Ministry of Defence

Synopsis of Causation

Chronic Lymphoproliferative Disorders

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Chronic lymphoproliferative disorders are a heterogeneous group of malignant clonal proliferations of lymphocytes. They are classified as sub-types of non-Hodgkin's lymphoma and include disorders of B-, T- and NK-cell lineages all of which are further classified as distinct entities. Chronic B-cell lymphoproliferative disorders are much more common and in general have an indolent clinical course.

2. Clinical Features

2.1. The clinical presentations and natural histories of chronic lymphoproliferative disorders are extremely heterogeneous. The annual incidence is approximately 10/100,000 and is increasing in developed countries. Chronic B-cell lymphoproliferative disorders account for more than 90% of lymphoid malignancies with T-cell and NK-cell neoplasms being relatively uncommon.

2.2. Many patients are asymptomatic at the time of first presentation, with the diagnosis being made as an incidental finding after a routine medical examination or blood test, for example, full blood count.

2.3. Patients may present with lymphadenopathy, systemic symptoms such as weight loss, night sweats and fever or the symptoms of anaemia and thrombocytopenia. Enlargement of the spleen and, less frequently, the liver is not uncommon. Patients can also have a monoclonal protein present which can in certain cases lead to the development of hyperviscosity symptoms.

2.4. The definitive diagnosis is made on the characteristic lymphocyte morphology and immunophenotype usually from samples of peripheral blood or lymph nodes. A knowledge of the correct diagnosis is essential to predict outcome and direct therapy in this heterogeneous group of disorders.

2.5. The majority of patients who are diagnosed with chronic lymphoproliferative disorders are elderly (median age 65) and in general they occur more frequently in males (male:female ratio approximately 2:1).

3. Aetiology

3.1. The development of a chronic lymphoproliferative disorder requires a number of distinct but poorly understood transforming events to occur within the affected cells, and the clinical heterogeneity arises from these tumour progenitors being transformed at different stages in the differentiation of the cell.

3.2. Over the last 30 years there have been several classification systems used for chronic lymphoproliferative disease as opinions about the disease have changed and advances in diagnostic techniques have been made. As a result epidemiological studies have tended to assume this heterogeneous group of disorders to be one cohesive pathological entity, which fails to recognise the pathogenic processes that are reflected in the current WHO classification system.[1] Interpretation of epidemiological studies is therefore difficult and may contain artefacts. In addition, some highly significant risk factors may not be evident.

3.3. **Altered immunity**

3.3.1. **Inherited syndromes and susceptibility via individual inherited genetic sequences**. Several studies have suggested a slight excess of cases occurring in blood relatives. There is a range of rare but well defined and usually simply inherited conditions that have an excess of lymphoproliferative disease as part of the syndrome, for example, ataxia telangiectasia, Wiskott-Aldrich syndrome and common variable immunodeficiency. The potential underlying genetic defects in heterozygotes could represent a major initiating cause of a lymphoproliferative disorder although it would be unlikely to be the only step required to manifest the disease in this population.

3.3.2. **Immunodeficiency due to past medical history**. There is a higher risk of developing chronic lymphoproliferative disorders in individuals receiving long-term immunosuppressive drug therapy such as transplant recipients and patients with autoimmune diseases. An increased risk is also seen in patients suffering from a variety of autoimmune conditions, for example, rheumatoid arthritis, Sjögren's syndrome and coeliac disease, independent of immunosuppressive treatments.

3.3.3. **Infections**. Human immunodeficiency virus (HIV), human T-cell lymphotrophic virus type 1 (HTLV-1), human herpes virus-8 (HHV8) and Epstein-Barr virus are all associated with an increased risk of certain types of lymphoproliferative disease, most probably by causing immunosuppression. HTLV is a retrovirus that is endemic in southern Japan and the Caribbean basin. Infection with HTLV-1, especially in early childhood, is strongly related to the development of adult T-cell leukaemia/lymphoma with an estimated cumulative lifetime risk of approximately 5%. HTLV can be transmitted both sexually and by blood transfusion. Unlike HTLV-1, EBV infection is a highly prevalent

infection in the adult population (approximately 90% of individuals in developed countries having evidence of previous infection by the age of 40). The association between EBV and lymphoma is well described for both Burkitt's lymphoma and immunodeficiency-associated lymphoma. Nearly all cases of endemic Burkitt's lymphoma (in Africa) can be shown to contain EBV viral genomic DNA, but the frequency is less than 20% in sporadic cases in developed countries. Natural killer (NK) cell lymphoma is an aggressive and refractory form of lymphoma which is strongly associated with EBV and although rare in the west has a relatively high incidence in south-east Asia. In addition, the Gram negative bacterium, *Helicobacter pylori*, is associated with the development of gastric non-Hodgkin's lymphoma (NHL) of B-cell origin arising from the mucosa-associated lymphoid tissue (MALT).

