within their original environment for a long period of time. Involvement of multiple mucosal sites or disseminated disease may also occur, more commonly in nongastrointestinal MALT lymphomas [(8)].

Various treatment modalities are available for the management of patients with OAML, including surgical resection, radiotherapy, single-agent or combination

chemotherapy, and immunotherapy with monoclonal antibodies. Recently, antichlamydial antibiotic therapy was also proposed as a novel treatment option [4].

All therapeutic strategies are associated with unique short- and long-term efficacy and toxicities, which need to be carefully weighed. The final treatment decision requires a multidisciplinary approach, taking into account the extent of the disease, the impact of the lymphoma on the eye and visual function, and finally patient and disease-related prognostic factors [4].

Definition

Mucosa-associated lymphoid tissue lymphoma is now incorporated into the Revised European–American Lymphoma (REAL) and the World Health Organization (WHO) classification systems as extranodal marginal zone B-cell lymphoma, MALT type. It is a distinct type of lymphoma with unique clinicopathologic features [7].

The term MALT lymphoma denotes a characteristic arrangement of lymphoid tissue found in certain mucosal surfaces, having distinct features from other forms of primary non-Hodgkin extranodal lymphoma [1].

Extranodal marginal zone B cell lymphoma of MALT type arises in a number of extra-nodal sites , most frequently in the stomach (60– 70%) but can also occur in various nongastric tissues, including the salivary glands, conjunctiva, orbit, larynx, lungs, breasts, kidneys, liver, prostate, skin, and intracranial dura [7].

In recent decades, the incidence of MALT-type OAL has increased rapidly, with annual rates reaching 6% [9].

Aetiology

Mucosa-associated lymphoid tissue lymphomas typically arise in tissues or organs that are normally devoid of any organized lymphoid tissue, such as the orbital region, indicating that lymphoma at these sites arises from MALT acquired as a result of a chronic antigenic stimulation by microbial pathogens or autoimmune disorder [(10)].

MALT lymphomas usually occur in the context of chronic inflammation related to infectious disease, such as Helicobacter pylori (Hp)-associated chronic gastritis or autoimmune disorders, such as Sjo'gren syndrome or Hashimoto thyroiditis [(11)].

A pathogenic link between some infectious agents and NHL, mostly marginal zone lymphoma of MALT type, has been reported [(12)].

After the discovery of the pathogenic association between Hp and gastric MALT lymphoma (GML), other microorganisms have been linked to low grade B-cell lymphomas including Chlamydia psittaci (Cp) and ocular adnexal MALT lymphomas (OAML) [(11)].

The role of infectious agents is inferred from the fact that OAML share clinicopathologic features with gastric

MALT lymphomas, for which the central etiological role of H. pylori has been firmly established. Both ocular adnexal MALT lymphomas and gastric MALT lymphomas are characterized by an indolent course, a large prevalence of marginal zone B-cell histologic type, and a varying degree of infiltrating reactive T-cells [(1)].

The aetiology of OAML is currently unclear, even though it is becoming more and more evident that infectious agents underlying chronic eye infection, as Chlamydia, herpes simplex and adenovirus may play a role in ocular lymphomagenesis [(10)].

Many studies have been performed on chromosomal aberrations of extranodal marginal zone lymphomas. However, only a few have been published so far on ocular adnexal marginal zone lymphomas (OAMZL) [(13)].

Various cytogenetic abnormalities have been observed in MALT lymphomas, such as t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), t(3;14)(p14.1;q32), and trisomy 3 and 18 [(14)] (see page 23).

The identification of the causative agent in these lymphoma entities have led to substantial progress in understanding the physiopathology of the disease and, most importantly, to new therapeutic strategies [(11)].