UPDATE ON LYMPHOMA PATHOLOGY: I
EPIDEMIOLOGY AND THE ROLE OF
VIRUSES AND RADIATION IN THE
PATHOGENESIS OF LYMPHOID NEOPLASIA

RW Blewitt, Consultant Pathologist, Lancaster and Kendal Hospitals

INTRODUCTION
An average human contains about 500g lymphocytes, equivalent to an organ one third the size of the liver, but far more likely to undergo neoplastic transformation. Lymphocytes are the most extensively studied and complex cell type in the body, and this is equally true for their tumours. Enormous advances have been achieved in the epidemiology, cytogenetics, and classification of lymphoid tumours. In these papers we shall see how remarkably close we are to understanding the cause of some types of lymphoid cancer. Part I will concentrate on epidemiology and the role of viruses and radiation. The contribution to lymphoid neoplasia of genetic mutations will be reviewed in Part II, and the new classification will be presented in a subsequent part.

Scope and definitions
Lymphoid neoplasms range from leukaemias, which present primarily to the haematologist, to solid tumours (e.g. lymphomas) which can present to any medical speciality (Figure 1).

Incidence of lymphoid neoplasms (a)
Terminology
Let us first be clear on terms:
INCIDENCE means new cases recognised, and incidence rates are commonly given as number of new cases per 100,000 population per year. Age-specific incidence rates are the number of new cases from a particular age range (e.g. 45 - 49 years), usually scaled up to cases per 100,000 per year.

PREVALENCE means all cases, newly and previously diagnosed. Prevalence rate will commonly be the number of cases per 100,000 population per year.

(b) Relative incidence rates
Lymphomas are by far the commonest type of lymphoid neoplasm (Figure 2) accounting for more than 50% of cases. Overall, there are many more cases of non-Hodgkin's lymphoma than Hodgkin's disease (ratio 5.8:1), but in young adults Hodgkin's disease is the more common (see age-specific incidence rates). Taken together, lymphoid neoplasms approach the common epithelial cancers in terms of incidence and mortality rates (Figure 3). Lymphoid neoplasms cause about 5% of all cancer deaths and rank sixth in both incidence and mortality rates.

(c) Clinical impact
With a population of 310,000 in the Morecambe Bay area we can expect about eighty new cases of lymphoid neoplasm...
every year, of which about forty-five will be lymphomas. These figures can be multiplied by a factor of at least four to obtain an estimate of prevalence.

Lymphoid tumours are often clinically demanding; they can affect all ages and are never benign, but are frequently of long duration. Diagnosis is often difficult. Many types of lymphoid tumour respond well to chemotherapy and radiotherapy and they can sometimes be cured by intensive treatment. Patients may need medical support for years.

(d) Sex incidence
All lymphoid tumours have a bias towards the male sex (Figure 4).

(e) Age-specific incidence
The incidence of all types of lymphoid neoplasm is strikingly dependent upon age (Figures 5 and 6). The peak incidence of acute lymphoblastic leukaemia is in very young children. Chronic lymphocytic leukaemia and myeloma are clearly similar diseases of old age and appear to increase exponentially with age. Non-Hodgkin's lymphoma curve resembles chronic lymphocytic leukaemia and myeloma but is displaced to the left, affecting middle age as well as the elderly. The risk of developing non-Hodgkin's lymphoma doubles for each decade of life, but the disease is still quite rare below forty years. The risk of developing chronic lymphocytic leukaemia or myeloma doubles every six years, and is virtually nil before forty years of age.

(f) Simple analysis of age-specific incidence curves
Age-specific incidence curves can be quite revealing and have attracted the attention of the mathematical mind (see part g, below). In Figures 5 and 6, for example, one might make the following hypotheses:

1. acute lymphoblastic leukaemia is somehow a consequence of the period of proliferation of lymphocyte precursors in early life.
2. Hodgkin’s disease seems to occur when EB virus infection is active in young adults.
3. chronic lymphocytic leukaemia and myeloma are part of the ageing process.

(g) Mathematical analysis of age-specific incidence curves
Plotted on logarithmic axes, many age-specific incidence curves for cancers, degenerative and autoimmune conditions form straight lines. Figure 7 shows moderate success for chronic lymphocytic leukaemia and myeloma, and for non-Hodgkin’s lymphoma over the age of forty. The slopes of these curves have been taken to indicate the number of mutations required in a cell in order to cause cancer. For chronic lymphocytic leukaemia and myeloma this would be about seven, and this is very similar to results for common cancers of the elderly such as carcinoma of the colon, stomach or prostate. This type of analysis, however, assumes that the successive mutations are equally likely. As we shall see, this may well not be accurate. Certainly, the age-specific incidence curves for lymphoid neoplasia cannot be produced by a single mutation.

