What are lymphomas?

by Alex Goodell | View online

Introduction

Blood disorders can be divided into those that arise from the myeloid linage (AML, CML) and those that are derived from the lymphoid lineage. In the lymphoid lineage, we have B cells, T cells, and NK cells. Any of these cells can become neoplastic and show uncontrolled growth. Over the years, physicians have noticed that there are a defined set of lymphoid neoplasms, some of which more classically arise from the bone marrow (*leukemias*) and others which classically arise in the secondary lymphoid tissue and form tumors (*lymphomas*). Now, that distinction is less important. We've now realized that some of the diseases traditionally called lymphomas can present as leukemias, and vise-versa. So, now, you'll see some of these diseases with names like "leukemia/lymphoma," recognizing that some of these conditions can present in either way, but is due to the same genetic defects. A good example is small lymphocytic lymphoma (SLL), which is the same disease as chronic lymphocytic leukemia (CLL), and is now just referred to as SLL/CLL.

One last point I was confused about: just because something is a leukemia doesn't mean that it is a proliferation of precursor (*blast*) cells – that is characteristic of an acute leukemia, but not a chronic leukemia.

Unfortunately, many systems have existed to classify the lymphoid neoplasms. According to Robbins, "few areas of pathology evoked as much controversy as the classification of lymphoid neoplasms." Initially, there was a history of bad pathology classifications, so clinicians invented a system called the **Working formulation** that placed the lymphomas into low-grade, intermediate-grade, and high-grade based on their rate of growth and subsequent prognosis; you may here this classification on the wards. Pathologists eventually fought back, and created a system called the **REAL classification** (ostensibly standing for a Revised European-American classification of Lymphoid neoplasms…). Now, the current standard is the 2008 **WHO classification**.

The WHO classification is actually really straightforward: all 80+ lymphoid neoplasms can be broken into these five categories:

1. Precursor B-cell neoplasms (neoplasms of immature B cells)
2. Peripheral B-cell neoplasms (neoplasms of mature B cells)
3. Precursor T-cell neoplasms (neoplasms of immature T cells)
4. Peripheral T-cell and NK-cell neoplasms (neoplasms of mature T cells and NK cells)
5. Hodgkin lymphoma (neoplasms of Reed-Sternberg cells and variants)

Please see diagram below.

