Hi Doc,
I Have Lumps On My Neck

Dr Lee Yuh Shan
Senior Consultant
Haematology

Dr Thomas Ho
General Surgeon
Oncology

Diffuse Large B-cell Lymphoma (DLBCL) is an aggressive type of non-Hodgkin lymphoma that affects B-lymphocytes, a type of blood cell that produces antibodies to ward off infections. Previously known as a single disease entity, recent understanding has shown how DLBCL can be further divided into different molecular subtypes which have different prognosis and treatment outcomes.

In Parkway Cancer Centre's "Hi Doc, I have lumps on my neck" webinar from the "Hi Doc" Continuing Medical Education (CME) Empowerment Series, Dr Lee Yuh Shan, Senior Consultant, Haematology from Parkway Cancer Centre discussed the classification of DLBCL subtypes and how these different subtypes influence prognosis and treatment outcomes. This was preceded by a presentation by Dr Thomas Ho, General Surgeon and Surgical Oncology at Gleneagles Hospital and Mount Alvernia Hospital on a clinical approach to patients with neck lumps.

An evaluation of neck lumps

Dr Ho began the CME webinar by highlighting that lumps can occur anywhere in the neck, attributing them to congenital, inflammatory or neoplastic causes.

He reminded participants of the main causes of lymphadenopathy, emphasising that large lymph nodes can provide an underlying pathology. He expanded on this further by breaking down the evaluation of neck masses into three simple steps:

Step 1 – History and examination

A history and examination of the neck lump can be carried out by looking at the following:

- Duration and growth of the lump
- Patient's symptoms – local or constitutional
- Location of the lump
- Whether the lump is solitary or hidden and unilateral or bilateral
- The lump's fixity, tenderness and consistency

Step 2 – Ultrasound and nasendoscopy to evaluate the lump

Step 3 – Fine needle aspiration and excisional biopsy

This step is critical as this allows doctors to differentiate a cystic mass from an inflammatory mass, and a benign mass from a malignant one.

These three steps form the typical diagnosis process for patients presenting with neck lumps. However, Dr Ho shared that recent developments in cancer care has allowed for a one-stop solution that allows steps 1–3 to be carried out in a single instance, offering patients results in 2–3 days.

Differential diagnosis for common neck masses

Dr Ho ended his talk by highlighting the differential diagnosis for congenital, inflammatory and neoplastic masses.

Congenital masses are lumps occurring in childhood that become evident only in young adulthood or later on. Dr Ho warned against mistaking congenital masses such as branchial cleft cysts for abscesses, sharing that branchial cleft cysts usually occur because of the failure of the pharyngo-branchial ducts. These cysts typically present when the cyst becomes infected, usually after an upper respiratory tract infection. It can be identified as a tender inflammatory mass in the anterior triangle of the neck.

Dr Ho also highlighted the important differential diagnosis of thyroglossal duct cysts that may not always arise in the midline, particularly with infrahyoid cysts which tend to be pulled to the side rather than the midline. Typically, this cyst elevates with tongue protrusion.

Lymphangioma and haemangioma both present as smooth, compressible lumps in the neck. While lymphangioma can be transilluminated, haemangioma can be differentiated by superficial veins and vessels presenting in red- or bluish-coloured masses.

Inflammatory masses can be either acute or chronic. An acute presentation of submandibular abscess, for instance, may require a simple incision and drainage, while more chronic cases of enlarged, solitary lymph nodes are usually reactive and tend to go away after a few weeks.

For persistent cases, Dr Ho advised doctors to investigate further with fine needle aspiration and imaging. He also stressed the importance of considering immunosuppression in the case of younger patients, and lymphoma in the case of older patients.

Finally, Dr Ho touched on neoplastic lumps which can be either benign or malignant. In the case of malignant masses, he emphasised the importance of knowing where the primary site is as these can typically be metastatic lesions to the neck from squamous cell carcinoma (SCC). He then highlighted how SCC can be identified by red, fully-defined nodules with ulcerated surfaces, while basal cell carcinoma (BCC) can be identified by pink, translucent nodules with rogue edges over sun-exposed areas.

He also shared how to identify benign lumps such as sebaceous cysts and epidermis cysts, which are characterised by punctum and cheesy contents. These sometimes present with infections, redness and swelling. He then shared on lipomas, which are asymptomatic ill-defined small masses which can be identified by pushing them to the side and watching the nodule move slightly away.