(h) Temporal trends in incidence
The incidence of non-Hodgkin's lymphoma has for many years been increasing, at a present rate of 3% per year and slightly more in the elderly. The increase is probably genuine, and not due to improvements in diagnosis, because mortality rates have risen in parallel with incidence, and there has been no increase in Hodgkin’s disease, acute lymphoblastic leukaemia, chronic lymphocytic leukaemia or myeloma. The cause of the increase is not known; increasingly exposure to ultraviolet light has been one suggestion. Non-Hodgkin's lymphoma is not unique in this respect; longterm increases have been recorded for melanoma, lung cancer in females, brain tumours and cancers of the breast, testis and oesophagus.

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**Figure 4** Sex ratios in lymphoid neoplasia

**Figure 5** Age-specific incidence for Hodgkin’s disease (HD) and non-Hodgkin’s lymphoma (NHL)

**Figure 6** Age-specific incidence rates for acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL) and myeloma (MM)

**Figure 7** Plot of log incidence against log age for non-Hodgkin’s lymphoma, chronic lymphocytic lymphoma and myeloma
RADIATION AND LYMPHOID NEOPLASIA

(a) Introduction
Radiation can certainly cause leukaemias; these are acute myeloid leukaemia and chronic myeloid leukaemia, and to a lesser extent acute lymphoblastic leukaemia, the particular type depending largely on the age of the individual\(^1\).

(b) A-bomb survivors
Atomic bomb survivors suffered an increase in leukaemia of up to 25-fold. This risk was dose-dependent and greatest in those who were youngest at the time of exposure. From these and other data it is calculated that the risk of death from leukaemia is doubled by a radiation dose of 1 Sievert (Sv)\(^{1,9}\).

This dose would take 500 years to accumulate from normal background radiation in the UK (2mSv/year).

(c) Chernobyl
The Chernobyl accident in 1986 has led to a huge increase in thyroid cancer in children (up to 100-fold) due to uptake and concentration of radio-iodine in the thyroid. So far, no increase in childhood leukaemia or other cancers has been reported\(^{10}\). There has, however, been a recent report of increased acute lymphoblastic leukaemia in infants exposed \textit{in utero} to the doubled background radiation in Greece\(^{11}\).

(d) Sensitivity of the fetus
It has long been realised that diagnostic x-rays carried out during pregnancy cause the fetus an increased risk of acute lymphoblastic leukaemia during childhood\(^{12}\). These doses of radiation are small and together with the recent Chernobyl data from Greece indicate that the fetus is exquisitely sensitive to the leukaemogenic effects of radiation.

(e) Effect of radiation on lymphoid tumours other than acute lymphoblastic leukaemia
It is generally accepted that radiation has no effect on the incidence of chronic lymphocytic leukaemia\(^{13}\), and there is no convincing evidence of an effect on lymphoma\(^{17}\) or myeloma\(^{18}\).

VIRUSES AND LYMPHOID NEOPLASIA

Introduction
There is no doubt that viruses cause lymphoma and leukaemias in animals\(^{19}\); a number of these diseases are of economic significance. Herpes virus is the cause of lymphoma in chickens (Marek’s disease) and retroviruses cause lymphoid leukaemia in cats, mice and cattle. A retrovirus causes the very rare adult T-cell leukaemia in humans, and there is strong evidence linking viruses to some commoner types of lymphoid neoplasm (Figure 8). The viruses are almost restricted to two groups: herpes, and retrovirus, but hepatiti C, a flavivirus, has recently been seen in human lymphomas\(^{20}\).

EB virus
EB virus can be found in tumour cells in all cases of tropical Burkitt’s lymphoma. The virus is present in Reed Sternberg cells in 40% of cases of Hodgkin’s disease\(^{21}\) and is responsible for the lymphomas which can develop in immunodeficient individuals.

Like other DNA viruses, EB virus infection can be acute, causing cell lysis and producing many new virus particles (productive), or chronic and relatively non-productive of virus (latent). Neoplastic transformation is thought to be a rare accidental event during the course of latent infection.