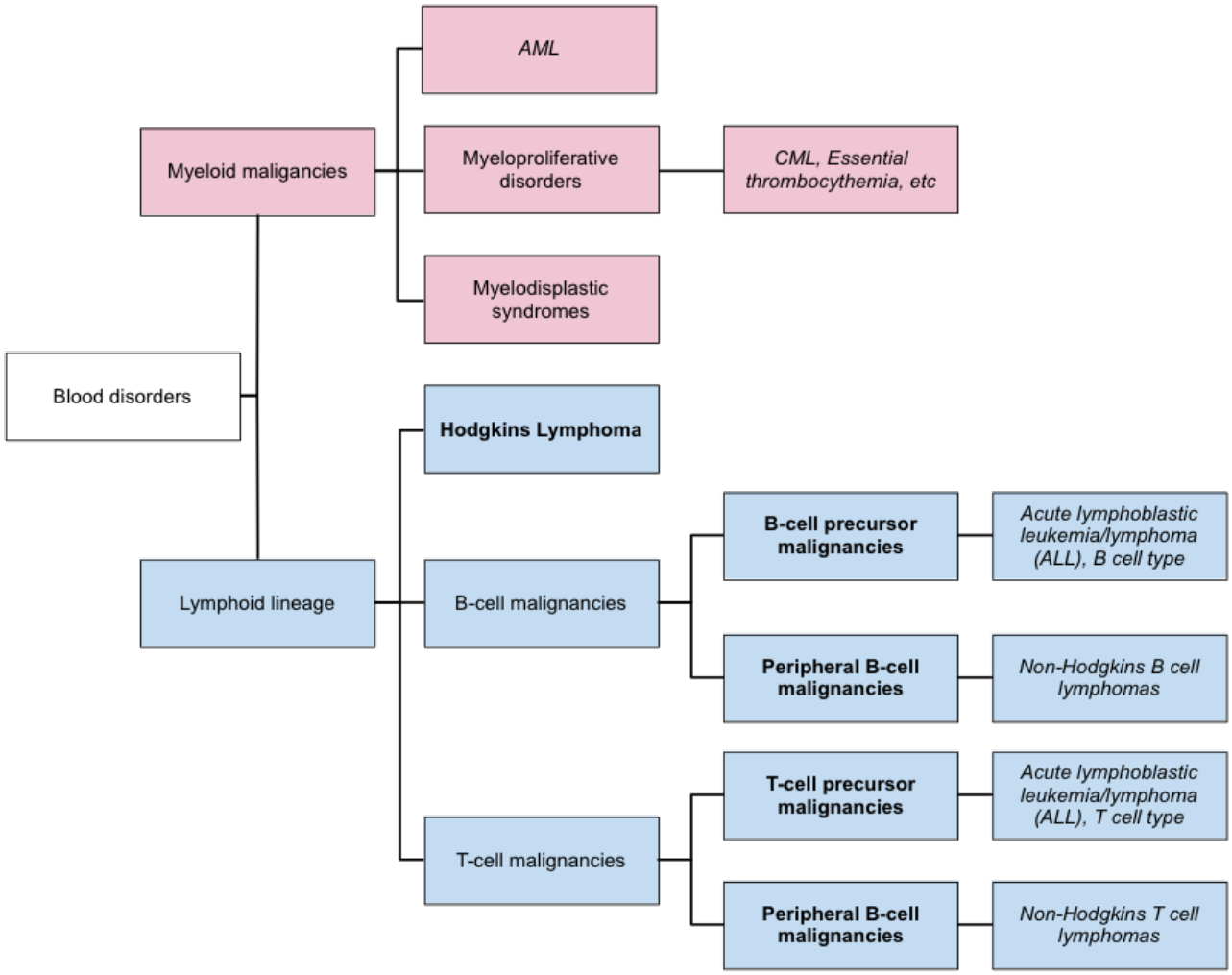

Figure 1. Diagram of lymphomas

Common characteristics

Here are some other big ideas about lymphoid neoplasms:

- All of the lymphomas are diagnoses via biopsy and **histological examination** by a pathologist – these are not clinical diagnoses
- Generally, these neoplasms resemble a stage of B-cell or T-cell differentiation. The majority look most similar to **B cells** (85-90%), while the remaining appear as T cells (10-15%), while NK cell lineage is very rare.
- **Antigen receptor rearrangement** generally occurs before the creation of the neoplasm. This means that most of the time, lymphomas are monoclonal. This is important as it assists in diagnosis (lots of monoclonal response suggests malignancy), and can be helpful in finding malignant cells after therapy
- Lymphoid neoplasms are associated with immune abnormalities; they can cause immunodeficiency and autoimmunity; also, individuals with congenital immune deficiencies are at a higher risk for developing lymphoid neoplasms.

Sections of lymphoid follicles

Another powerful method that is used to describe lymphomas concerns where in the lymph node the cancers arise.

Let's review a bit. Lymphoid tissue (primary and secondary) contains lymphoid nodules, which are also called **lymphoid follicles**, which contain native B cells. When these nodules become activated, the B-cells in the center of the nodule undergo maturation, many becoming plasma cells. Since plasma cells have a much larger cytoplasm-to-nucleus ratio, the center of the nodule becomes lighter-staining. This center area of lightness is referred to as the **germinal center** (Fig 1). Of course these germinal centers also contained the famed follicular dendritic cell; but these are difficult to differentiate on a plain H&E slide.