Importance of evaluative tests in differential diagnoses

Dr Ho finished his presentation by sharing other head and neck neoplasms and emphasising the importance of evaluative tests to differentiate diagnoses.

The case of a parotid mass, for instance, highlighted the importance of appreciating nodules occurring in the region that can be from the parotid. A separate case of a mass arising from the tail of the parotid showed that it is important to differentiate this from a level 2 cervical lymph node as they both occur at the same site.

Another example of submandibular tumour that can mimic solitary lymph nodes highlighted the importance of ultrasound and fine needle aspiration to differentiate it from a lymph node mass.

Dr Ho then also shared the case of a patient presenting with a large nodal mass arising from thyroid cancer. Finally, he shared the important differential diagnosis of a less common mass arising in upper lateral neck called carotid body tumour. Though usually pulsatile, this case was firm, slightly mobile and non-pulsatile. It was only with an ultrasound that he was able to identify that the mass arose from the bifurcation of the carotid artery.

DLBCL – diagnosis and prognosis

Dr Lee followed up on Dr Ho's presentation with a presentation on DLBCL. He shared that the most common cause of neck lymph nodes is lymphoma, with DLBCL being the most common lymphoma amongst adults.

In general, DLBCL can be divided based on immunohistochemistry and cell of origin (COO); anatomical site of disease; underlying chronic condition of patients; the intermediate zone between two different subtypes of closely related DLBCL; and genetic profile for few special subtypes of DLBCL.

Dr Lee highlighted the investigations required for DLBCL diagnosis, which include tests such as:

- Full blood count
- Renal and liver panel
- Calcium phosphate
- Uric acid
- Lactate dehydrogenase
- Chest X-rays or electrocardiogram
- PET-CT or CT scan
- Bone marrow study
- Viral screening for hepatitis B/C and HIV

Dr Lee then shared how to prognosticate the outcomes of DLBCL using the International Prognostic Index (IPI), which considers age, lactate dehydrogenase levels, performance status, clinical stages and extranodal involvement. These indicators help classify the patient into different groups to predict prognostic outcomes.

Classifying DLBCL subtypess

However, genetic mutation can affect prognostic outcomes. Dr Lee demonstrated how gene expression profiling (GEP) by COO can help differentiate DLBCL into at least 3 subtypes based on genetic mutations: germinal centre B-cell (GCB), activated B cell (ABC) and Type 3.

However, GEP is costly and not widely available. In response to this, Dr Lee shared a way to make genetic classification more clinically-friendly using enhanced Hans algorithms. Here, pathologists can use a few markers such as CD10, BCL-6 and MUM1 to subdivide DLBCL into at least GCB or ABC subtypes based on immunohistochemistry.

Dr Lee stressed the importance of identifying subtypes as GCB subtypes have better outcomes while non-GCB subtypes have less favourable outcomes.

Dr Lee then shared how next generation sequencing (NGS) allows DLBCL to be divided into further subtypes, mainly MCD, N1, BN2 and EZB, each demonstrating different outcomes in terms of disease control and overall survival.

Other DLBCL subtypes

In his presentation, Dr Lee also shared more about other DLBCL subtypes such as central nervous system (CNS) lymphoma - one of the most common CNS tumour in adults. CNS lymphoma is aggressive with poor outcomes when using conventional chemotherapy due to poor CNS penetration. As most CNS lymphoma is of the ABC subtype, outcomes are also poorer. Recent treatment approaches for CNS lymphoma use CNS-penetrating chemotherapy followed by autologous stem cell transplant.

He also shared about patients who present with mediastinal nodes called primary mediastinal B-cell lymphoma (PMBL). He highlighted how PMBL gene expression is more related to nodular sclerosing Hodgkin lymphoma. However, outcomes are favourable with intensive immuno-chemotherapy.

