

From the lab

In this issue -

Professor Peter Browett, Haematologist, University of Auckland, discusses a case of Polymyositis provides an update on Non-Hodgkin's Lymphoma.



Non-Hodgkin's Lymphoma Update

Key Points

- lymphomas are a heterogeneous group of malignancies with variable clinical presentation, response to therapy and prognosis.
- Indolent lymphomas, eg, follicular lymphoma, usually present with slowly progressive lymphadenopathy.
- Aggressive lymphomas, eg, diffuse large B-cell lymphoma, may present with either rapidly enlarging lymph node masses or extranodal disease.
- Diagnosis of lymphoma is made on the basis of a tissue biopsy.
- Therapeutic decisions are based on subtype of lymphoma and stage of disease.

Non-Hodgkin's lymphomas comprise 2 to 3 per cent of all cancers, and in New Zealand are the sixth most commonly diagnosed cancer. They can present in all age groups, although the median age of onset is 60 to 65 years, with a steadily increasing incidence documented over the past three decades. The difficulty for the primary care clinician is that lymphomas are a very diverse group of lymphoid malignancies, leading to significant variability in clinical presentation and approach to therapy.

Risk factors

In most patients, it is not possible to identify environmental or other risk factors that have predisposed to the development of their lymphoma. However, HIV infection is associated with an increased risk of lymphoma, and there is also an increased incidence in patients on long term immunosuppressive therapy following solid organ transplantation. There is also an association with some chronic inflammatory disorders, eg, Sjogren's syndrome, and gastric mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) has been causally linked with *Helicobacter pylori* infection.

Clinical presentation

Although there are many subtypes of non-Hodgkin's lymphoma, the two most commonly diagnosed are follicular lymphoma (approximately 25 per cent of cases), which is an indolent form of the disease, and diffuse large B-cell lymphoma (approximately 30 per cent of cases), which is a high grade or aggressive lymphoma.

Patients with indolent lymphomas usually present with slowly progressive lymphadenopathy which may have been present for several months before the patient is diagnosed. Extranodal involvement and the presence of systemic or B symptoms, eg, fevers, sweats and weight loss, are less common except in the more advanced stages of the disease. Bone marrow involvement is not uncommon at presentation, and this may result in anaemia and cytopenias.

In contrast, the more aggressive lymphomas, of which diffuse large B-cell lymphoma is the most commonly seen, have a much more variable clinical presentation. Many patients present with rapidly enlarging lymphadenopathy, with symptoms related to the site of lymph node enlargement. Twenty to 30 per cent of patients with aggressive lymphoma will present with extranodal disease, common sites of involvement being the gastrointestinal tract, skin, bone marrow, thyroid and central nervous system. Consequently, patients with lymphoma may present with a wide and often unexpected spectrum of symptoms and signs. Systemic symptoms are also more common in patients with aggressive lymphoma, and in rare circumstances fever alone can be the only presenting feature.



Diagnosis

Tissue biopsy and histologic review remain the key investigations in the accurate diagnosis and subtyping of non-Hodgkin's lymphoma. Often this requires review by a pathologist with expertise in Lymphoma, with immunophenotypic, cytogenetic and molecular studies providing valuable supplementary information in some cases.

Fine needle aspiration (FNA) is a useful adjunct in diagnosis of lymphoma and frequently provides additional information on morphology, immunophenotype and molecular genetics of lymphoma cells. An FNA may also be useful in excluding lymphoma or other significant pathology, but on its own is not recommended for the initial diagnosis of lymphoma. Lymphomas are subtyped using the WHO classification for lymphoid malignancies. In addition to morphology, the WHO classification also takes account of immunophenotype, genetic and clinical features. This information helps to guide clinicians in selection of the most appropriate therapy for an individual patient.

Initial evaluation

In New Zealand, patients with newly diagnosed lymphoma are usually referred to a major cancer treatment centre where their management is shared between haematologists, oncologists and radiologists. Because of the complexity of these cases, most centres have multidisciplinary meetings where clinical presentation, pathology, ancillary laboratory investigations and imaging are reviewed before recommendations are made.

