

## CHAPTER 9 APPROACH TO THE PATIENT

### 9.1 Introduction

Reaching a diagnosis of lymphoma in patients who may present with a varied range of clinical features is often challenging. Patients may have peripheral lymphadenopathy plus or minus splenomegaly, or a constitutional illness characterised by weight loss and fever. Less commonly extranodal lymphoma may involve a specific organ or organs. The approach to diagnosis will clearly vary, depending on the modes of presentation described above. However, once a definitive histologic diagnosis is achieved, the patient enters a common pathway typical of the management of all patients with malignant disease. This involves staging, prognostic assessment, and a treatment plan reflecting either a curative or palliative approach. This required delineation of treatment modalities, which may be surgery, radiotherapy, chemotherapy, biological, or supportive therapy. Often a combination of treatments is used in a multi-modality management approach.

Developing appropriate guidelines for lymphoma is complicated by the wide variability of clinical presentation. Patients may be referred to almost any medical speciality. Therefore, the guidelines need to be recognised across the spectrum of specialities as distinct from a single unit. The accurate workup of patients with lymphomas requires integrating a series of various investigations.

The following issues are discussed in this chapter:

- peripheral lymphadenopathy
- thoracic and intra-abdominal disease
- splenomegaly
- weight loss
- fever
- biopsy
- staging
- multidisciplinary management
- follow up

### 9.2 Peripheral lymphadenopathy

Apart from malignant diseases involving lymph nodes, for example, lymphoma or metastatic tumour, infectious and immunological diseases may cause lymphadenopathy. In general practice, less than 1% of patients who present with peripheral lymphadenopathy actually have malignant disease. Of the patients with benign lymphadenopathy, the majority have non-specific or reactive aetiology requiring few diagnostic tests.

Enlarged intra-abdominal or retroperitoneal nodes are usually malignant. By contrast, intra-thoracic lymphadenopathy in the young can be associated with infectious mononucleosis and sarcoid. However, tuberculosis is a common cause of lymphadenopathy at any site in certain immigrant groups.

Evaluation of patients requires the usual full medical history, physical examination and, in some circumstances, certain laboratory tests. Only a small percentage will require some form of lymph node biopsy.

Over the age of 50 years, the chance of malignant disease as a cause of lymphadenopathy increases. Nodes less than 1 cm in diameter generally reflect benign causes, while a diameter greater than 2 cm serves as a discriminate predicting malignant or granulomatous disease. Tender lymph nodes are

usually benign. Patients can usually be triaged to observation after blood tests for infectious mononucleosis and toxoplasmosis unless there are symptoms and signs of an underlying systemic illness.

Retrospective analysis of various series of patients has led to the development of algorithms to identify patients with peripheral lymphadenopathy who require biopsy. To develop a model to differentiate patients whose biopsy results do not lead to treatment (normal, hyperplastic or benign inflammatory lymph nodes) from those whose biopsy results do lead to treatment (malignant or granulomatous nodes), the medical records and histopathology slides of 123 patients aged 9–25 who underwent biopsies of enlarged peripheral lymph nodes were reviewed for pathological diagnoses. Fifty-eight per cent of patients had biopsy results that did not lead to treatment and 42% had results that did lead to treatment. A predictive model was developed that assigned 95% of the cases to the correct biopsy group, based on lymph node size, history of recent ear, nose and throat (ENT) symptoms, and chest x-ray. When tested prospectively on new patients, the model classified 97% of 33 patients correctly. It was concluded that this simple model could help select adolescents and young adults with peripheral lymphadenopathy for biopsy.

The predictive features for biopsy were lymph nodes greater than 2 cm in diameter and an abnormal chest x-ray while recent ear, nose and throat symptoms had a negative predictive value.<sup>1</sup>

Similarly, in another study, the charts of 249 patients with enlarged lymph nodes were audited to provide a primary care database and to clarify recommendations for evaluation of lymphadenopathy. A firm diagnosis was made in only 36 patients, despite an average of 1.7 visits and two laboratory tests per patient tested. Serious or treatable causes of lymphadenopathy were rare and were always accompanied by clinical conditions that suggested further evaluation. Lymph nodes were biopsied in only 3% of patients. No patient was found to have a prolonged disabling illness without a prompt diagnosis. The data suggest that in patients without associated signs or symptoms, a period of observation is safe and likely to save unnecessary expense in biopsy.<sup>2</sup>

A further study evaluated 220 lymphadenopathy patients. It identified five variables: lymph node size, location (supraclavicular or non-supraclavicular), age (greater or lesser than 40 years), texture (non-hard or hard), and tenderness. Positive predictive values indicating biopsy were found for age >40, supraclavicular location, node size >2.25 cm, hard texture, and lack of pain.<sup>3</sup>

