lymphocytes are usually small or morphologically "villous", and the leukemic manifestation of SMZL is named splenic lymphoma with villous lymphocytes (SLVL). The typical immunophenotype is $CD19^+CD20^+CD22^+CD45^+$ and the clone is often also $CD\ 103^+$ and $CD38^+$. Moreover, CD11c is highly associated with SMZL. The genetics and pathogenesis of SMZL are poorly understood and specific prognostic features are lacking. Aberrant karyotypes are seen as gains of 3/3q and 12q, deletions of 7q and 6q and translocations involving 8q/1q/l4q. Trisomy 3 and deletions of chromosome 7q22-34 are most common and found in approximately 25 and 45% of cases, respectively. A strong association has been described between usage of the IGVH1-2 and deletion 7q and 14q alterations. Clinical and epidemiological data suggest that chronic hepatitis C virus (HCV) infection may have an etiological role in a subset of cases. MicroRNA (miR)-26b, a miRNA known to have tumor suppressive properties, has been shown to be downregulated in HCV positive cases. Recent data suggest that certain SMZL subtypes could derive from progenitor populations adapted to particular antigenic challenges through selection of VH domain specificities, in particular the IGHV 1-2(*)04 allele.

The anti-CD20 antibody rituximab is mostly effective in MZL patients as monotherapy, but for many patients with symptomatic splenomegaly, splenectomy is still a therapeutic option.

In summary, the presence of lymphocytosis in the blood in patients with a suspicion of lymphoma requires careful evaluation for the presence of neoplastic lymphocytes, especially in the absence of easily accessible enlarged lymph nodes. The differential diagnosis between the WHO defined mature B-cell malignancies has improved by using multiple-color flow cytometry of phenotypic data of the lymphoma cells. This method is also of value for characterization of the immune cells in the microenvironment and blood. Molecular/cytogenetic analyses have a role in classification of the disease and for understanding of pathogenesis. Therapeutic decisions are always dependant on the specific diagnosis, prognostic factors and a careful clinical evaluation of the patient.

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PRIMARY GASTROINTESTINAL LYMPHOMAS

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Epidemiology and classification

Primary gastrointestinal lymphomas comprise less than 5% of all lymphomas diagnosed in the western world, with a variable geographical and ethnic incidence. The biology and management vary with the main diagnostic (WHO) subtypes which include Gastric MALT lymphomas, Enteropathy associated T-cell lymphoma (EATCL). Other lymphomas which frequently involve the gastrointestinal tract include diffuse large B-cell lymphoma, mantle cell lymphoma and Burkitts lymphoma; but are not considered primary gut lymphomas and will not be covered in this lecture. The pathogenesis of MALT and EATCL lymphomas is linked to abnormal antigen drive (gluten/*Helicobacter* infection) resulting in chronic inflammation and lymphoma development. The lymphomas are otherwise radically different; MALT lymphomas are indolent B-NHL, which respond to antigen-drive withdrawal and minimal therapy with an overall survival (OS) > 80% at 5 years, whereas EATCL is an aggressive T-cell lymphomas associated with a poor outcome.

Gastric MALT lymphoma

***Clinical features*:** Gastric MALT lymphomas incidence in the Western World is approximately 6 per

million, with a median onset at 60 years, slight female predominance and almost invariable association with Helicobacter pylori infection. Patients typically present with non-specific dyspeptic type symptoms and the diagnosis is made gastroscopically. 80% of patients have Stage I/II disease.

***Pathology*:** The pathological appearance is of small- to medium-sized round or minimally irregular cells, with clumped nuclear chromatin, abundant pale cytoplasm and lymphoepithelial lesions. The cells express pan-B markers but are CD5, 10 and 23 negative. The t(11;18(q21;q21) detectable by FISH is present in up to 50% of cases with PCR-detectable immunoglobulin gene rearrangements in 90% of cases.

***Management*:** H pylori eradication is standard treatment for all patients and in those with disease confined to the mucosa and submucosa results in a durable CR in 70% of cases. For persistant or progressive disease chemotherapy with Chlorambucil +/- Rituximab or loco-regional radiotherapy with 20 Gy are standard approaches. There is no evidence that more intensive therapy results in a better outcome. Life long follow-up should include regular endoscopy.

Enteropathy-associated T cell lymphoma

***Clinical features*:** Coeliac disease (CD) is caused by gluten intolerance resulting in small intestinal subvillous atrophy and malabsorption of variable severity which is managed with a gluten free diet (GFD). Coeliacs have a 20 fold increased rate of developing lymphoma with 60–75% of them sub-typed as EATCL. Clinical presentation follows 3 patterns (1) development of refractory coeliac disease (RCDII) despite adherence to a GFD (2) acute presentation with gut perforation/acute severe malabsorption despite adherence to a GFD and (3) acute presentation as in (2) with no previous diagnosis of CD. EATCL diagnosis can be challenging as it is usually confined to the small intestine and tissue is usually obtained surgically or by endoscopy (gastroscopy/double balloon entersocopy).

***Pathology*:** EATCL is characterised by a monomorphic population of medium to large cells with round or angulated vesicular nuclei, prominent nucleoli and moderate to abundant, pale-staining cytoplasm with expression of $CD3^+$, $CD5^+$, $CD7^+$, $CD8^{+/-}$, CD4- and $CD103^+$.

***Management*:** The 5 year OS is 20% with conventional chemotherapy and this poor outcome is thought to be related to poor patient performance status secondary to nutritional deficiency/gastrointestinal surgery and the chemo-refractoriness inherent to T-cell lymphomas. Outcome can be improved using intensive nutritional support and primary chemotherapy followed by an autologous transplantation for patients under the age of 65 resulting in a 5 year OS of between 50–60%.

***Refractory coeliac disease*:** Patients who are diagnosed with an RCDII prodrome are interesting both for insights into EATCL lymphomagenesis and also because they may respond to less intensive therapy, thus reducing the risk of EATCL transformation. RCD II is characterised by sub-villous atrophy, loss of CD8 intra-epithelial lymphocytes and clonal T-lymphocytes with 70% progression to EATCL within 5 years. A small study of patients with RCDII who responded to Cladribine therapy had a 5 year OS of 83% which may be improved further by autologous SCT.

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MATURE T- AND NK- CELL NEOPLASMS

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The mature or peripheral T-cell neoplasms are a biologically and clinically heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes. Natural killer (NK) cells are closely related to T cells and neoplasms derived from these are therefore considered within the same group. The World Health Organization (WHO) classification of haemopoietic malignancies has divided this group of disorders into those with predominantly leukaemic (disseminated), nodal, extra-nodal or cutaneous presentation. Within the WHO classification these malignancies are differentiated on the basis not only of clinical features but also of morphology, immunophenotype and genetics.

The mature T-cell and NK-cell neoplasms account for approximately 10–12% of all lymphoid malignancies, usually affect adults and most of the entities described are more commonly reported in males than in females. The median age at diagnosis for the group as a whole is 61 years with a range of 17–90 years. There is geographical variation in the frequency of the different subtypes and in Europe peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL) account for