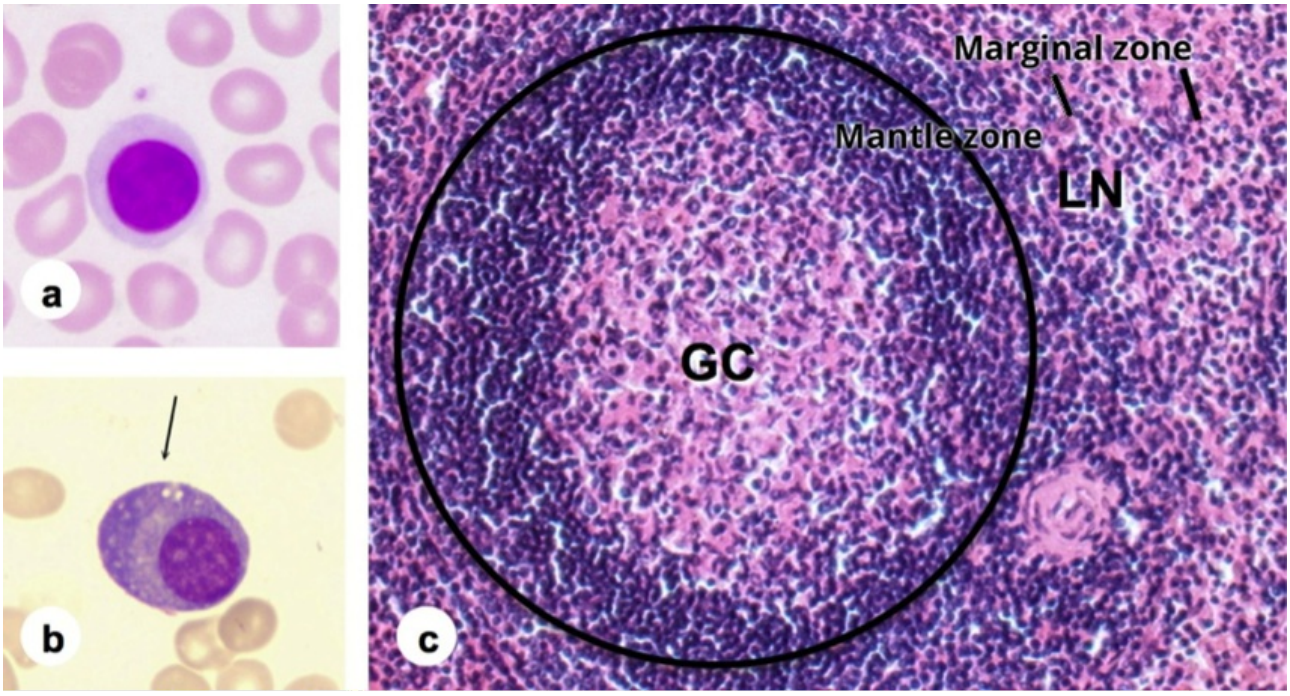

Figure 2. (a) Non-activated B cell. Note the small cytoplasm-to-nucleus ratio. (b) An activated B-cell has turned into a plasma cell, with a large amount of cytoplasm. (c) A lymph nodule (LN - circle) with the plasma cell center of germinal center (GC). Note the mantle zone, with its dark, highly-condensed B cells and the outer marginal zone.

Surrounding the germinal center is a ring of small, dark, tightly-packed B cells which comprise the **mantle zone**. Directly outsize of the mantle zone is the **marginal zone**, which is also comprised of B-cells. Lymphomas can arise from each of these areas, and are thus classified as **follicular** (germinal center), **mantle zone**, or **marginal zone** lymphomas.

Now that we remember a bit about the internal structure of the lymph tissue, let's remind ourselves a bit about the MALT. As Adnan taught us in his 5.7.1 LO, there are only two primary lymphoid organs: the thymus and the bone marrow. In terms of secondary lymphoid tissue, we have the lymph nodes, the spleen, **mucosal-associated lymphoid tissue (MALT)** and the bronchus-associated lymphoid tissue (BALT). The MALT is a huge collection of blood cells that monitor and protect our alimentary tract. In fact, it holds 70% of our immune cells! Included in the MALT are our tonsils, Peyer's patches in the ilium, and our appendix

(see my 4.1.1 Lymph histology).

