

Marginal zone B-cell lymphoma of  
mucosa-associated lymphoid  
tissue (MALT lymphoma)

# WHO MALT lymphoma

- Definition: extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is an extranodal lymphoma comprising morphologically heterogeneous small B-cells including marginal zone (centrocyte-like) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblasts and centroblast-like cells.

# WHO MALT lymphoma

- There is plasma cell differentiation in a proportion of the cases.
- The infiltrate is in the marginal zone of reactive B-cell follicles and extends into the interfollicular region.
- In epithelial tissues, the neoplastic cells typically infiltrate the epithelium, forming lymphoepithelial lesions.

# WHO MALT lymphoma

## ■ Synonyms:

- Rappaport: well-differentiated lymphocytic, plasmacytoid lymphocytic, poorly-differentiated lymphocytic.
- Kiel: immunocytoma.
- Lukes-Collins: lymphocytic, plasmacytic-lymphocytic, small cleaved cell.

# WHO MALT lymphoma

- Epidemiology: MALT lymphoma comprises 7-8% of all B-cell lymphomas and up to 50% of primary gastric lymphoma.
- Most cases occur in adults with a median age of 61 and a slight female preponderance (M:F ratio 1:1.2).

# WHO MALT lymphoma

- There appears to be a higher incidence of gastric MALT lymphomas in north-east Italy
- A special subtype previously known as  $\alpha$  chain disease and now called immunoproliferative small intestinal disease (IPSID) occurs in the Middle East and the Cape region of South Africa.

# Precursor lesions/conditions

- In many cases of MALT lymphoma, there is a history of chronic inflammatory, often autoimmune disorders that result in accumulation of extranodal lymphoid tissue. Examples: *H. pylori* associated chronic gastritis, Sjögren syndrome or Hashimoto thyroiditis.

# Precursor lesions/conditions

- In the first study in which the association of gastric MALT lymphoma with *H. pylori* infection was examined the organism was present in over 90% of cases.
- Subsequent studies have shown a lower incidence but also that the density and detectability of *H. pylori* decreases as lymphoma evolves from chronic gastritis.



# Precursor lesions/conditions

- The organism may be undetectable using histopathological techniques in patients who are seropositive.
- Patients with certain autoimmune diseases (Sjögren Sd., Hashimoto thyroiditis) are at increased risk of developing MALT lymphoma.

# Precursor lesions/conditions

- Pats. with Sjögren syndrome (SS) or lymphoepithelial sialadenitis (LESA) have a 44-fold increased risk of developing overt lymphoma, comprising about 4-7% of pats.
- Aprox. 85% of lymphomas in pats. with SS/LESA are MALT lymphomas.

# Precursor lesions/conditions

- Pats. with Hashimoto thyroiditis have a 3-fold excess risk of developing lymphoma and a 70-fold increased risk of thyroid lymphoma, for an overall lymphoma risk of 0.5-1.5% of the pats. 94% of thyroid lymphomas have evidence of thyroiditis in the adjacent gland.
- Chronic intestinal infections are postulated to be an underlying cause of IPSID.

# Sites of involvement

- The gastrointestinal (GI) tract is the most common site of MALT lymphoma, comprising 50% of all cases, and within the GI tract, the stomach is the most common location (85%). The small intestine and colon are typically involved in pts. with IPSID.

# Sites of involvement

- Other common sites include lung (14%), head & neck (14%), ocular adnexae (12%), skin (11%), thyroid (4%), and breast (4%).

# Clinical features

- The majority of pts present with stage I or II disease.
- Aprox. 20% of pts have bone marrow involvement, but the frequency seems to vary among primary sites, being lower for gastric cases and higher for primary ocular adnexal or pulmonary cases.

# Clinical features

- Multiple extranodal sites may be involved in up to 10% of the cases at the time of presentation.
- Multifocal nodal involvement is rare (7.5% of the cases in a recent series).
- Application of staging systems for nodal lymphomas can be misleading in MALT type lymphomas, since involvement of multiple extranodal sites, particularly within the same organ (e.g. salivary gland, skin), may not reflect truly disseminated disease.

# Clinical features

- Despite plasmacytic differentiation in many of the cases, a serum paraprotein (M-component) is rare in MALT lymphomas. The major exception is IPSID, in which an aberrant alpha heavy chain can usually be found in the peripheral blood.



# Aetiology

- Continued proliferation of gastric MALT lymphoma cells from pts. infected with *H. pylori* depends on the presence of T cells specifically activated by *H. pylori* antigens. The importance of this stimulation in vivo has been clearly demonstrated by the induction of remissions in gastric MALT lymphomas with antibiotic therapy.

# Aetiology

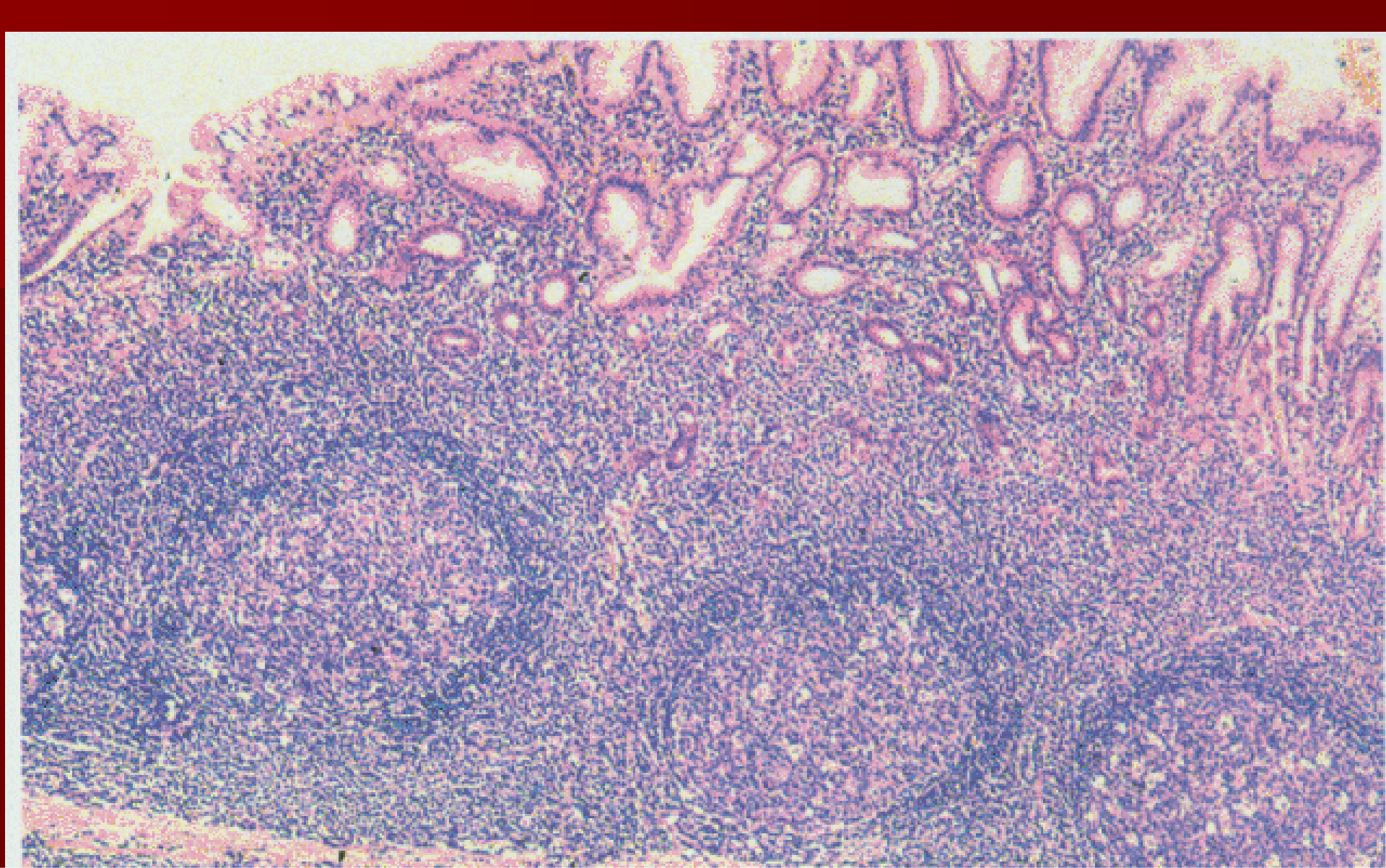
- A role for antigenic stimulation by *Borrelia burgdorferi* has been proposed for some cases of cutaneous MALT lymphoma.
- It has been suggested that “acquired MALT” secondary to autoimmune disease or infection in these sites may form the substrate for lymphoma development.