Treatment for newly diagnosed DLBCL

Dr Lee shared that newly diagnosed DLBCL can be treated by the R CHOP or R EPOCH approach:

R CHOP	R EPOCH
R - Rituximab (antibody)	R - Rituximab (antibody)
C - Cyclophosphamide	E - Etoposide (infusion)
H - Doxorubicin	P - Prednisolone
O - Vincristine	O - Vincristine (infusion)
P - Prednisolone	C - Cyclophosphamide
	H - Doxorubicin (infusion)

Though there is generally no difference in the two approaches, Dr Lee advised that R EPOCH should be used in PMBL and double hit lymphoma (DHL) for these highly aggressive lymphoma.

Double Hit Lymphoma

DHL is the most aggressive form of GCB DLBCL. Dr Lee shared that GCB DLBCL has better prognosis than ABC DLBCL in general. However in DHL, genetic mutation of cMYC with either BCL2 or BCL6 mutations make this disease highly aggressive.

He emphasised the need to do interphase fluorescence in situ hybridisation (FISH) study in cases of GCB DLBCL with BCL2 or BCL6 mutations to confirm the translocation of these mutations, and shares that dose-adjusted R EPOCH gives the best treatment outcome for such cases.

In a case study of a patient with CD10+ GCB subtype, BCL2 expression, Ki-67 of 60-90% and cMYC, Dr Lee shared how a FISH study carried out confirmed the translocation of cMYC and BCL2 mutations, allowing him to conclude DHL in the patient. Dr Lee highlighted that without a good diagnosis, the patient would have been treated with R CHOP without good outcomes. With R EPOCH, the patient has been in remission for 5 years and counting.

Impact of COO on treatment and treatment outcomes

Does understanding of COO help with treatment? Dr Lee responds by sharing that clinical trials that have been conducted did not show benefit of additional treatment and that the search for better treatment continues.

On whether treatment can be tailored based on COO, Dr Lee shared that response for ibrutinib targeted agents can be predominantly seen in ABC subtypes of DLBCL. However, he noted patients who cannot complete the treatment because of side effects, especially in the elderly. He highlighted that for younger patients under 60 years, additional ibrutinib helps improve disease control and overall survival, but he emphasised that it is crucial to ensure the patient is fit enough for treatment.

Dr Lee also shared how different DLBCL subtypes responded to salvage treatment in relapsed or refractory settings with additional targeted agents. He showed that while R-ICE chemotherapy regime resulted in no difference for GCB and non-GCB subtypes, GCB subtypes were more sensitive to salvage treatment using R-DHAP compared to non-GCB subtypes. This showed that COO is still important in relapsed or refractory settings.

He then wrapped up the section by sharing about targeted treatment for DHL, as well as targeted agents for primary testicular lymphoma (PTL) and Epstein Barr virus primary CNS lymphoma (EBV-PCNSL).

In summary

To summarise his presentation, Dr Lee reminded participants that DLBCL is the most common lymphoma in adults, with at least three subtypes based on immunohistochemistry and further subtypes based on next generation sequencing. Each have different predicted outcomes.

He then reminded participants that although the backbone of chemotherapy is with R CHOP, certain subtypes require R EPOCH for better outcomes. He then ended off his presentation by emphasising that DLBCL by COO or recurrent mutation may change how we treat DLBCL both in newly diagnosed and relapsed settings in future.

PCC
PARKWAY CANCER CENTRE

CANHOPE REGIONAL OFFICES

SINGAPORE (HEAD OFFICE)
Singapore: enquiry@canhope.org

BANGLADESH
Dhaka: dhaka@canhope.org

CHINA
Beijing: beijing@canhope.org

INDIA
New Delhi: newdelhi@canhope.org

INDONESIA
Jakarta: jakarta@canhope.org
Bandung: bandung@canhope.org
Medan: medan@canhope.org
Semarang: semarang@canhope.org
Solo: solo@canhope.org
Surabaya: surabaya@canhope.org
Yogyakarta: yogyakarta@canhope.org

MALAYSIA
Johor Bahru: jb@canhope.org
Kuching, Sarawak: kuching@canhope.org
Kota Kinabalu, Sabah: kk@canhope.org

MYANMAR
Yangon: yangon@canhope.org
Mandalay: mandalay@canhope.org

PHILIPPINES
Manila: manila@canhope.org

SRI LANKA
Colombo: colombo@canhope.org

VIETNAM
Ho Chi Minh: hcmc@canhope.org
Hanoi: hanoi@canhope.org

(65) 6738 9333
www.parkwaycancercentre.com
Parkway Cancer Centre