Initial staging of a newly diagnosed lymphoma patient includes a careful history and examination, assessment of full blood count, renal and hepatic function, as well as a bone marrow examination in many cases. Serum lactate dehydrogenase and $\beta 2$ microglobulin levels will also be requested as these provide prognostic information. Additional imaging will be undertaken to stage the lymphoma further. This usually includes body CT scanning, but in certain circumstances may also include MRI imaging and in some overseas centres PET scanning. Patients with high risk disease may also require a CSF examination to exclude CNS disease.

Therapy

The indolent lymphomas have a lengthy median survival in the order of eight to 10 years, although at present the majority of these patients are not cured of their disease. Patients who are asymptomatic at diagnosis can be managed with a careful "wait and watch" strategy, with introduction of therapy when they develop symptoms related to disease progression. The optimal approach to more advanced disease is controversial, although recent studies have shown improved response rates, and event-free and overall survival for patients treated with a combination chemotherapy regimen in conjunction with the anti-CD20 monoclonal antibody, rituximab (MabThera). At present, MabThera is only funded for second-line therapy in follicular lymphoma, although this is currently under review. Localised disease may be treated with radiation therapy alone, with current studies exploring the benefit of additional chemotherapy and antibody therapy in this setting.

Aggressive lymphomas, eg, diffuse large B-cell (DLBC) lymphoma, are potentially curable using intensive combination therapy with the most commonly used regimen being CHOP chemotherapy (cyclophosphamide, adriamycin, vincristine and prednisone) combined with MabThera. Patients with localised disease may also benefit from local radiation therapy. Patients with relapsed or refractory lymphoma may be considered for high-dose therapy and autologous stem cell transplantation if they respond to a second line chemotherapy regimen.

Dr Peter Browett

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From the lab

In this issue -

Richard Steele, FRCPA, Immunologist, Wellington Hospital,
discusses a case of Polymyositis



A case of Polymyositis

A 60-year-old woman presents with muscle and joint aches, and gradual onset of weakness, particularly getting up from a chair or climbing stairs. Examination shows symmetrical proximal muscle weakness in upper and lower limbs. Blood tests reveal a positive rheumatoid factor; positive antinuclear antibody (ANA) 1:2560, speckled pattern; creatine kinase (CK) of 2800U/L (reference range 30-180U/L). How would you further investigate this patient?

Based on the clinical and laboratory data presented, this woman has the presumptive diagnosis of polymyositis. There is a significant morbidity and mortality associated with this condition, and therefore all further investigations should be carried out urgently, with the assistance of a specialist with expertise in managing this condition. Depending upon local resources this may include a neurologist, general physician, immunologist or rheumatologist. Delays in treatment may lead to worsening of the weakness and a reduction

in the chances of a good outcome.

It is important when assessing this woman that other forms of muscle disease or possibly neuropathies are considered. These include the following:

- other forms of idiopathic inflammatory myopathy (in particular inclusion body myositis)
- drug-induced myopathies/myositis (including statins, corticosteroids, antimalarials, eg, hydroxychloroquine, antiretrovirals and alcohol)
- other conditions associated with muscle weakness (diabetes, thyroid disease, Cushing's syndrome, other forms of connective tissue disease, eg, SLE, sarcoid pyomyositis, myasthenia gravis, amyotrophic lateral sclerosis, HIV, parasitic disease)
- inherited disease of muscle, including mitochondrial myopathies (MERRF/MELAS), muscular dystrophy and myotonic dystrophy.

A careful history and examination with the information available above should rule out most of these conditions and do not require extensive as well as expensive investigations.

Further investigation of this woman would include inflammatory indices (ESR, CRP), looking for antibodies associated with polymyositis. There are many antibodies associated with polymyositis but the only one that is readily available through New Zealand laboratories is anti-Jo-I antibodies. This is found in only about 30 per cent of patients with this condition.

Jo-I antibodies are associated with a number of clinical features, including interstitial lung disease and Raynaud's phenomenon. The presence of interstitial lung disease is an ominous sign and worsens the prognosis. If other "ENA" antibodies are found, eg, anti-SSa,

anti-SSb, anti-RNP or anti-Sm, it suggests there may be another connective tissue disease, such as MCTD or overlap syndrome. The positive rheumatoid factor and speckled ANA are suggestive this may be the case with this woman.

The definitive diagnosis of polymyositis requires a muscle *biopsy* (possibly guided by MRI or EMG) and the characteristic EMG changes. I would again emphasise the need for early involvement of specialist care.

Dr Richard Steele

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