# Morphology

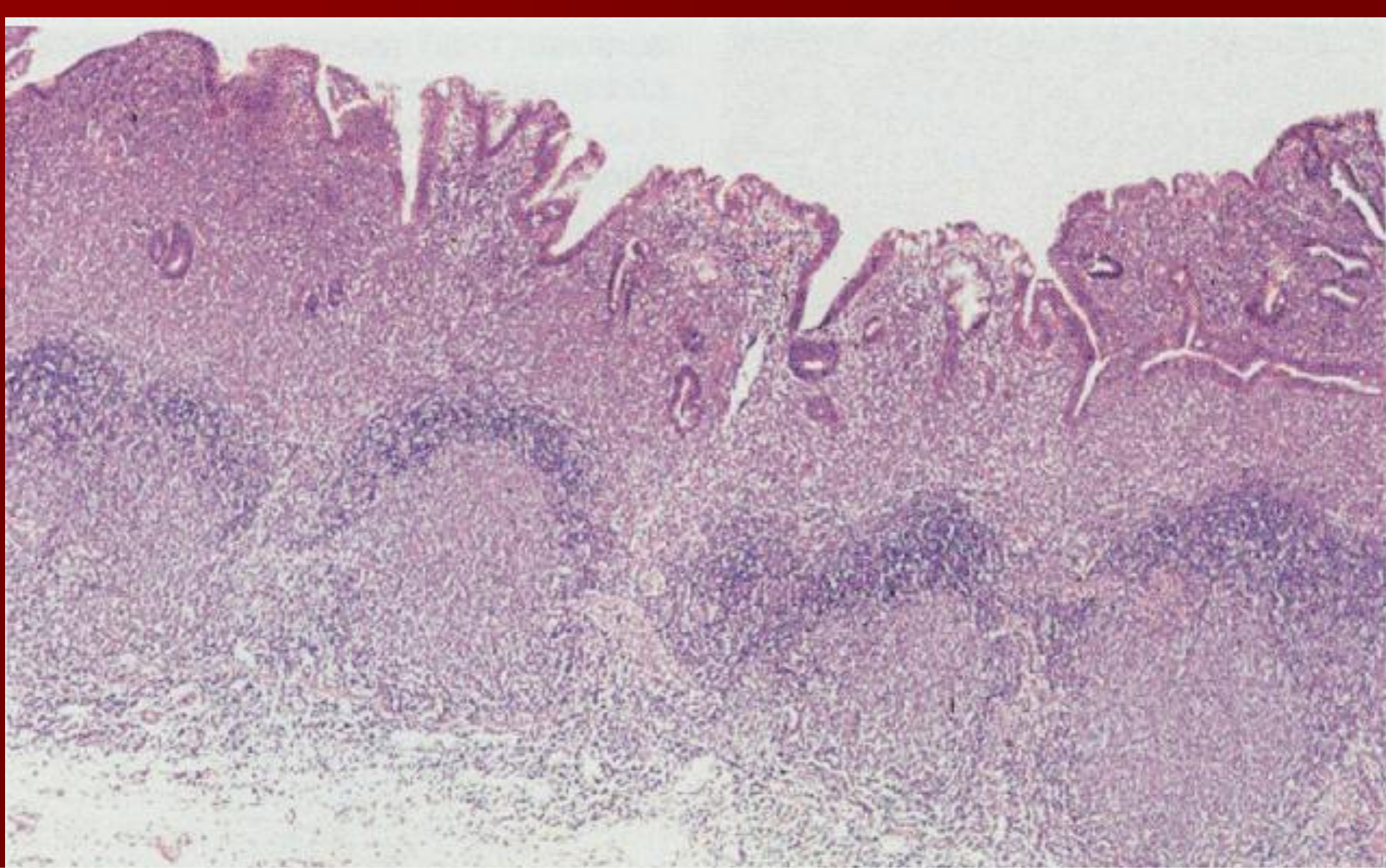
- The lymphoma cells infiltrate around reactive B-cell follicles, external to a preserved follicle mantle, in a marginal zone distribution and spread out to form larger confluent areas which eventually overrun some or most of the follicles.