<table>
<thead>
<tr>
<th>VIRUS NAME</th>
<th>TYPE</th>
<th>GENOME</th>
<th>DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Herpes</td>
<td>DNA</td>
<td>Hodgkin’s disease, Burkitts lymphoma, lymphoma in immunosuppressed patients</td>
</tr>
<tr>
<td>Human Herpes virus 8 (HHV-8)</td>
<td>Herpes</td>
<td>DNA</td>
<td>Primary effusion lymphoma (and Kaposi’s sarcoma)</td>
</tr>
<tr>
<td>Human T-leukaemia virus (HTLV-1)</td>
<td>Retrovirus</td>
<td>RNA</td>
<td>Adult T-cell leukaemia</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>Retrovirus</td>
<td>RNA</td>
<td>Allows EBV to cause lymphomas</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Flavivirus</td>
<td>RNA</td>
<td>? lymphoplasmacytic lymphoma and extranodal lymphoma</td>
</tr>
</tbody>
</table>

Figure 8 Viruses and human lymphoid neoplasms

Probably a genetic mutation is required in addition to the virus eg 8;14 translocation in Burkitt’s lymphoma. Some types of herpes virus produce viral cyclins (see Part II) which drive the mitotic cycle\(^{22}\), but the mechanism by which EB virus causes cancer is not known.

EB virus only infects B-lymphocytes, causing them to proliferate and express viral antigens on the cell surface. These evoke a massive proliferative response in T-lymphocytes which can be seen in blood smears as “atypical mononuclear cells.” The T-cells gradually destroy the infected B-lymphocytes. These events underlie the familiar acute illness of infectious mononucleosis (glandular fever), and correspond with the productive viral cycle.

After the acute illness EB virus can persist in the body indefinitely. In fact the vast majority of people carry EB virus as a life-long asymptomatic infection in which the immune system keeps in check small numbers of infected B-lymphocytes. Immunosuppression can change this balance.

Lymphomas in individuals who are immunodeficient or immunosuppressed
Immunodeficiency due to HIV infection or therapeutic immunosuppression for transplantation causes a considerable increase in incidence of lymphoma\(^{23,24}\). These tumours are different from common lymphomas in the following respects:

- They are all high-grade B-cell lymphomas
- Almost all contain EB virus
- They very often occur outside lymph nodes, in organs such as the brain
- Post-transplant cases have on rare occasions regressed on reversal of the immunosuppression.

RETROVIRUSES
These are small RNA viruses which cause tumours directly, rather than as a rare accident\(^{25}\). The virus consists of only three or four genes which are integrated into the host DNA; this process can itself cause genetic damage (ie a mutation). The viruses fall into two groups:

- slow transforming, which cause cancers after prolonged latent periods
fast transforming, which cause cancer almost immediately because they carry and insert into the host an extra growth-promoting gene or “oncogene”. In human lymphoid neoplasia, however, insertion of “oncogenes” by viruses does not appear to be a significant factor[21].

Hepatitis C
There is some recent evidence that chronic hepatitis C infection may increase the risk of developing certain types of lymphoma, mostly lymphoplasmacytic lymphoma (which may produce cryoglobulinemia) and extranodal lymphomas in sites such as the liver and salivary glands[23]. The virus is probably acting merely as a cause of chronic lymphocytic proliferation analogous to autoimmune disease and Helicobacter infection in the stomach (see Part II).

Clusters of leukaemia
A number of disparate areas have been found to show a higher than expected incidence rate of acute lymphoblastic leukaemia (Figure 9).

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>PERIOD</th>
<th>OBSERVED/EXPECTED CASES</th>
<th>AUTHOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glenrothes</td>
<td>1951-1967</td>
<td>5.0</td>
<td>Kinlen 1988[22]</td>
</tr>
<tr>
<td>Caithness</td>
<td>1979-1986</td>
<td>5.0</td>
<td>Heasman 1988[23]</td>
</tr>
<tr>
<td>Aldermaston</td>
<td>1972-1985</td>
<td>2.0</td>
<td>Roman 1987[25]</td>
</tr>
</tbody>
</table>

Figure 9 Some reported “clusters” of acute lymphoblastic leukaemia

Suspicion fell initially on radioactivity, as three of the sites listed in Figure 9 contain nuclear installations. Glenrothes, however, is a relatively non-radioactive new town, and the increased radiation exposure to infants due to Sellafield emissions is estimated at 0.3 mSv per year (background about 2mSv/yr) which is far too small to explain a tenfold increase in leukaemia.

The present and popular hypothesis, due to Kinlen, is that population mixing in rural areas causes a mini-epidemic of a viral (or other) infection which can rarely lead to acute lymphoblastic leukaemia in children[22]. Consistent with this is the finding that acute lymphoblastic leukaemia is more common (up to 2-fold) in rural areas with higher socioeconomic status[26].

In Part 11 of this review we shall cover what is perhaps the fundamental causal factor in lymphoid neoplasia: genetic mutations.

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101