Epidemiology and Environmental aspects of Marginal Zone Lymphomas

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Disclosures

- Advisory Boards and Honoraria
  - Roche
  - Janssen/Pharmacyclics
  - Gilead
  - Abbvie
  - Sanofi/genzyme
  - Medimmune
  - Infinity

MZL

- Group of rare lymphomas arising from memory B cells which normally reside in the 'marginal zone' of secondary lymphoid follicles
- MZL cells usually located in spleen and mucosa-associated lymphoid tissues
- Significant aetiological, clinical and pathological heterogeneity
- 3 distinct sub-types based on site of involvement
  - Extranodal (MALT, GIT, thyroid, orbit, leptomeninges, skin)
  - Nodal
  - Splenic (with or without villous lymphocytes)

MZL: Incidence

- 5-17% of all NHL in adults
- MALT accounts for 50-70% MZL and 7-8% of NHL
  - Association with chronic antigen stimulation (infection, autoimmune disease)
  - Stomach is commonest extra-nodal site
  - Other sites include: ocular/adnexal, lung, skin, salivary glands
- Splenic MZL accounts for 20% of all MZL
- Nodal MZL least common (10%)

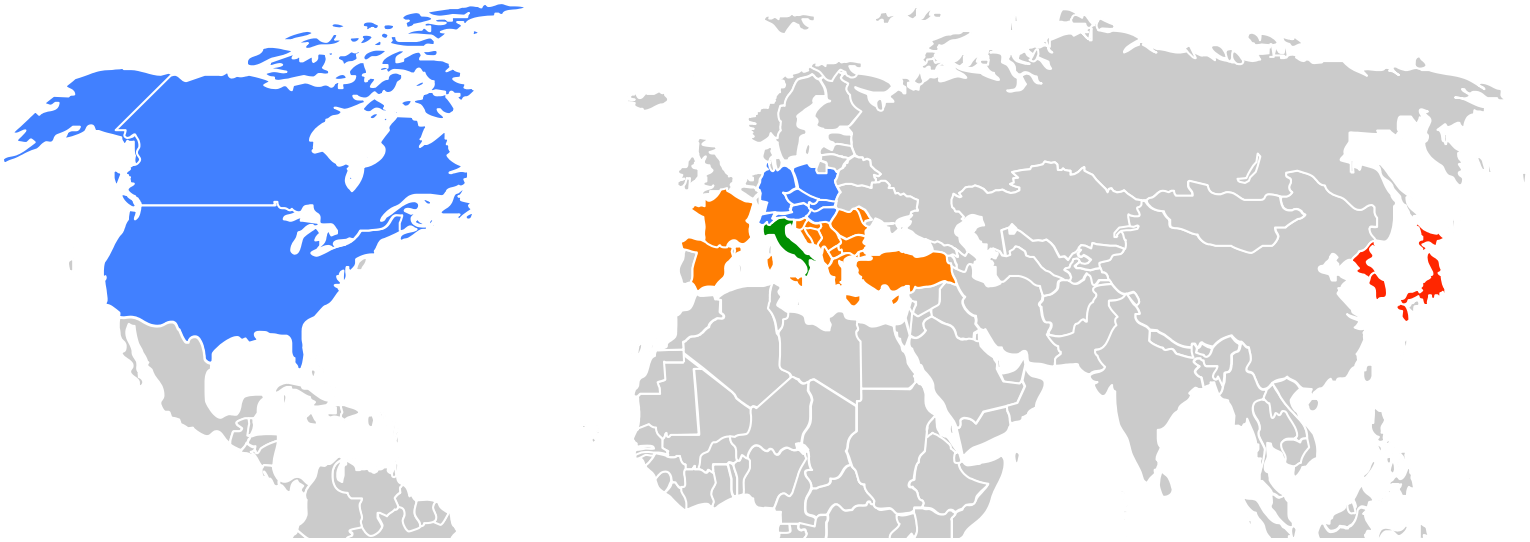
Extranodal MZL: Patient Demographics

- Overall M=F
- Differences in gender incidence by anatomical site eg gastric M>F, salivary glands F>M
- Median age 66 years
- Less favourable prognosis for GI and lung sites compared to ocular, skin and thyroid
- Older age adverse prognostic factor