# MALT Lymphoma Stomach



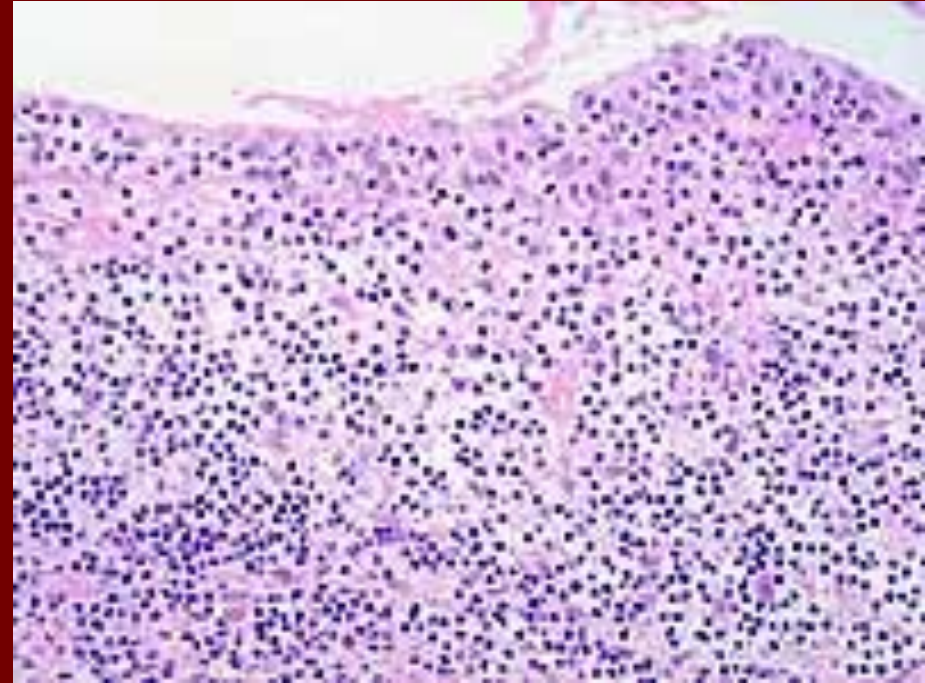
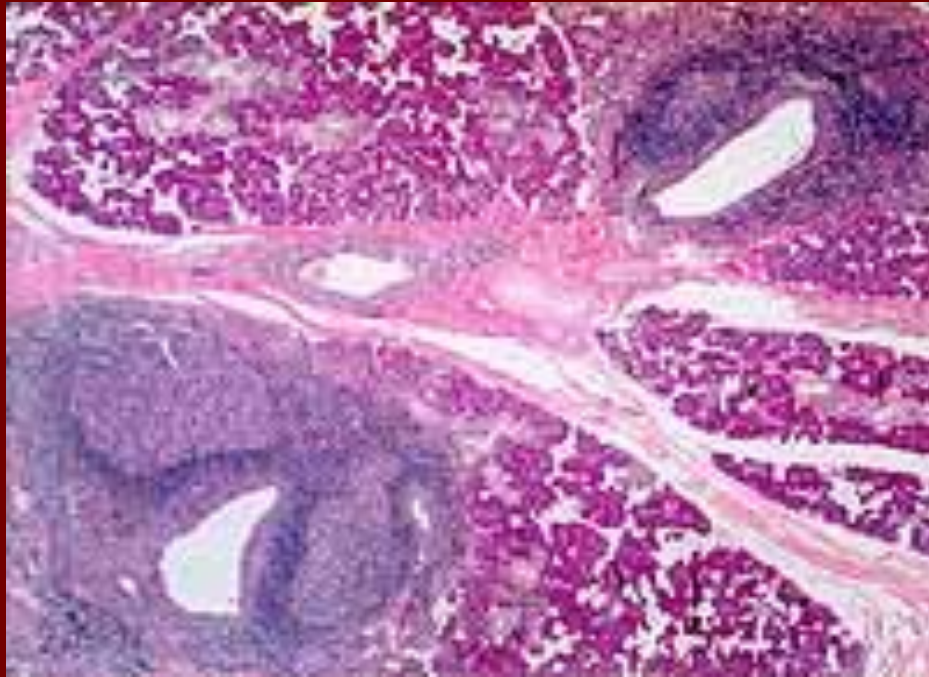


**Gastric MALT lymphoma, tumor cells surround reactive follicles**



**Gastric MALT lymphoma, tumor cells colonize the follicles**

# MALT Lymphoma-Parotid



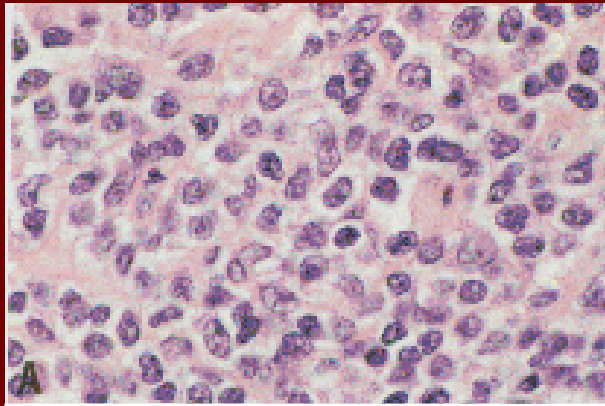
# Morphology

- The characteristic marginal zone B-cells have small to medium-sized, slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nucleoli, resembling those of centrocytes; they have relatively abundant, pale cytoplasm. The accumulation of more pale-staining cytoplasm may lead to a monocytoid appearance.

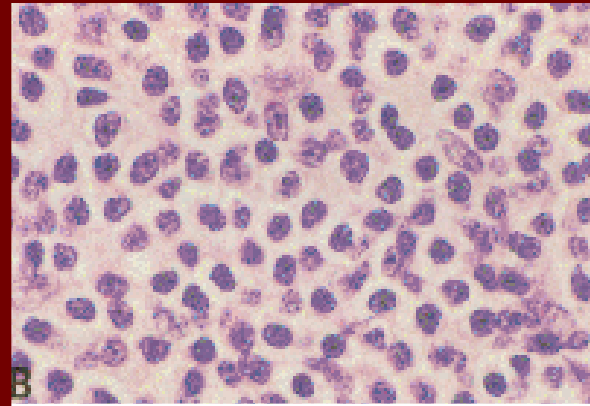


# Morphology

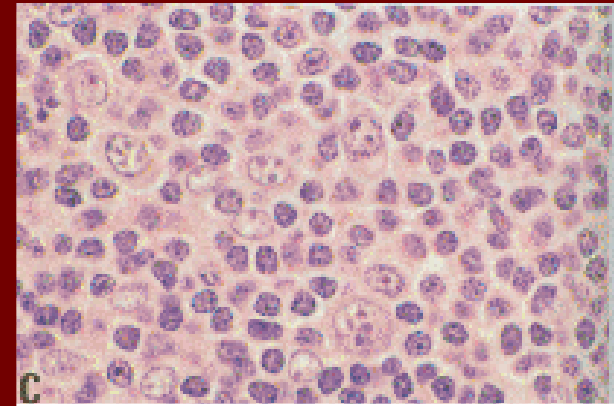
- Alternatively, the marginal zone cells may more closely resemble small lymphocytes.
- Plasmacytic differentiation is present in about 1/3 of gastric MALT-type lymphomas and is a constant and often a striking feature in thyroid MALT-type lymphomas and in IPSID.