3.4. **Occupational links**

3.4.1. **Agriculture**. Various occupations related to agriculture have been associated with an excess risk of lymphoproliferative disease leading to suggestions that contact with herbicides, pesticides and solvents could be important determinants of risk.[2] However, results of various studies have not been consistent and no firm biological evidence has been found to support causal links between such substances and lymphoproliferative disorders. It has been clearly demonstrated that veterans of the Vietnam War show an excess of NHL which remains unexplained.[3] Exposure to defoliants has been suggested as a cause but the excess is confined to naval veterans.

3.4.2. **Petrochemical industry**. At least four studies have shown a statistical excess of NHL within the petrochemical industry.[4] However, two cohort studies were negative[5,6] indicating that the risk is likely to be weak or of uncertain significance.

3.4.3. **Other industries**. A wide variety of other industries have been named as having an excess risk of NHL including fire fighters, asbestos exposed workers, nickel refinery workers and those in the wood and building trades. All the risks are either low or based on very small numbers. They have little support from biological studies and are also unsupported by independent studies.

3.5. **Lifestyles and other exposures.** Most studies have shown little statistically significant relationship between NHL and cigarette smoking. There is also only sparse evidence for a relationship with exposure to ionising radiation, amounting to very little risk consequential on the atomic bomb explosions[7] or from diagnostic x-rays.[8] There is little conclusive evidence as regards dietary factors and electromagnetic fields, and attempts to associate residential proximity to industrial sites with an increased risk have not produced convincing results.[9] Suggestions of links to hair dyes have been challenged.[10] There is also no consistent evidence that risk is increased by high exposure to solar ultraviolet light radiation.[11]

4. Prognosis

4.1. It is impossible to generalise regarding the outcome of chronic lymphoproliferative disorders due to the heterogeneity of the group and the different behaviour of each disease entity. Furthermore, within each entity there is a wide variation in potential outcomes, although it can be stated that in the majority of cases survival is measured in terms of years rather than months.

4.2. Many patients do not require any treatment when first diagnosed, with an expectant or "watch and wait" approach employed. In very indolent disease patients may never require treatment for their lymphoproliferative disease and remain asymptomatic during their lifetime. The aims of treatment are to control symptoms or other effects of the tumours.

4.3. Chronic lymphoproliferative disorders are incurable using conventional treatments and tend to run an indolent course with treatment being required when there is symptomatic disease progression. Treatment modalities include chemotherapy and radiotherapy with varying degrees of response and remission. Newer agents, such as monoclonal antibodies, can improve the response rates for some tumours and achieve responses in patients refractory to other forms of chemotherapy.

4.4. The only potential curative treatment for these disorders is through allogeneic haemopoietic stem cell transplantation. However, this approach is only suitable for the minority of younger and fitter patients and is associated with a high mortality and morbidity. Therefore, it is still considered as an experimental treatment in chronic lymphoproliferative disorders and should only be performed in the setting of a well designed clinical trial in younger patients with aggressive or poorer risk disease.

5. Summary

5.1. Chronic lymphoproliferative disorders consist of a group of distinct pathological entities in which there is heterogeneity of clinical behaviour both between and within the different entities.

5.2. Although the molecular basis for the pathogenesis of these disorders is becoming better understood, the aetiology is complex, with causal links unclear in the majority of cases.

5.3. Owing to the indolent nature of these conditions and the wide variation in their behaviour, prognosis is difficult to predict. Treatment is in general intended to control rather than cure the diseases.

6. Related Synopses

7. Glossary

anaemia	A deficiency of red blood cells.
ataxia telangiectasia	A rare genetic disorder in which cells in the body do not have the ability to repair damage to DNA caused by ionising radiation.
Epstein-Barr virus	A common virus that remains dormant in most people. It has the potential to cause B cells to multiply uncontrollably in some patients with weakened immune systems.
heterogeneous	Composed of various cell types.
heterozygotes	Organisms with heterozygous genes (carrying two different alleles of a gene).
Hodgkin's disease	A clonal proliferation of B cells giving rise to a lymphoma characterised by the presence of Reed-Sternberg cells.
hyperviscosity	Excessive blood thickness.
immunophenotype	The expression of markers on a cell which allow it to be more accurately identified.
indolent	Slow in growth or development accompanied by little or no pain.
lymphadenopathy	Disease or swelling of the lymph nodes.
lymphocyte	A type of white blood cell that help the body fight infection.
neoplasm	New abnormal growth of tissue.
pathogenesis	The beginning and development of disease within body tissues.
Sjogren's syndrome	A chronic disease of the body's connective tissue. Characterised by dry eyes, dry mouth, and arthritis.
thrombocytopenia	A condition in which there is an abnormally small number of platelets in the circulating blood.
Wiskott-Aldrich syndrome	A rare X-linked recessive disease characterised by eczema, thrombocytopenia (low platelet counts), immune deficiency, and bloody diarrhoea (due to the low platelet counts).

8. References

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