Understanding the classification of Hodgkin lymphoma

The lymphomas are a complex group of cancers comprising more than 50 related but distinct diseases. Research over the past few decades has led to the introduction of more and more sophisticated tests for lymphoma. This has meant that more subtypes of lymphoma are being recognised all the time. It is therefore not surprising that arranging lymphomas into groups (classification) has caused some confusion among doctors for many years.

In this article we will:

- summarise how lymphomas have been classified over the years
- explain how lymphomas are classified now
- explain why it is important to find out which type of lymphoma you have
- briefly describe the five subtypes of Hodgkin lymphoma.

What is lymphoma?

Lymphoma is a cancer of the lymphatic system. The lymphatic system is a complex network of tubes (lymphatic vessels), glands (lymph nodes) and other organs, including the spleen and thymus gland. The vessels and glands hold a fluid called lymph, which is partly made up of cells called lymphocytes. These cells are involved in the body’s immune system. If they start to grow out of control or don’t die off after their normal lifespan they can build up in the lymph nodes or in other places. When lymphocytes become cancerous like this, the condition is known as lymphoma.

The history of lymphoma classification

As diagnostic tests have become more sophisticated and understanding of the biology of the lymphatic system has improved, several different classifications of lymphoma have been described over the last 30 to 40 years. Each of these systems gained popularity for a while, but was then replaced by a newer classification system.

Consequently, the names of many types of lymphoma have changed several times, new types have been recognised, and some lymphomas have been reclassified as another type, with a new name. This has been a source of confusion for both patients and healthcare professionals involved in the treatment of lymphomas.
In view of this, a group of lymphoma experts from around the world developed a new classification system for lymphoma in 2001 – the World Health Organisation (WHO) classification. It has already been shown to be more precise than any of the previous classifications, and is now used by most major lymphoma treatment centres.

The WHO classification is being regularly updated as new scientific discoveries are made which improve our understanding of these conditions. For example, new research studies which investigate the genetic make-up of lymphomas are showing that within each type described in the WHO classification, it might be possible to identify patients whose lymphoma is likely to respond well to treatment and those who might not do so well with a standard treatment. As this research progresses over the next few years it is likely that the WHO classification will change.

The information in this article is based on the latest WHO classification, published in 2008.

Making an accurate diagnosis of lymphoma

Why is it important to make an accurate diagnosis?
Accurate diagnosis is fundamental to giving people with lymphoma appropriate advice about treatment. Without accurate diagnosis there is a danger that a lymphoma would not be treated with the most suitable treatment for that particular type of lymphoma. This could mean that you would not have the best chance of going into remission and of long-term survival and you might also develop treatment side effects that could have been avoided.

Accurate diagnosis depends on several factors, including the obtaining of a good biopsy (where a small sample of tissue or a whole lymph node is removed for analysis) and the availability of specialised laboratory facilities and expert pathologists to interpret the tissue sample.

Obtaining the tissue sample
An adequate amount of tissue must be taken at biopsy. This is fairly straightforward for lymph nodes near the surface of the body, for example in the neck, and it is usual to remove a whole lymph node wherever possible. For sampling deeper tissues, a needle can be used to take smaller biopsies, often with the help of ultrasound or computed tomography (CT) scanning to locate the affected lymph node or organ.

To obtain adequate tissue for diagnosis in this way, the biopsies must be performed by experts in these procedures. As techniques for diagnosis improve, the amounts of tissue required to obtain an accurate diagnosis are getting smaller.

Analysis of the tissue sample
The pathology laboratory must have a full range of modern techniques which are essential to lymphoma diagnosis. The biopsies must be interpreted by pathologists who are experts in lymphoma, working closely with oncologists and/or haematologists who also have a special interest in lymphoma. It is important that there is close interaction between pathologists and clinicians in reaching an accurate diagnosis because factors such as your age and sex and your symptoms must also be taken into account.
The WHO classification system

The WHO classification system includes all types of lymphoma – both Hodgkin lymphomas (formerly known as Hodgkin’s disease) and non-Hodgkin lymphomas (which means all the lymphomas that aren’t Hodgkin lymphoma). Several factors are used in this classification system to decide exactly what type of lymphoma someone has:

- The appearance of the lymphoma cells under the microscope is the technique that has been used for the longest time – this is known as the **morphology**.

- The presence of molecules on the surface of the lymphoma cell can be detected using specially prepared antibodies that target these molecules – this is known as **immunophenotyping**. This can be done by treating the cells with specialised antibody stains or with fluorescent compounds (**immunohistochemistry**). The pattern of staining or fluorescence of the cells gives precise information about the identity of the lymphoma. This information is often supplemented by information obtained using a technique known as **flow cytometry**. Flow cytometry can be a more sensitive way of getting information and can detect small amounts of lymphoma which might not be detectable by routine pathology tests.

- The presence of certain genetic abnormalities which are known to exist in some types of lymphoma can help pathologists to identify a lymphoma – this is called **cytogenetics**. In some types of lymphoma a test known as FISH, which stands for ‘fluorescence in-situ hybridisation’, is also used to look for genetic changes in lymphoma cells.

