Diagnostic features of gastric extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue

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Abstract

Gastric extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue may be difficult to distinguish from florid gastritis and other small B-cell lymphomas. The following review details a practical summary of the morphologic features, immunohistochemical markers, and molecular tests that currently provide for an accurate diagnosis in daily practice.

Keywords gastric lymphoma; MALT lymphoma; marginal zone lymphoma

Introduction

The gastrointestinal tract is the most common location of extranodal lymphomas and the stomach is the most frequent site of involvement. Of the small B-cell lymphomas, extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALTOMAs) are the most common, indicating that familiarity with these lesions is essential for practicing pathologists. *Helicobacter pylori* infection has been well established as a causative factor and is associated with the vast majority of cases.

The aim of this review is to provide a practical summary of the histological, immunohistochemical, and molecular features of gastric MALTOMA which best aid pathologists in making the diagnosis. In order to underscore the interpretive dilemma gastric MALTOMA can sometimes present, we will begin with a brief history of its contentious diagnostic evolution.

A brief history of gastric MALTOMA

In 1958, the term *gastric pseudolymphoma* was coined to describe a series of lesions that were originally called lymphoma but, upon review, were determined to represent benign lymphoid proliferations as they were characterized by reactive follicles with associated mixed inflammatory infiltrates and overall good patient survival.[1,2] Twenty five years later, Isaacson and Write published a seminal paper with the first detailed descriptions of gastric MALTOMA and strongly called into question the use of the term pseudolymphoma.[3] With this in mind, Abbondanzo and Sobin of the Armed Forces Institute of Pathology followed up with a reappraisal of 97 so-called gastric pseudolymphomas.[4] They hypothesized that some were likely MALTOMAs of the type described by Isaacson and Wright.[3] The authors ultimately reclassified a majority of the pseudolymphomas as MALTOMAS based on updated morphological and immunohistochemical criteria. Not surprisingly, they concluded that the term gastric pseudolymphoma should be abandoned.[4]

The history behind the diagnostic evolution of gastric MALTOMA serves to highlight the complexity of making the diagnosis on pure morphologic grounds. Thus, it should be no surprise that incorporation of ancillary testing has become essential in diagnosing these lesions. That being said, all MALTOMA diagnoses begin with careful evaluation of characteristic histologic features.

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Histologic features

There are two situations which commonly arise when considering a morphologic diagnosis of gastric lymphoma. The first is distinguishing lymphoma from benign in the presence of an exuberant inflammatory infiltrate and the second is classifying the lesion once the decision has been made that one is in fact dealing with a lymphoma. We will begin by discussing the former.

Architectural evaluation

The most salient feature of gastric MALTOMA is a dense expansive lymphoid infiltrate seen at low power causing disruption and architectural distortion of the gastric mucosa (Figure 1). A gastric biopsy harboring a lymphoplasmacytic infiltrate that does not alter the glandular architecture by infiltrating through, pushing aside, replacing, and/or destroying glands is not a gastric MALTOMA.

At the time of diagnosis, most MALTOMAs involve the superficial layers of the gastric wall. They infiltrate through the mucosa and superficial submucosa, pushing apart the glands and lifting them off the muscularis mucosa, which is usually also disrupted by the infiltrate. One can occasionally see the remains of the background chronic gastritis in which the lymphoma arose. Sometimes this is evident in other biopsy fragments. In other cases the chronic, often plasma cell-rich, inflammation may overlie the lymphoma. Active inflammation is usually minimal unless there is an associated ulcer.

Confusion arises in cases of severe chronic active gastritis which can certainly appear destructive at low power and thus mimic a lymphoma (Figure 2). These are recognized as inflammatory processes by their abundant accompanying acute inflammation and polymorphous mix of mononuclear cells. The glandular destruction is usually a result of the active inflammation which is readily apparent as neutrophilic infiltrates among glandular epithelium.

The presence of secondary lymphoid follicles pushing aside gastric glands may also cause diagnostic confusion. Gastric MALTOMAs simulate mucosa associated lymphoid tissue (MALT) found elsewhere in the gastrointestinal tract, exemplified in the Peyer patches of the terminal ileum. The lymphoid follicles of MALT are characterized by reactive germinal centers surrounded by a mantle zone and an outermost marginal zone. The marginal zone is usually not as well defined as the mantle zone and consists of small post follicular center B-cells that have a monocytoid appearance due to their more abundant and often clear cytoplasm. These monocytoid cells impart a paler look to