Centrocytes



Monocytoid lymphocytes



Small lymphocytes with scattered centroblasts

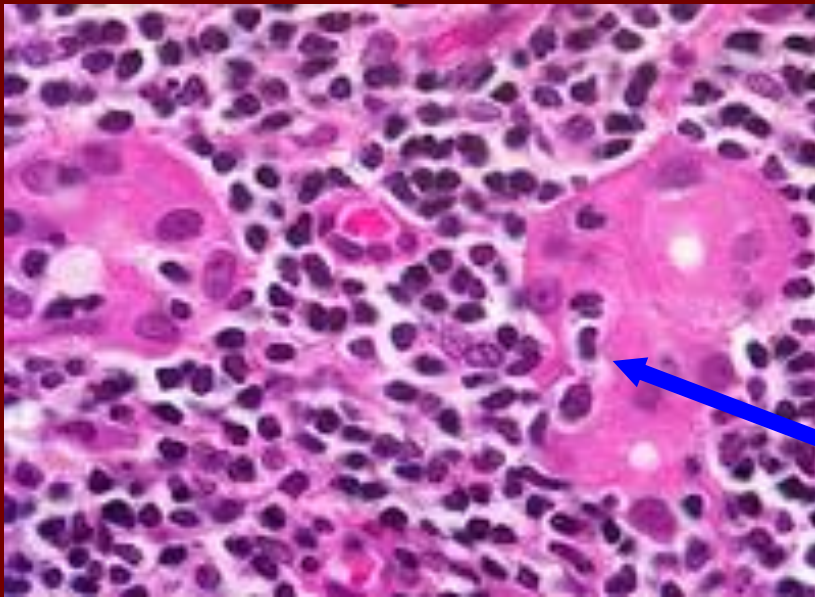
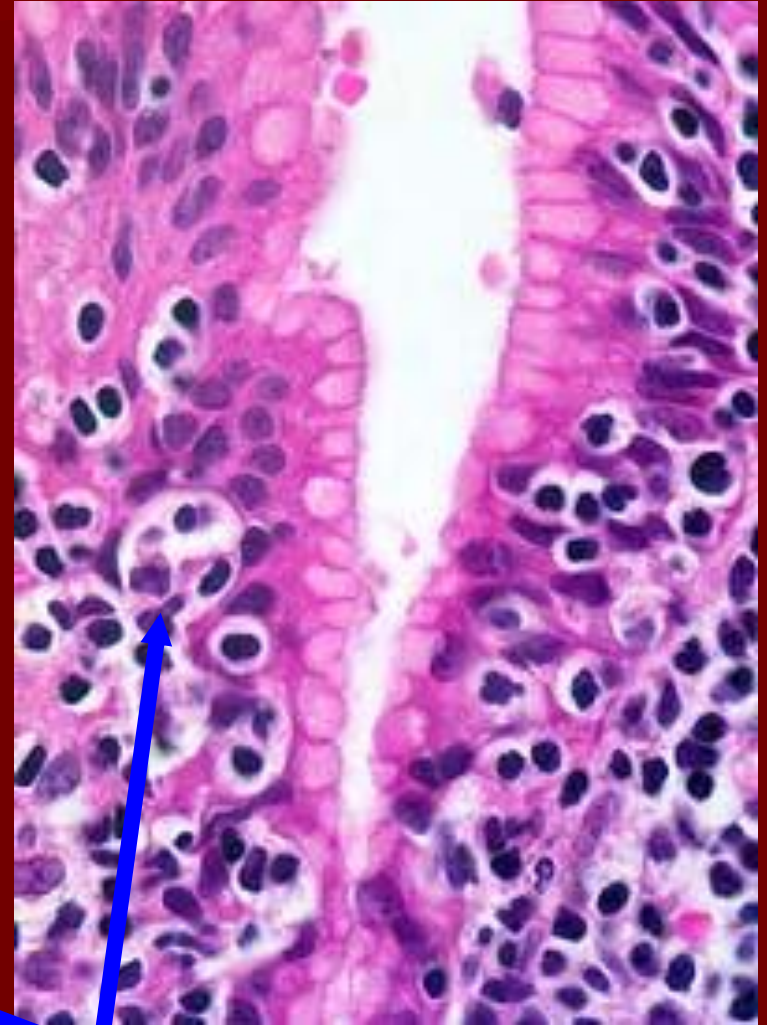
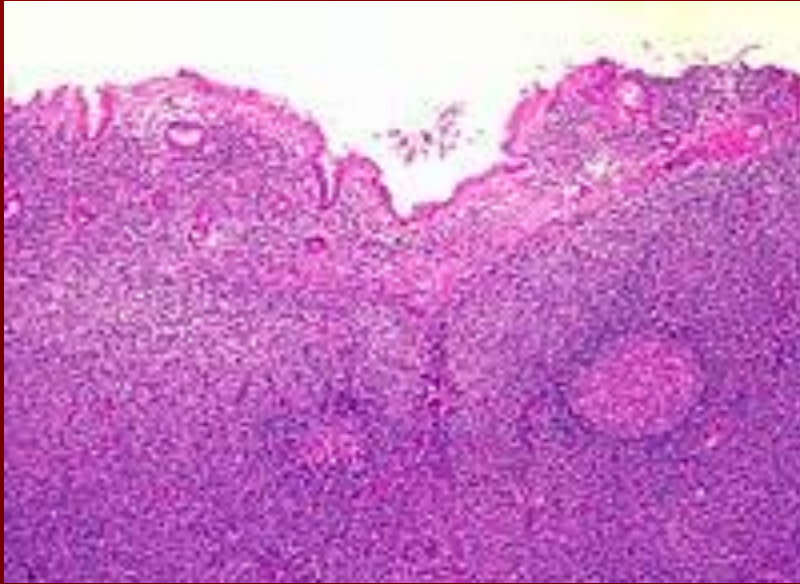
# Morphology

- Large cells resembling centroblasts or immunoblasts are usually present, but are in the minority.
- In glandular tissues epithelium is often invaded and discrete aggregates of lymphoma cells resulting in the so-called lymphoepithelial lesions.

# Morphology

- Lymphoepithelial lesions are aggregates of three or more marginal zone cells with distortion or destruction of the epithelium, often together with eosinophilic degeneration of epithelial cells.
- The lymphoma cells sometimes specifically colonise the germinal centres of the reactive follicles and in extreme examples, this can lead to a close resemblance to follicular lymphoma.

