Marginal zone lymphoma: Associated autoimmunity & auto-immune disorders

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### MZL: Associated autoimmunity & auto-immune disorders

<table>
<thead>
<tr>
<th>AI disorders</th>
<th>B-cell NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>• affect 5-9% of the world population</td>
<td>• 10\textsuperscript{th} most common cancer world wide</td>
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<tr>
<td>• &gt;80 chronic illnesses</td>
<td>• 3-4% of all malignancies</td>
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Both seem to share the loss of regulatory checkpoints in the normal B-cell proliferation
### Epidemiological studies - Associations between SS, SLE, HT, AIHA, ITP and NHL/MZL

<table>
<thead>
<tr>
<th>AID</th>
<th>Study – type/period</th>
<th>Statiscal analysis</th>
<th>Association estimate (95% CI)</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Engels 2005 [11]</td>
<td>Case-control</td>
<td>RR</td>
<td>4.9 (0.6-43)</td>
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<td></td>
<td>Ekström 2008 [13]</td>
<td>Case-control</td>
<td>OR</td>
<td>4.7 (1.79-12.6)</td>
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<td></td>
<td>Anderson 2009 [9]</td>
<td>Case-control</td>
<td>OR</td>
<td>1.9 (1.5-2.3)</td>
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<td></td>
<td>Goldin 2009 [8]</td>
<td>Case-control</td>
<td>OR</td>
<td>11.7 (5.7-24)</td>
</tr>
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<td></td>
<td>Solari-Luque 2011 [12]</td>
<td>Cohort</td>
<td>SIR</td>
<td>15.6 (8.7-28.2)</td>
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<td></td>
<td>Fallah 2014 [12]</td>
<td>Cohort</td>
<td>SIR</td>
<td>4.9 (4.2-5.8)</td>
</tr>
</tbody>
</table>

| **SLE** | Zintzaras 2005 [21] | Meta-analysis | SIR | 7.4 (3.3-17) | - |
| | Engels 2005 [11] | Case-control | OR | 1.3 (0.3-5.5) | - |
| | Ekström 2008 [13] | Case-control | OR | 2.69 (1.8-4.5) | 7.52 (3.39-16.7) |
| | Anderson 2009 [9] | Case-control | OR | 1.5 (1.2-1.9) | 2.8 (1.7-4.7) |
| | Goldin 2009 [8] | Case-control | OR | 3.3 (2.1-5.3) | - |
| | Demattey 2015 [18] | Case-control | SIR | 4.4 (2.3-5.3) | - |
| | Fallah 2014 [12] | Cohort | SIR | 4.4 (2.6-5.3) | - |
| | Damró 2015 [10] | Case-control | PR | - | 0.04% (p=0.666) |

| **HT** | Thielemann 2002 [39] | Cohort | PR | - | 23% |
| | Anderson 2009 [9] | Case-control | OR | 1.1 (0.8-1.4) | - |
| | Goldin 2009 [8] | Case-control | OR | 3.0 (1.2-7.6) | 1.0 (0.4-2.2) |
| | Fallah 2014 | Cohort | SIR | 1.4 (1.2-1.6) | - |
| | Damró 2015 [10] | Case-control | PR | - | 20.8% (p=0.008) |

| **AIHA** | Ekström 2008 [13] | Case-control | OR | 2.57 (1.27-5.21) | 2.23 (0.24-21.0) |
| | Anderson 2009 [9] | Case-control | OR | 6.5 (4.4-9.4) | - |
| | Goldin 2009 [8] | Case-control | OR | 5.0 (2.5-9.7) | - |
| | Fallah 2014 [12] | Cohort | SIR | 2.72 (21.3-34) | - |
| | Damró 2015 [10] | Case-control | PR | - | 0.04% (p<0.01) |

| **ITP** | Ekström 2008 [13] | Case-control | OR | 2.13 (0.4-6.7) | - |
| | Goldin 2009 [8] | Case-control | OR | 2.4 (1.0-5.5) | - |
| | Fallah 2014 [12] | Cohort | SIR | 7.5 (3.9-9.4) | - |
| | Damró 2015 [10] | Case-control | PR | - | 20.8% (p<0.00) |

MZL: Associated autoimmunity & auto-immune disorders

Lymphomagenesis in the context of autoimmunity

- Chronic inflammatory response & AG stimulation
- Immunosurveillance deficiency
- Resistance to apoptosis & deregulate lymphocyte reactivity
- Control of B-cell activation
  - NF-kB: regulates survival and proliferation in B cells;
  - BAFF (B-cell activating factor): Lower levels lead to immunodeficiency, higher levels to immunological hyperactivity/autoimmunity;
- Immunosuppressive treatment

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Sjögren Syndrome (SS)

- 3\textsuperscript{rd} most common systemic AID
- 9F:1M
- Onset 40-60y
- Chronic inflammation of the exocrine glands
  - Acquired MALT
  - Epithelium destruction
- ↑RR6.6x to develop a lymphoma
- ↑RR30x to develop ENMZL of the salivary gland
- Average interval between dx (SS-ENMZL): 7.5y

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Hashimoto’s Thyroiditis (HT)

- Affects mostly women
- Onset 45-65y
- Chronic inflammation
  - Acquired MALT
  - Atrophic thyroid follicles
  - Epithelium destruction
- ENMZL 25% of all primary thyroid lymphoma (PTL)
- HT → PTL: 40-80x greater risk than in general population
- HT→ENMZL: 67x risk
- HT-associated ENMZL is 3x more common in women (peak at 70y)
- Diagnostic interval HT→ENMZL: 2-3 decades
- HT patients are also at a greater risk of developing MALT lymphomas in organs other than the thyroid
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**Systemic lupus erythematosus (SLE)**

- Systemic AIDs
- Affects mostly women
- Systemic chronic inflammation
- NHL risk is increased 2.7-4.1x
- Average age at NHL dx: 50y
- Diagnostic interval SLE → NHL: 6.7-17.8y
- 7.5RR to develop ENMZL (although DLBCL is the most common lymphoma subtype associated to SLE)
- Role of immunosuppressant agents as a risk factor for NHL/ENMZL development is controversial.

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Immune thrombocytopenic purpura (ITP) & Autoimmune haemolytic anaemia (AIHA)

- These are frequent complications seen in the course of many NHL and AID
  - Both are seen in about 10-15% of patients with SMZL and NMZL
- Overlapping occurrences: paraneoplastic syndrome?
  - More commonly occur synchronously with MZL diagnosis (Dasanu et al, 2015)
  - Other AIDs tend to precede MZL diagnosis

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Prognosis

- MZL: indolent behavior
- Most patients are diagnosed at an early stage (I/II)
- Management may include a ‘watch & wait’ approach
- ENMZL: OS >80% at 5y*
- NMZL: OS 55-75% at 5y*
- For non localised lymphomas, high tumour burden or high grade transformation: chemotherapy or chemo-immunotherapy


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Final comments

- The most consistent associations AID-ENMZL
  - SS
  - HT
  - SLE
  - ITP & AIHA

- Chronic antigenic stimulation plays a key role in most MZL

- AID are less frequently reported in SMZL and NMZL.

- AID-related risk factors for lymphoma development are thought to be:
  - Older age at dx;
  - Long standing disease;
  - Severity of disease;