- The person’s **age, sex and medical history** (eg past illnesses or drug therapies) and the clinical features of the lymphoma (eg the places in the body where the lymphoma first appeared or is found to have spread to) are also important in reaching a diagnosis in certain lymphomas.

The WHO classification is particularly useful because the types of lymphoma it describes usually have a very well-characterised pattern of symptoms and signs and also a typical way of responding to treatment.

This article is concerned with the types of lymphoma that the WHO classification system classes as Hodgkin lymphomas. (If you would like information on the classification of the non-Hodgkin lymphomas, please phone our helpline on 0808 808 5555 to ask for the information sheet, ‘Understanding the classification of non-Hodgkin lymphomas’.)

The different types of Hodgkin lymphoma

Hodgkin lymphoma can be divided into two main types, the ‘classical’ Hodgkin lymphomas (there are four of these) and nodular lymphocyte-predominant Hodgkin lymphoma:

- **Classical Hodgkin lymphomas**:
  - nodular sclerosis Hodgkin lymphoma
  - mixed cellularity Hodgkin lymphoma
  - lymphocyte-depleted Hodgkin lymphoma
  - lymphocyte-rich Hodgkin lymphoma

- **Nodular lymphocyte-predominant Hodgkin lymphoma**.
Classical Hodgkin lymphoma

About 19 out of 20 people with Hodgkin lymphoma will have one of the classical types. The main identifying characteristic of the classical Hodgkin lymphomas is a cell seen under the microscope called the Reed–Sternberg cell. This cell isn’t seen in nodular lymphocyte-predominant Hodgkin lymphoma (or in any of the non-Hodgkin lymphomas).

The most common types of classical Hodgkin lymphoma are nodular sclerosis Hodgkin lymphoma and mixed cellularity Hodgkin lymphoma and these two types account for 80–90% of all Hodgkin lymphomas. They share many symptoms and signs, although there are some important differences between them:

- **Nodular sclerosis Hodgkin lymphoma** is most common in young adults in their 20s and 30s. Most people with this type of Hodgkin lymphoma have early-stage disease when they are diagnosed, usually affecting lymph nodes in the neck and chest.

- **Mixed cellularity Hodgkin lymphoma** is less common than nodular sclerosis Hodgkin lymphoma. It tends to affect an older age group (the average age of people with this lymphoma is 38) and is more common in men. This type of Hodgkin lymphoma can sometimes first appear in the abdomen and spleen and it doesn’t affect the chest as commonly as the nodular sclerosis type does.

The other two types of classical Hodgkin lymphoma are much less common:

- **Lymphocyte-rich classical Hodgkin lymphoma** mainly affects people in their 30s and 40s, is more common in men and is similar to nodular lymphocyte-predominant Hodgkin lymphoma (see below) except that it relapses less commonly.

- **Lymphocyte-depleted classical Hodgkin lymphoma** is the rarest of the four types of classical Hodgkin lymphoma. It typically affects people in their 30s, men more than women, and it often appears in the abdomen. It is more common in developing countries and in people who are HIV-positive.

Nodular lymphocyte-predominant Hodgkin lymphoma

Only 1 in 20 people with Hodgkin lymphoma have nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). This form of Hodgkin lymphoma typically affects people aged 30–50 and it is more common in men. Pathologists diagnose NLPHL when they see a particular type of cell, the 'lymphocyte-predominant' (LP) cell under the microscope. This cell is sometimes called a 'popcorn cell' and it is unique to this kind of Hodgkin lymphoma.

NLPHL usually comes to light when it is still at an early stage, often appearing first in the lymph nodes in the neck. It has a very good outlook, and over 90% of people go into remission after an excision biopsy (removal of the whole lymph node in a surgical procedure) and radiotherapy. NLPHL can relapse later on and require another course of treatment and this can occur after as long as 10 years after treatment has finished. In some cases, the relapse takes the form of a non-Hodgkin lymphoma (this process of a lymphoma coming back in a different form is known as 'transformation').
Conclusions

- The classification of lymphomas has always been a very complicated subject and several systems have been used over the years.

- The current WHO classification system will no doubt be updated and changed as research continues to reveal more about each lymphoma and shows how the lymphomas are interrelated. For example, recent studies have shown that there is a degree of overlap between classical Hodgkin lymphoma and diffuse large B-cell lymphomas (which are non-Hodgkin lymphomas).

- Classification of lymphomas is very important because having your type of lymphoma accurately identified means that your medical team will be able to tell how you might progress and how best to treat you.

- Classifying and grouping the lymphomas like this also helps researchers find out more about why lymphomas develop and how they might be prevented or treated in the future.

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More information

The Lymphoma Association produces a wide range of booklets and information sheets on all aspects of lymphomas and their treatments. Visit our website at www.lymphomas.org.uk or telephone our freephone helpline on 0808 808 5555 if you would like to receive any of this information or if you would like to talk to someone about your lymphoma.

References