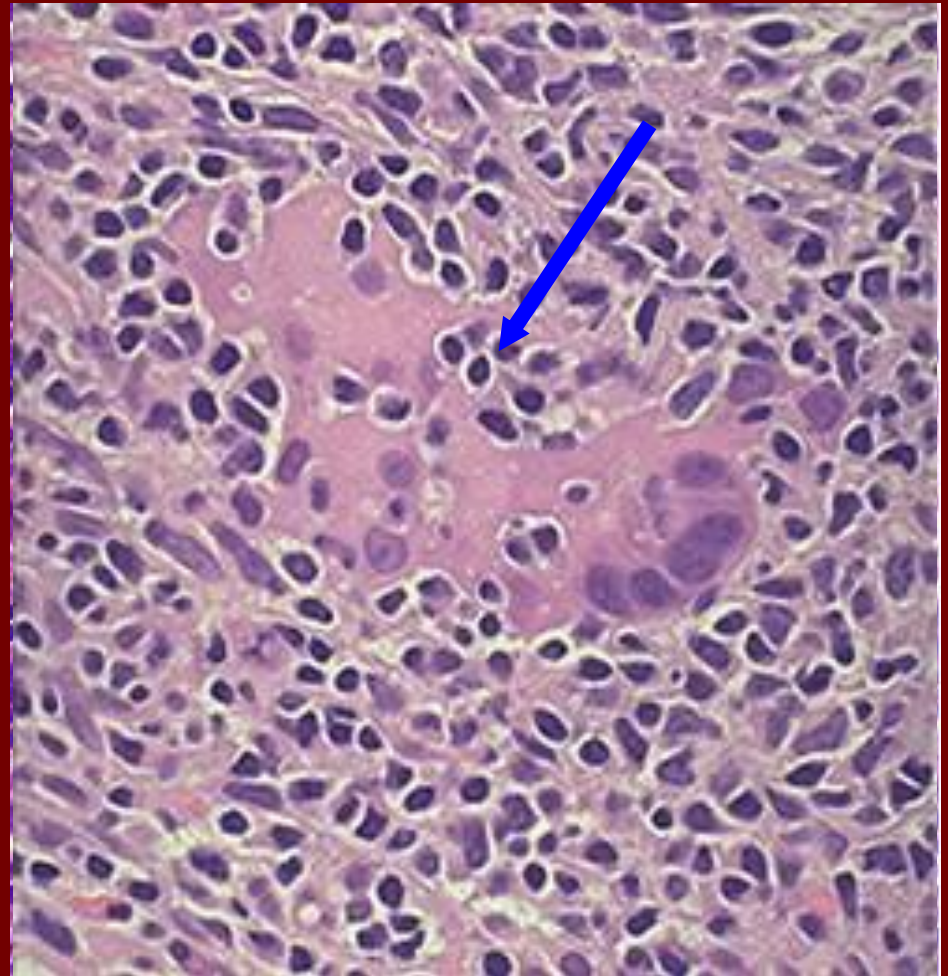
# MALT Lymphoma-Stomach



Lymphoepithelial lesions

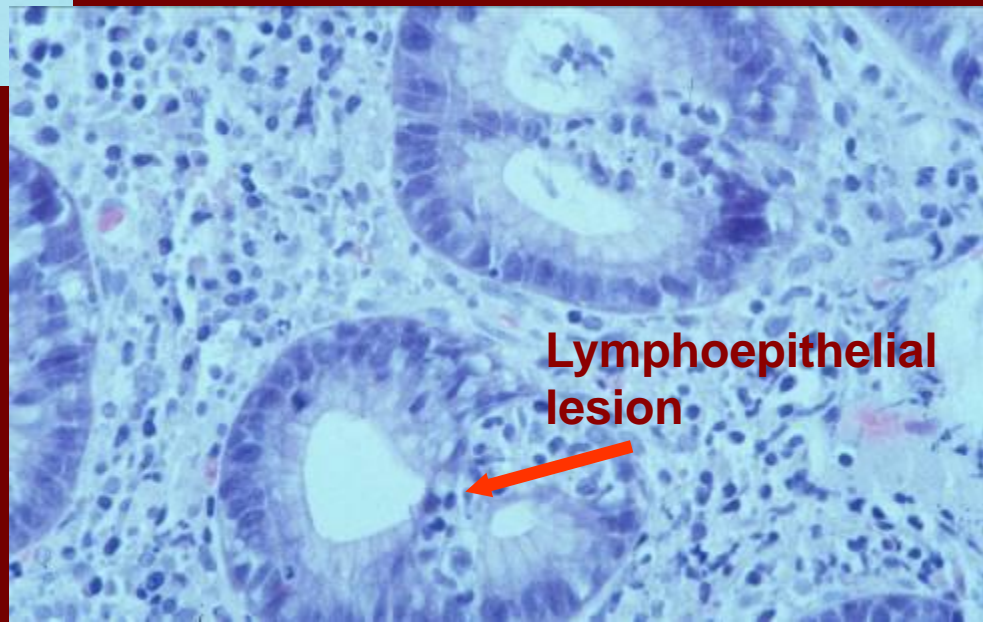
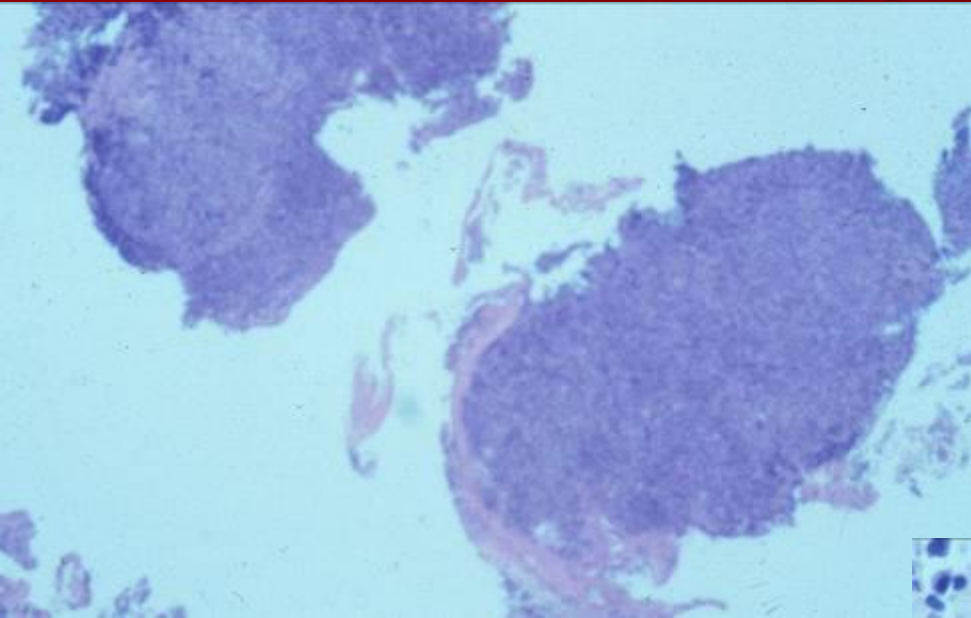
# Microscopic findings

- Lymphoepithelial lesions:
  - $\geq 3$  marginal zone lymphocytes with distortion or destruction of epithelium