MZL: Patient Demographics

Patient Characteristics	Extranodal MZL (Gastric)	Extranodal MZL (Other sites)	Splenic MZL	Nodal MZL
Median age (years)	66	66	65	69
Gender	M > F	Small intestine, skin, kidney: M>F Ocular/adnexal, lung, colon: M=F Salivary gland, thyroid: F>M	F > M	M > F
Incidence (per 1,000,000 person y)	3.8	0.9-1.4	1.6	5.7
Clinical features	• Asymptomatic • Gastritis • Gastric ulcers • Weight loss	• Small intestine: malabsorption, diarrhoea • Ocular/adnexal: orbital swelling, neurology • Skin: rash, pruritis	• Splenomegaly • Weight loss infection • Fatigue • Bleeding • **BM involvement**	• Inferior survival

Geographic Distribution of various MZL sub-types



- Gastric MALT highest incidence in Italy
- Ocular/adnexal MALT most frequently in Japan and Korea
- Skin - Northern Europe and USA and Canada
- Small intestine -Southern Europe and Middle East

Colour Key: Green = MALT lymphoma of stomach; Red = Ocular/Adnexal Lymphoma; Blue = Skin MZL; Orange = Small Intestine MZL. NB: MZL = Marginal Zone Lymphoma; MALT = Mucosa-Associated Lymphoid Tissue

MZL: Environmental Risk Factors

- Infections
- Autoimmune disease
- Smoking and Alcohol only moderate association
- No occupational risks identified

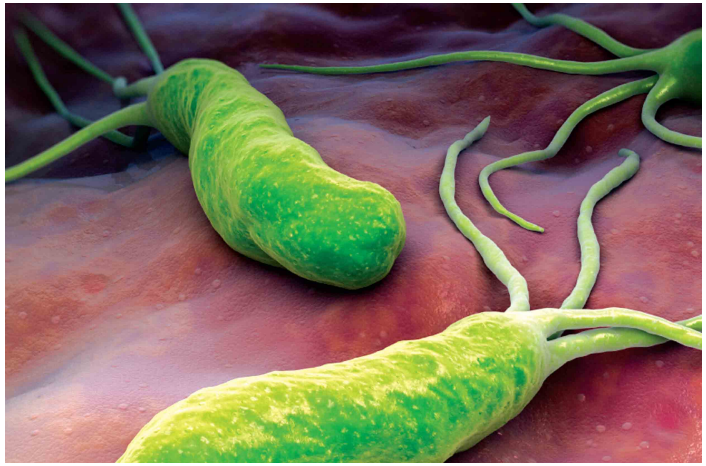
MZL: Infections

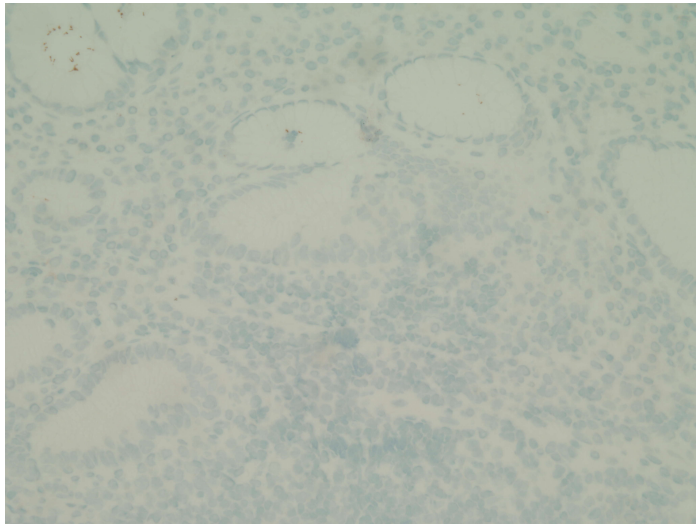
- Pathogenetic mechanisms not fully understood
- Some cases have robust association eg H.Pylori and gastric MALT, others more tenuous
- Chronic stimulation of the host immune response with persistent lymphocyte activation leads to lympho-proliferation and clonal B cell malignancy

Helicobacter Pylori

- Gram negative spiral rod-shaped bacterium
- Adapted to survive the stomach environment
- Overall Global prevalence of ~ 50%
- Wide variation in prevalence - highest in S America, Sub-Saharan Africa and Middle East
- Form of gastric disease (gastritis, carcinoma, MALT) relates to other co-factors eg host genetics
- Gastric MALT accounts for <5% of primary gastric neoplasms
- Association of *H.Pylori* with MALT well established
  - Prevalence of infection maps to disease
  - Evidence of infection serologically, in GIT and in the tumour
  - Tumour response to eradication of infection