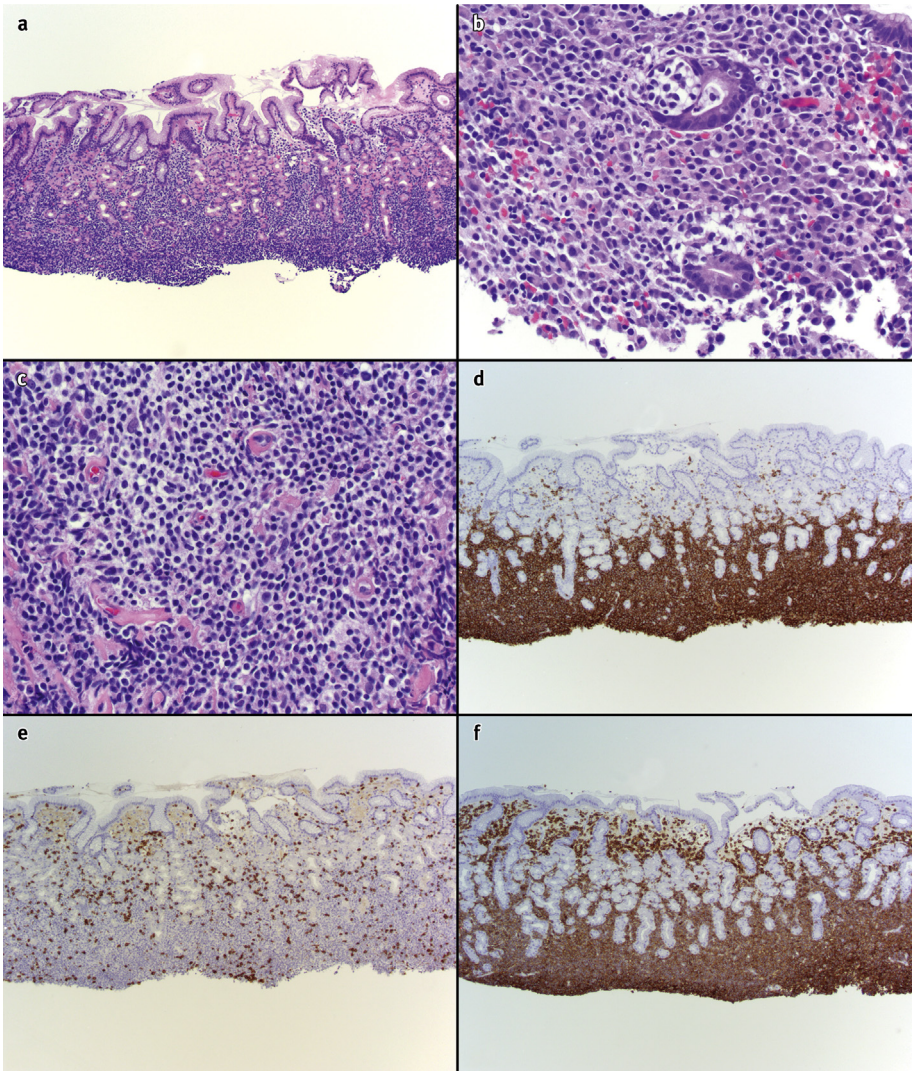

Figure 1 Gastric MALTOMA: low power (10×) assessment demonstrates a dense expansive lymphoid infiltrate that alters the mucosal architecture primarily by pushing aside and replacing the oxyntic glands (**a**). High power fields (40×) show areas of extreme plasmacytoid differentiation with lymphoepithelial lesions (**b**) in addition to sheets of monocytoid cells with abundant clear cytoplasm (**c**). Notice, however, that in each high power field we do not see a polymorphous mix of mononuclear and other inflammatory cells. Immunohistochemical stains (all 10×) for CD20 (**d**), CD3 (**e**), and CD43 (**f**) highlight an expansive population of CD20 positive B-cells with aberrant CD43 expression.

the marginal zone when compared to the inner mantle zone. The challenge to the pathologist is to determine whether these secondary follicles are a component of MALTOMA versus an inflammatory process. In gastric MALTOMA, the neoplastic marginal zone lymphocytes spread outwards to form diffuse interfollicular sheets. These interfollicular zones would usually be occupied by polymorphous T-cells in reactive states, so sheets of interfollicular monomorphous B-cells should always raise suspicion for lymphoma.

The neoplastic marginal zone lymphocytes also spread inwards and encroach upon the germinal centers; a process frequently termed "follicular colonization" (Figure 3). The germinal centers may eventually become atrophic and be concealed by the infiltrating marginal zone cells, imparting a nodular look to the lymphoma. Cryptic germinal centers may be difficult to see on H&E stained slides but CD21, CD23, or CD35 immunohistochemical markers can be used to highlight residual follicular dendritic cells and thus facilitate their identification, though from a diagnostic standpoint this is usually not necessary.

Cytologic evaluation

In most cases, the high power cytologic features of MALTOMA serve primarily to confirm one's initial low power suspicion of malignancy. At high power, MALTOMAs demonstrate a population of only slightly atypical small lymphocytes with round to irregular nuclear contours. The neoplastic cells may have a monocytoid appearance (Figure 1) as described above, resemble small cleaved centrocytes, or show plasmacytoid differentiation (Figure 1). There may be considerable heterogeneity in the tumor cell populations between cases and also within a given case. Scattered single large cells resembling centroblasts or immunoblasts are sometimes present (Figure 4) but do not constitute a high proportion of the infiltrate and, unless present in diffuse sheets, do not indicate large cell transformation. In fact, if high