# MALT Lymphoma

## Stomach



Lymphoepithelial  
lesion

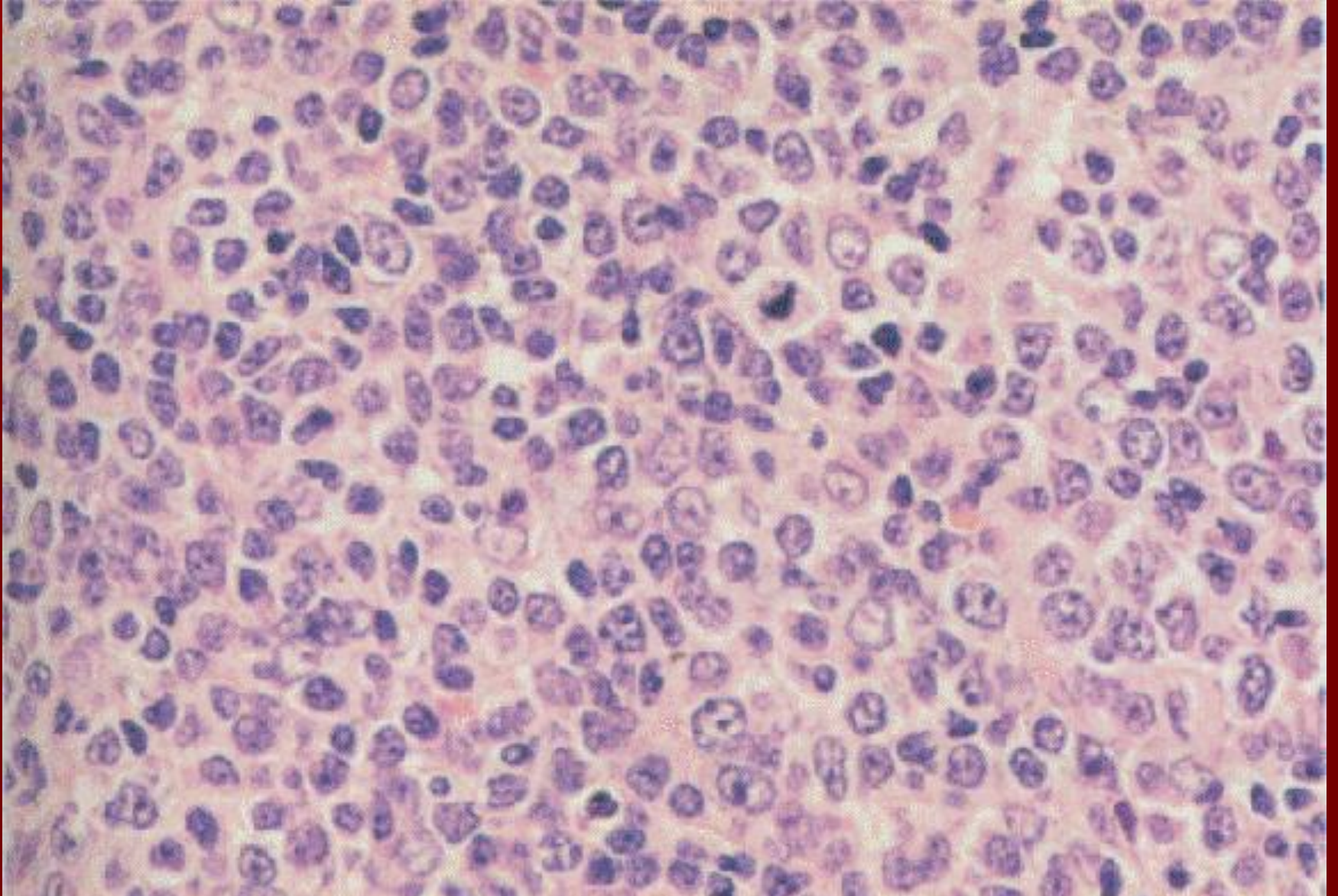
# Morphology

- MALT lymphoma is defined as a lymphoma composed predominantly of small cells. Transformed centroblast- or immunoblast-like cells may be present in variable numbers in MALT lymphoma but when solid or sheet-like proliferations of transformed cells are present the tumour should be diagnosed as diffuse large B-cell lymphoma and the presence of accompanying MALT lymphoma noted.



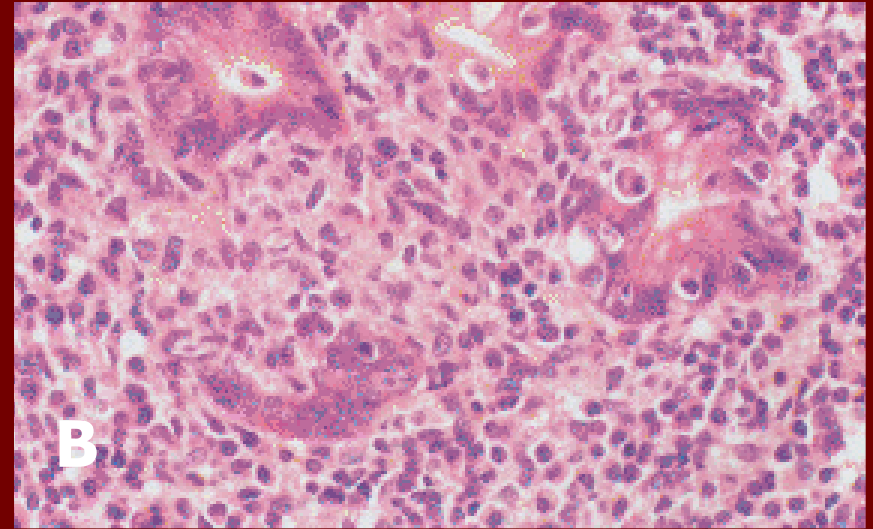
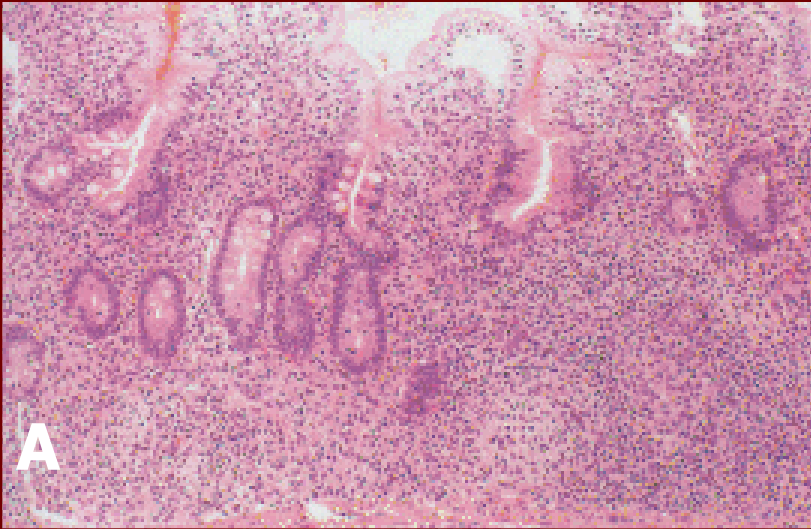
# Morphology

- The term “high-grade MALT lymphoma” should not be used, and the term “MALT lymphoma” should not be applied to a large B-cell lymphoma even if it has arisen in a MALT site.
- The histological features of IPSID are similar to those of other cases of MALT lymphoma, but typically show striking plasmacytic differentiation.



MALT lymphoma with increase in large cells

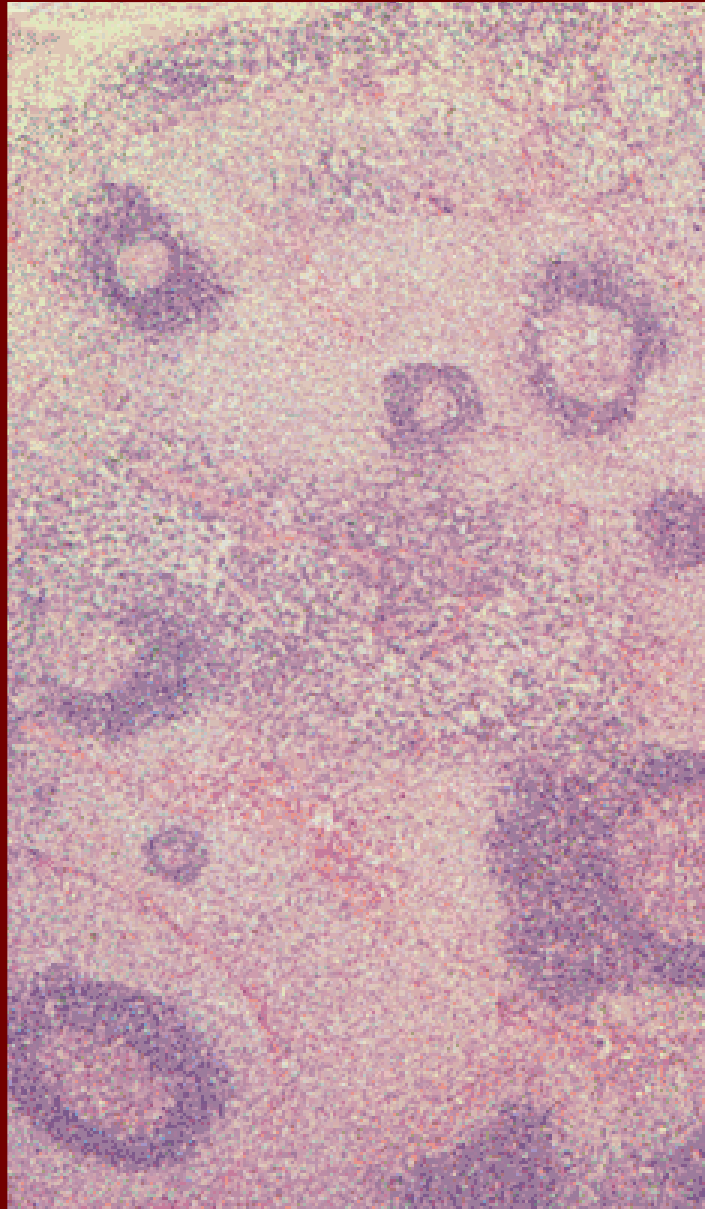
# IPSID



- A. Clusters of marginal zone lymphoma cells surround the follicles.  
The lamina propria is infiltrated by plasma cells
- B. Marginal zone lymphoma cells and plasma cells surround intestinal crypts with LELs

# Morphology

- In lymph nodes, MALT lymphoma invades the marginal zone with subsequent interfollicular expansion.
- Discrete aggregates of monocytoid B cells may be present in a parafollicular and perisinusoidal distribution.
- Cytological heterogeneity is still present and both plasma cell differentiation and follicular colonisation may be seen.