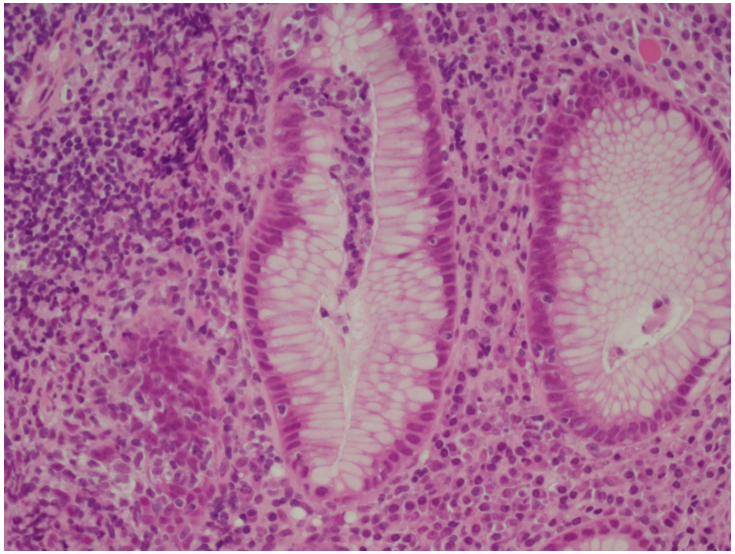
Gastric MALT lymphoma and *H.pylori*

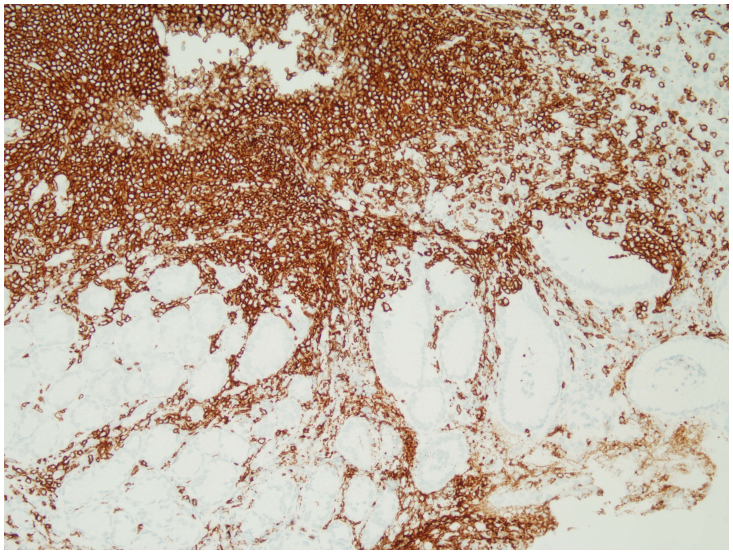




- 1991 Wotherspoon *et al* described association between *H.pylori* and gastric MALT lymphoma, with 92% cases positive
- *H.pylori* eradication therapy results in 80% ORR, but is rarely successful in negative cases (15-30% ORR)
- Prevalence of *H.pylori* infection is decreasing with associated reduction in gastric MALT (GML)
- RMH series of 104 patients between 1995 -2013
  - Prevalence of *H.pylori* infection was 50%
  - 1995-2004 prevalence was 60% compared to 32% 2005-13