Investigation can follow an algorithm based on patient's age, history and physical findings as described above. Full blood count may provide definitive diagnostic information, as can simple serological studies for EBV, CMV, HIV and other viruses, and so on. It might be obvious that lymph node biopsy is required, for example, lymph nodes over 2 cm in diameter or hard, or in older patients, or if there is doubt delayed for a few weeks. Early biopsy should occur if malignancy is suggested, for example, firm or hard, non-tender cervical lymph nodes, supraclavicular lymphadenopathy or firm lymphadenopathy.<sup>4</sup>

Guideline — Indicator — peripheral lymph node biopsy outcome	Level of evidence	Refs
Predicted indicators for lymph node biopsy are age greater than 40 years, supraclavicular location, node diameter over 2.25 cm, firm-hard texture, and lack of tenderness.	III	1–4

Guideline — Fine-needle aspiration biopsy	Level of evidence	Refs
Fine-needle aspiration (FNA) is generally the biopsy investigation of choice in the initial triage in peripheral lymphadenopathy. It should be accompanied by flow cytometry (FCM) studies.	IV	5–13

In patients suspected of primary head and neck cancer, ENT examination is warranted and any mucosal lesions should be biopsied first. FNA is valuable as a triage procedure in distinguishing between carcinoma and lymphoma. However, an inconclusive or negative report may not exclude lymphoma, therefore excisional lymph node biopsy may be the next step.<sup>14</sup> If the FNA is reported as lymphoma, excision lymph node biopsy is required for definitive diagnosis and subtyping. In some circumstances clinicians may feel that immediate excisional lymph node biopsy should be undertaken as the initial biopsy to expedite the diagnostic process.

Guideline — Definitive tissue biopsy	Level of evidence	Refs
Excisional lymph node biopsy is essential for the primary diagnosis, subtyping and clinical management of lymphoma presenting as peripheral lymphadenopathy.	IV	6, 9, 11, 15–18

In some centres, needle core biopsy has been used in the diagnosis of peripheral lymphadenopathy but this is not generally recommended except for recurrent disease or staging.

Where a lymphoma is suspected, referral to a specialised clinic may be more appropriate than referral to a general surgeon for biopsy. A full blood count prior to biopsy may exclude patients who have, for instance, B-cell chronic lymphocytic leukaemia or other haematological conditions. Cell marker studies should be carried out prior to biopsy if there is a significant lymphocytosis. Similarly, female patients with axillary lymph nodes should have careful breast examination. A chest x-ray prior to biopsy will alert clinicians to the presence or absence of more extensive disease.

In some centres, ultrasound is used to assist in the differential diagnosis of benign and malignant lymphadenopathy, however this still appears to be an investigational approach.<sup>19</sup> As well, some surgeons use intraoperative ultrasound to select the most appropriate node for excisional biopsy.

Guideline — Indicator — minimum investigations before surgical biopsy	Level of evidence	Refs
Full blood count and chest x-ray should be performed before biopsy.	IV	24

### 9.3 Thoracic and intra-abdominal presentations

#### 9.3.1 Mediastinal mass

The differential diagnosis may include sarcoidosis, tuberculosis, metastatic carcinoma and thymoma. Mediastinoscopy with biopsy may be an appropriate approach to biopsy. In some circumstances, bone marrow biopsy prior to the procedure may be appropriate. The rare instances of lymphoma involving lung parenchyma (isolated) may require open thoracotomy and lung biopsy.

### 9.3.2 Abdominal and retroperitoneal lymphadenopathy

As described in the pathology section, an alternative to open biopsy is, in fact, CT-guided core biopsies or laparoscopic lymph node biopsy, depending on the location of the lesions to be biopsied.<sup>20</sup> These issues are discussed in Chapter 4.

## 9.4 Splenomegaly

The presence of an enlarged spleen is easily determined by ultrasonography and is less costly than CT. However, CT does offer the advantage of visualising intra-abdominal lymph nodes, which will be important where lymphoma is suspected. In differential diagnosis, if the patient has associated lymphadenopathy, a lymphoma (or leukaemia, etc.) is likely. Causes of splenomegaly such as the following must be distinguished:

- reticulo-endothelial hypoplasia
- immune hyperplasia
- portal hypertension
- infiltrative disease of spleen (metabolic or benign or malignant cellular infiltrate), and
- extramedullary haemopoiesis

A significantly enlarged spleen, for example, greater than 8 cm below the left costal margin, is usually due to a malignant haematological cause (excluding malaria or kala-azar in the tropics).

Investigation may be more specifically directed after a full blood count and assessment of any apparent underlying systemic illness. Bone marrow biopsy and/or biopsy of any lymphadenopathy may be indicated.

Rarely, splenectomy will be performed for diagnostic purposes where no other site of disease is detected.