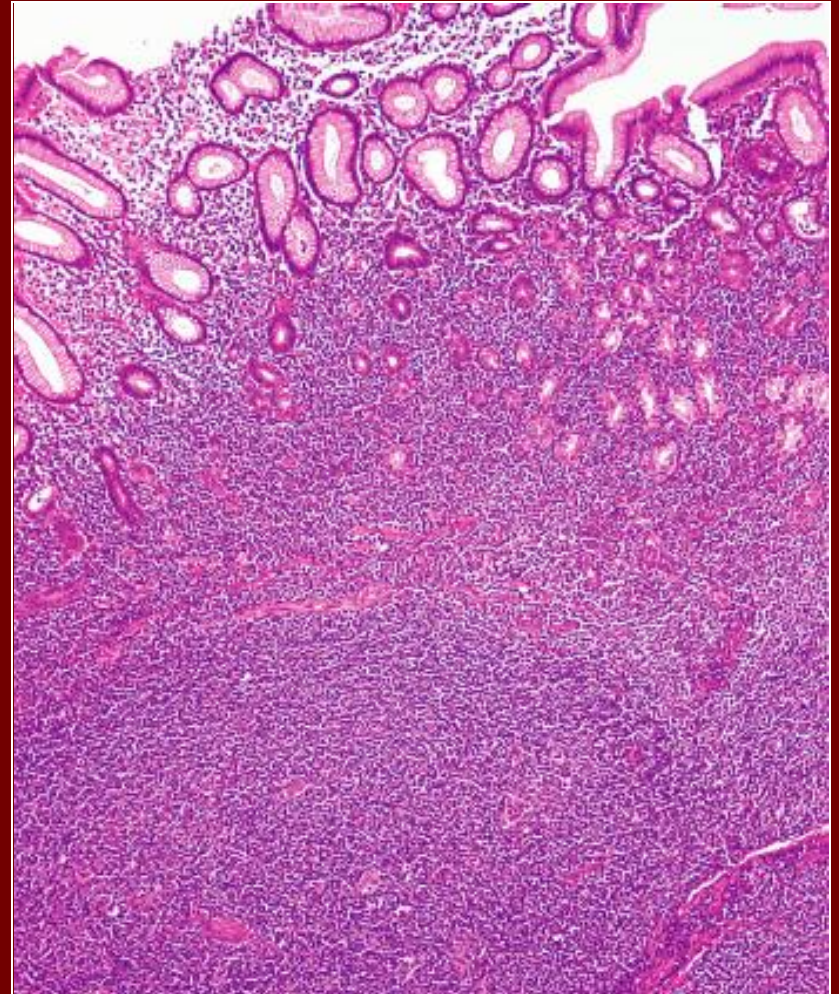
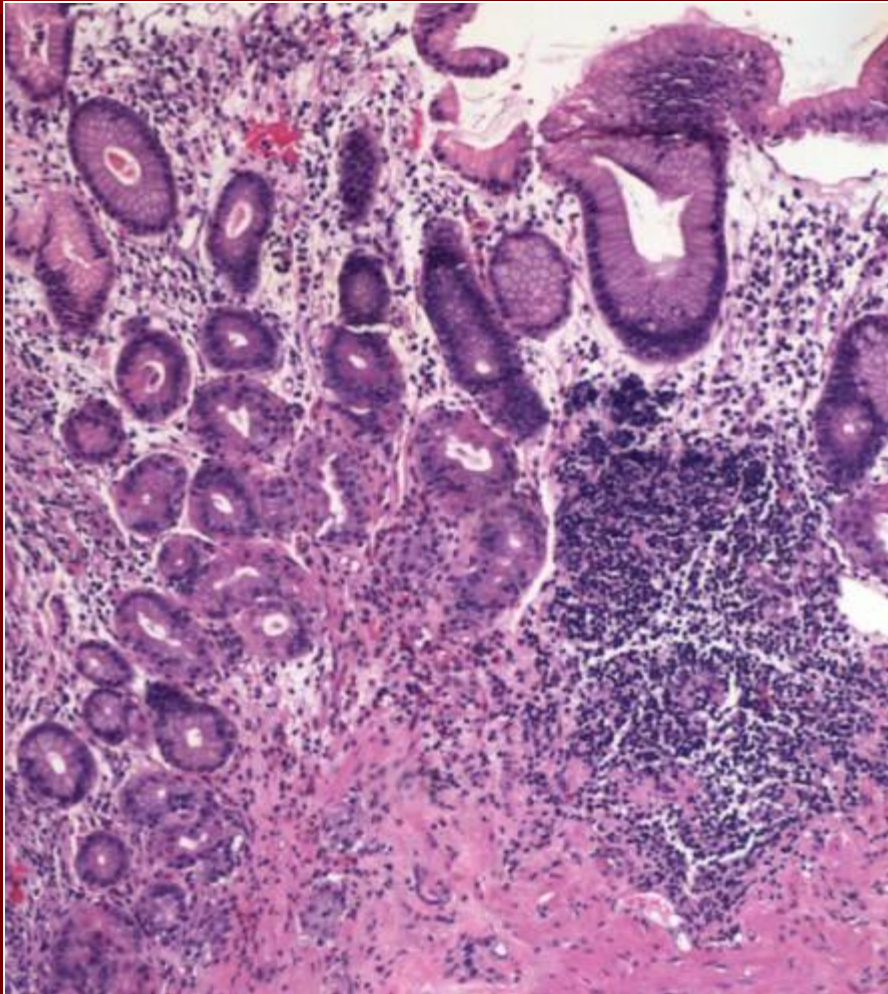


Gastric lymph node with MALT lymphoma

# Differential diagnosis

- Includes reactive processes (H.pylori gastritis, lymphoepithelial sialadenitis, Hashimoto thyroiditis), and other small B-cell lymphomas (follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma).
- Distinction from reactive processes is based mainly on the presence of destructive infiltrates of extrafollicular B cells, typically with the morphology of marginal zone cells.

# Gastritis vs MALT lymphoma



# Differential diagnosis

- In borderline cases, immunophenotyping or molecular genetic analysis to assess B-cell clonality are necessary to establish or exclude a diagnosis of MALT lymphoma.
- Distinction from other small B-cell lymphomas is based on a combination of the characteristic morphologic and immunophenotypic features.



# Immunophenotype

- Tumour cells typically express IgM, and less often IgA or IgG, and show light chain restriction.
- In IPSID, both the plasma cells and marginal zone cells express alpha heavy chain without any light chain

# Immunophenotype

- The tumour cells are CD20+, CD79a+, CD5-, CD10-, CD23-, CD43+/-, CD11c+/- (weak).
- The cells express the marginal zone cell-associated antigens CD21 and CD35. Staining for these antigens typically reveals expanded meshworks of FDCs corresponding to colonised follicles.