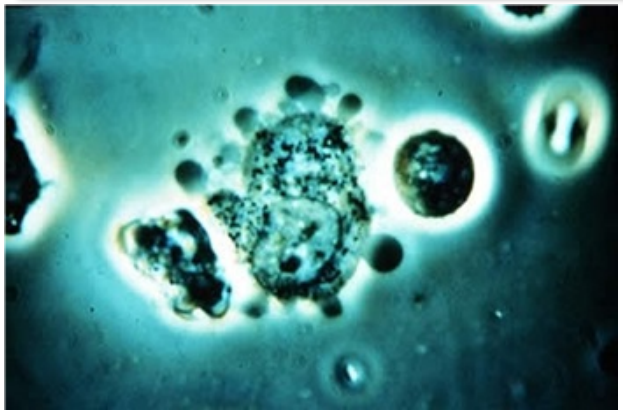
Gastric MALT lymphoma and *H.pylori*





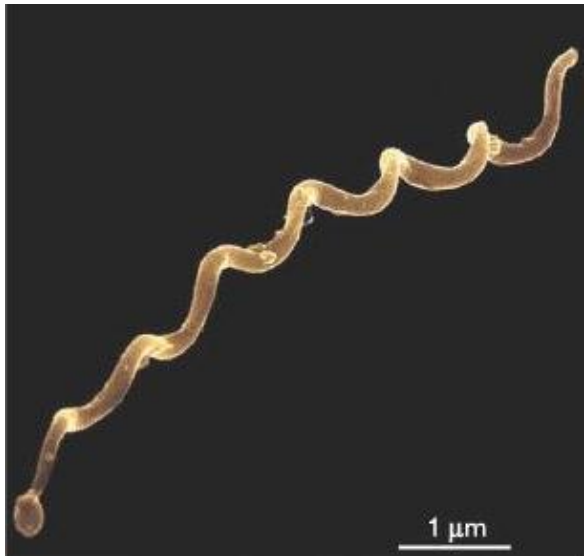
- CagA peptide is a secreted component related to the virulence of the organism
- Is taken up by epithelial cells and interacts with RAS/MEK/ERK pathway resulting in activation, migration and proliferation
- Also upregulates anti-apoptotic proteins (bcl-2) leading to persistent infection
- Inflammatory response generates reactive B and CD4+T-cells which stimulate neoplastic B cells leading to clonal expansion
- Variation in host immune response (IL-1)
- Further mutational events eg t(11:18)
- Broad spectrum of clinical features from none to gastric ulceration
- DLBCL component in 13%

Ocular/Adnexal lymphoma and *C.psittaci*



- *Chlamidophylia psittaci:* obligate intracellular bacterium found in birds
- Asymptomatic infection
- Overall prevalence 19% (47% in Germany to 11% in China)
- 50-70% of all ocular lymphomas
- IELSG study found 89% patients positive
- Antibiotics (doxycline) resulted in 65% ORR, 5y PFS 68%
- Clarithromycin may be effective at relapse
- 10y OS 81%