## 9.5 Weight loss

In the elderly, common causes of weight loss are depression, malignant disease and benign gastrointestinal disease. By contrast, in younger individuals, diabetes, hypothyroidism, psychiatric disturbance, infection and/or lymphoma need to be considered. Patients with fever and night sweats may have either malignancy or chronic infection. Objective confirmation that weight loss has occurred is important, with a focus on signs or symptoms that are associated with systemic disease that may cause weight loss.

Apart from general routine physical examination, a search for lymphadenopathy and/or splenomegaly should be made. Key laboratory investigations will be a full blood count, serum LDH, ESR, chest x-ray and, where appropriate, CT examination of the abdomen and bone marrow biopsy.

## 9.6 Fever

Careful history taking is necessary in terms of the potential for systemic disease, such as infection, inflammatory disease or malignancy, as well as drug reactions. The physical examination should compliment the history taking as outlined in Section 9.5.

Investigations will depend on clinical manifestations, but should include a full blood count with examination of the film with appropriate biochemistry and cultures. The course of the illness is critical, and either the patient recovers spontaneously or the initial examination leads to a diagnosis. For continued fever, the patient is diagnosed with fever of unknown origin, which requires more

intensive investigation. This may include CT scan of abdomen and chest, and bone marrow biopsy. The role of PET scanning is undergoing investigation in this setting.

The eventual diagnosis of lymphoma depends on a tissue biopsy. Peripheral lymph node excision biopsy is preferable and where there is intra-thoracic/abdominal or solid organ involvement, a radiologically guided core biopsy is frequently adopted. The diagnosis depends on obtaining adequate tissue to evaluate the histology of the tumour and subtype, as well as immunohistochemical and molecular diagnostic information.

## 9.7 Biopsy

Arrangements for an appropriate biopsy should be made with an experienced operator. The use of FNA, core or excision biopsy will depend on the nature and location of the target lesion as discussed in Chapter 8. It is critical that the biopsy be interpreted or reviewed by a pathologist expert in haematopathology. These issues are discussed elsewhere in the guidelines.<sup>21–23</sup>

Guideline — Expert haematopathologist for optimal diagnosis	Level of evidence	Refs
The biopsy should be reviewed by pathologist who is a recognised expert in haematopathology.	III	14, 20, 21

## 9.8 Staging

A synthesis of the information developed from the multidisciplinary approach described above allows identification of sites of disease, and from this, prognosis and a treatment approach. The Ann Arbor staging description is described in Section 11.7 and is applicable both to Hodgkin lymphoma and to the other varieties of lymphoma.

## 9.9 Multidisciplinary management

It is critical that centres develop an appropriate multidisciplinary team, in particular to correlate the investigative techniques — including histopathological, molecular and imaging information — with the clinical data. The various sub-specialities, especially medical/haematological oncology in conjunction with radiotherapeutic and surgical specialists, need to be familiar with the management protocols and guidelines.

Once a diagnosis of lymphoma is made, the patient should be managed in a multidisciplinary collaboration between the haemato-oncologist, radiotherapists, and other members of the medical team as required. After diagnosis, the next step is to determine disease extent by suitable staging. This will allow appropriate determinations of prognosis when the lymphoma subtype, clinical stage, serum LDH, presence or absence of constitutional features, performance status, and so on, can be assessed.

At this point, a treatment plan can be made in conjunction with the patient's informed views, with the aims of treatments defined in terms of potentially curative treatment or a palliative management plan. Apart from the adoption of appropriate defined protocols for management of the specific lymphoma subtypes and stages, the haemato-oncologist should be prepared to manage complications of both the disease and its treatments, and the various psychosocial problems that may be associated with such severe disease. The need for long-term follow up and the potential for late complications of treatment need to be recognised and discussed with the patient. In patients who have advanced disease where specific anti-lymphoma therapy is inadequate, appropriate supportive and symptomatic and palliative care measures need to be organised.<sup>24,25</sup>

Guideline — Best practice in multidisciplinary care	Level of evidence	Refs
Patients should be managed in a multidisciplinary clinic or setting.	IV	24, 25

### 9.10 Follow up

The need for long-term follow up should be recognised, particularly for patients with potentially ‘curable’ disease. This may best be the responsibility of one particular member of the multidisciplinary team. The follow-up program should encompass appropriate detection of (a) current or relapsed disease, and (b) long-term side effects of therapy.

In addition, it is appropriate to arrange general care by a general practitioner/family doctor to cope with other medical issues that the patient, progressively ageing, will encounter. This could include appropriate screening for other diseases such as breast and bowel cancer, and diabetes. Such patients often concentrate on their original disease, not appreciating that as the years pass, they are increasingly vulnerable to other medical problems.

For patients with relapsed or progressive disease that is not responding to appropriate anti-lymphoma therapy (chemotherapy, biologic modifiers, radiation, etc.), standard symptom control and palliative care measures are appropriate. These are generally not specific to lymphoma and are described in other papers and texts.

### 9.11 References

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