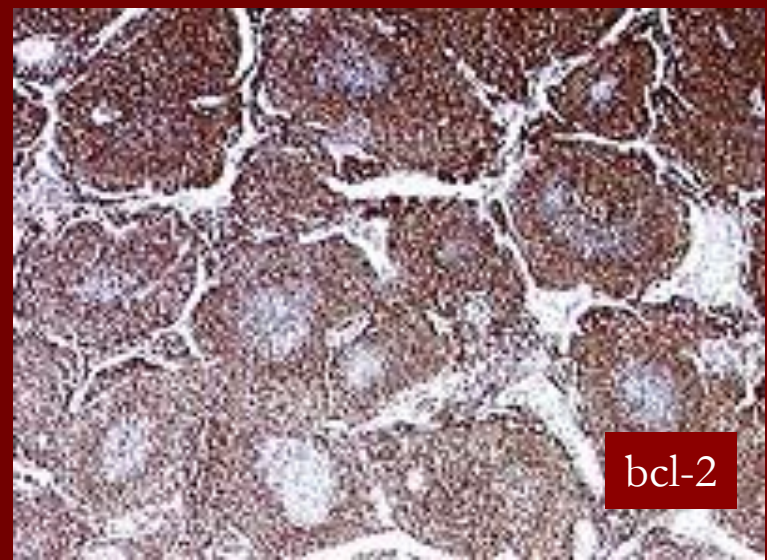
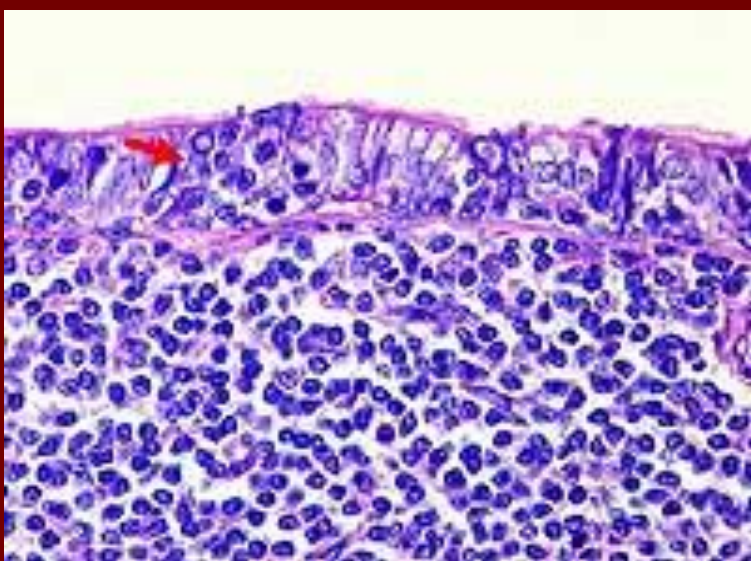
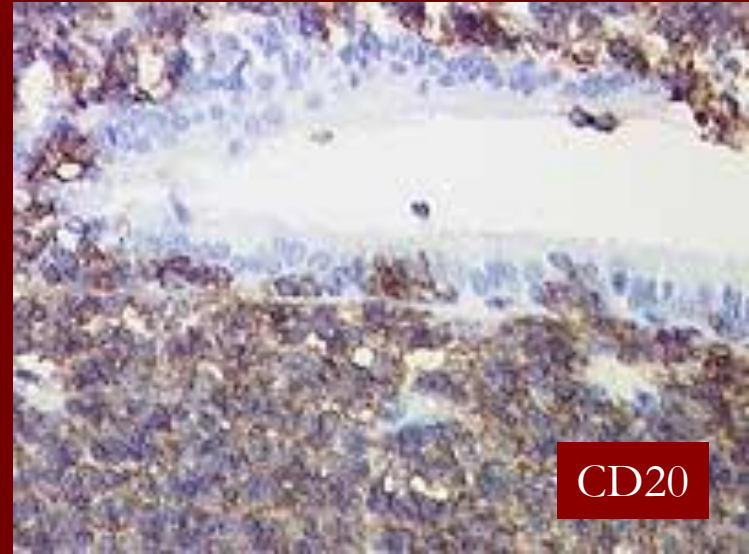
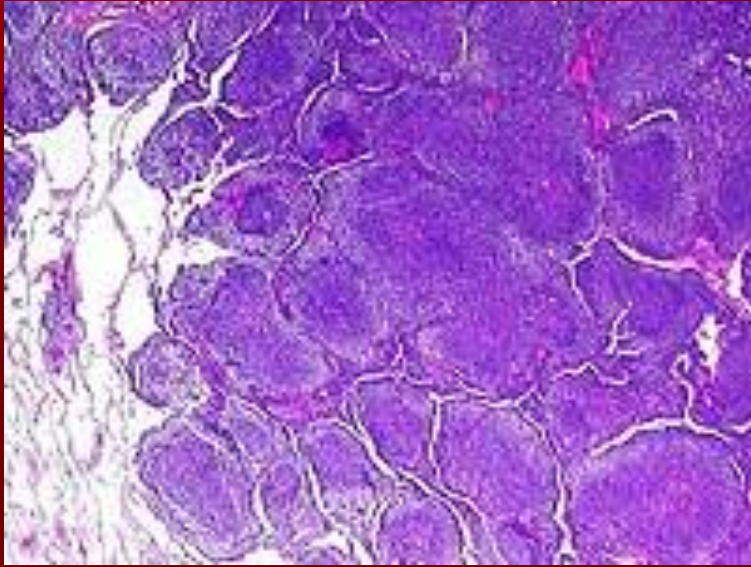
# Immunophenotype

- There is no specific marker for MALT lymphoma at present.
- The demonstration of Ig light chain restriction is important in the differential diagnosis with benign lymphoid infiltrates.

# Immunophenotype

- In the differential Dx with other small B-cell lymphomas, absence of the characteristic markers for those neoplasms is important:
  - Lack of CD5 is useful in distinction from mantle cell and small lymphocytic lymphoma,
  - Lack of CD10 is useful in distinction from FL.

# MALT Lymphoma-Lung



# Genetics

- Antigen receptor genes:
  - Ig heavy and light chain genes are rearranged and show somatic mutation of variable regions, consistent with derivation of post-germinal centre, memory B cell.

# Genetics

- Genetic abnormalities and oncogenes:
  - Trisomy 3 is found in 60% and  $t(11;18)(q21;q21)$  has been observed in 25-50% of the cases.
  - In contrast,  $t(11;18)$  is not found in primary large B cell gastric lymphoma. Recently, analysis of the  $t(11;18)$  breakpoint has shown fusion of the apoptosis-inhibitor gene API2 to a novel gene at 18q21, named MLT.
  - Neither  $t(14;18)$  nor  $t(11;14)$  is present.

# Postulated cell of origin

- Post germinal centre, marginal zone B-cell.



# Prognosis and predictive factors

- MALT lymphomas run an indolent natural course and are slow to disseminate.
- Recurrences may involve other extranodal sites.
- The tumours are sensitive to radiation therapy, and local treatment may be followed by prolonged disease-free intervals.

# Prognosis and predictive factors

- Involvement of multiple extranodal sites and even bone marrow involvement do not appear to confer a worse prognosis.
- In H.pylori-associated gastric MALT lymphoma, protracted remissions may be induced by antibiotic therapy for H. pylori.
- Cases with the t(11;18)(q21;q21) appear to be resistant to H.pylori eradication therapy.

# Prognosis and predictive factors

- In IPSID, remissions have followed therapy with broad spectrum antibiotics.
- Transformation to diffuse large B-cell lymphoma may occur.

# MALT Lymphoma-Stomach Transformation to Large B-Cell Lymphoma