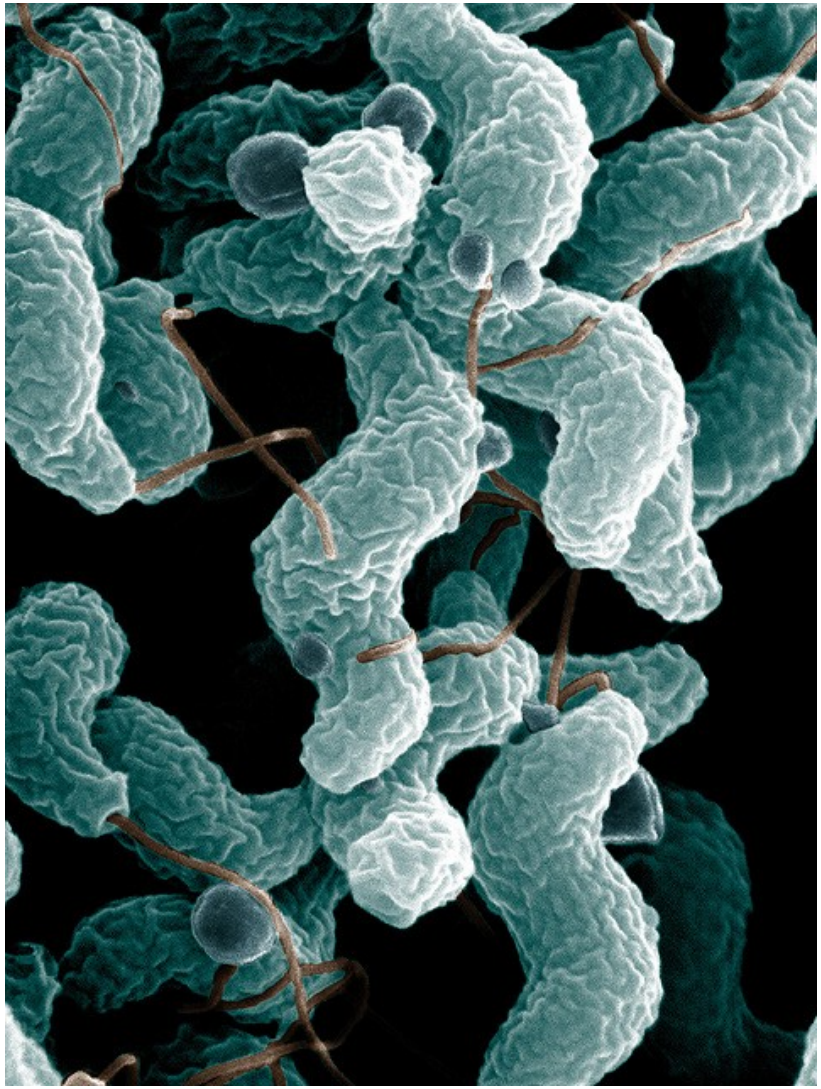
Skin MZL and *Borrelia burgdorferi*



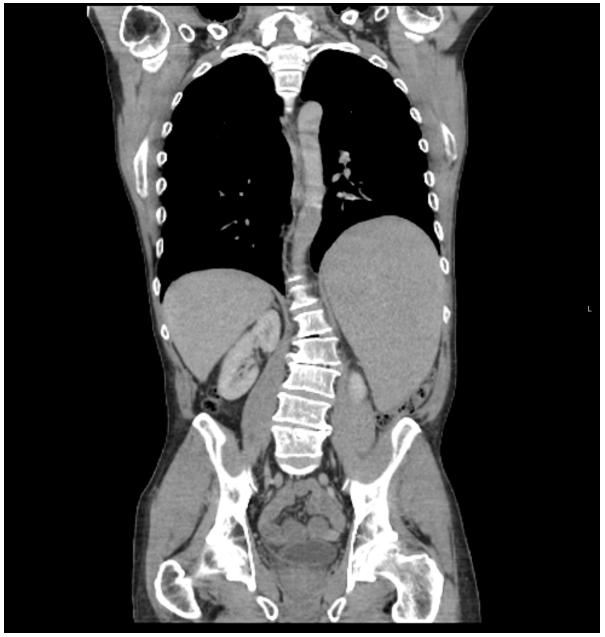
- *Borrelia burgdorferi* causes Lyme disease, endemic in North America and Central Europe
- Chronic antigen stimulation resulting in lymphocyte infiltration in the dermis
- Serology often negative but DNA positive 10-42%
- Antibiotic treatment recommended
- Indolent behaviour

Small intestine MZL and *C.jejune*

- *Campylobacter jejune is a* zoonotic multi-host pathogen carried by birds
- Positive in intestinal biopsies
- Chronic antigenic stimulation resulting in production of alpha-heavy chain from intestinal plasma cells and subsequent development of MZL
- Malabsorption syndrome, diarrhoea, abdominal pain
- Symptom control, nutritional support and antibiotics



Splenic/Nodal MZL and Hepatitis C virus



- HCV is a RNA virus transmitted through blood
- Variable geographical prevalence
- Stimulates polyclonal proliferation of B lymphocytes
- Chronic HCV infection associated with a 5 fold higher risk of MZL (splenic, nodal)
- Anti-viral therapy (IFN+/- ribovarin) has induced remissions in Splenic MZL and other HCV+ patients with indolent B-NHL

MZL: Associated Pathogens and Therapy

Patient Characteristics	Extranodal MZL (Gastric)	Extranodal MZL (Other sites)	Splenic MZL
Associated Pathogen	*H.pylori*	• Ocular/adnexal: *C.psittaci* • Small intestine: *C.jejune* • Skin: *B.burgdorferi* • Lung: *Mycobacterium spp*	Hepatitis C
Anti-infective therapy	Triple eradication (PPI, amoxicillin, clarithromycin) x 10-14 days	• *C.psittaci* : doxicycline (3 weeks) • *C.jejune*: tetracycline or metronidazole • *B.burgdorferi* : cephalosporins or tetracyclines	IFN-α +/- ribovarin

Conclusions

- MZL account for only 5-17% of NHL
- The rarity of MZL has made large- scale population based studies difficult
- Increasing evidence linking certain infectious pathogens with specific anatomical sub-types of MZL
- Tumour regression is seen in some cases following antibiotic/viral therapy
- For some infections the evidence is sparse or controversial
- Further work is needed to examine the relationship between infection and MZL