Pathogenesis of MALT lymphoma

A MALT lymphoma is a form of lymphoma that arises from the MALT, most commonly in the stomach, but could occur anywhere in the MALT. It arises in B-cells found in the **marginal zone of the lymphoid follicles** found in the MALT. For this reason it also called extranodal marginal zone B cell lymphoma or a MALToma.

MALT lymphomas are a form of **primary gastric lymphoma**, meaning that the cancer arose in the MALT as opposed to arising in an adjactent lymph node and traveling to the MALT. Primary lymphoma is the second most common gastric malignancy, accounting for 3% of gastric cancers; the most common cause is gastric adenocarcinoma.

Although the stomach is the most common site of a MALT lymphoma, the stomach normally doesn't have a lot of MALT – the famous Peyer's patches are in the ilium (and, interestingly, are the major histologic difference between the ilium and the other sections of the small intestine). How do MALTomas arise in the stomach then? Well, chronic inflammation of the stomach (gastritis) actually **induces the formation of lymphoid tissue** around the stomach. I bet you can guess what the major inflammatory agent is: H. pylori.

MALT lymphomas are wild because they undergo remission with the removal of H. pylori in 55-75% of cases. How is this possible, Alex? Isn't cancer defined as an uncontrolled growth of malignant cells? Well, it's interesting.

In general, remember that immune cells are generally short-lived compared to the other cells in our body. The one time when we want them to have an extended lifespan is during an infection. In order to do that, various cytokines, particularly IL-2, promote maturation and survival. These cytokines are released by damaged cells, through a pathway involving the transcription factor **NF-kB** (remember, this is what glucocorticoids block).

Well, when we have chronic H. pylori infection, we first adapt by forming MALT in the lining of the stomach. During this process, some B cells may undergo a oncogenic mutation that results in a **more active NF-kB**. In the continual presence of H. pylori, the combination of these mutations and endogenous NF-kB activation tips the scale towards too much B cell survival and promotes the growth of a tumor. Removal of H. pylori, however, tips the scale back, and the genetic mutations are not sufficient to maintain the survival of the tumor (Fig 3).

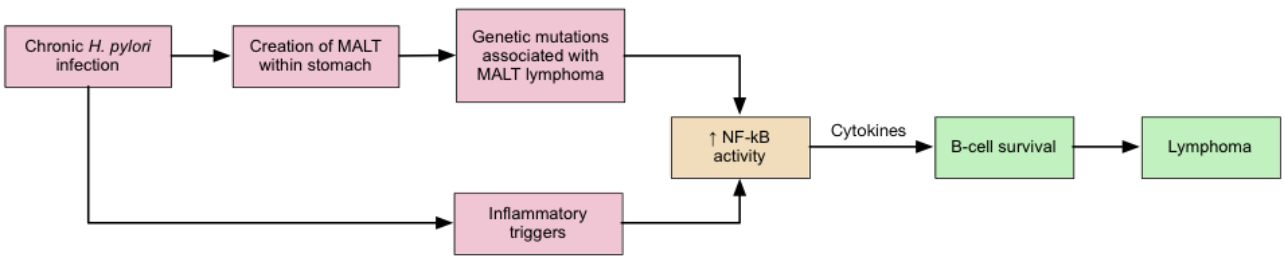

Figure 3. Figure 2. Schematic of MALT lymphoma pathogenesis.

Unfortunately, there are some more rare mutations that lead to a more aggressive form of the cancer which

retains its malignancy even in the absence of H. pylori. These tumors have metastatic potential.

Clinical presentation, diagnosis, and treatment

Most patients have abdominal pain, weight loss, or bleeding. At endoscopy, lymphoma may appear as an ulcer or mass. The diagnosis is established with endoscopic biopsy.

As noted above, 55%-75% of individuals will go into remission with the removal of H pylori. Individuals with the more rare aggressive forms may undergo radiation therapy. There is a 2% per year recurrence, thus endoscopy is recommended one every 6-24 months. Long-term survival is 90% for stage I and 35–65% for stage II.

References

- Robbins
- Adnan Syed
- Chu, Atlas of Histology with Functional and Clinical Correlations