Adelaide Small Biopsy Course

Haematolymphoid Pathology
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Small biopsies for Lymphoma Diagnosis

• Are they a good idea?

• WHO classification utilises:
  – clinical findings
  – morphology (cytology and architecture)
  – phenotype
  – genetics and molecular testing
Small biopsies for Lymphoma Diagnosis

• Are they a good idea?

• Radiologically guided core biopsies are quicker, cheaper and safer – so are here to stay

• As pathologists we need to gain maximum information from minimal material – but know when to say ‘Not diagnostic’.
Clinical notes: ? MCD

Sometimes, it is best to politely decline...
My Approach

• Is the biopsy sufficient for further workup?
  – History / other findings
  – What is the cell size?
  – What is the cell morphology?
  – Is there a specific architecture?

• This information guides ICC panel
My Approach

• Targeted Panels:
  – Lymphoma of small cell morphology
  – Lymphoma of intermediate or large cell morphology
  – Hodgkin panel
  – Additional T cell panel
Small cell panel

- CD3, CD5
- CD10, CD20, BCL6
- CD 21/35, CD 23
- BCL2
- CyclinD1
- Ki67
Large Cell Panel

- CD3, CD5
- CD10, CD20, BCL6
- CD 21/35
- BCL2
- CD 30
- CyclinD1
- c-myc, Ki67, MUM-1, EBV ISH
T cell panel

• It’s complicated!
  – Add pan-T markers to large cell panel
  – Cytotoxic markers
  – CD 56
  – BF1
  – PD-1, ICOS
  – Others as targeted
Hodgkin Panel

- CD 15, CD 30, CD 45
- CD 3, CD 20
- PAX 5
- EBV ISH
- Others as required
Case 1

Case 1
Case 1

BCL2

Ki67
Diagnosis

• Low grade follicular lymphoma
• (WHO grade 1-2 of 3)

– Morphology
  • Follicles lacking polarity and mantle
  • Small centrocyte like cells with few centroblasts
Case 1

• Low grade follicular lymphoma

  – Phenotype
    • CD 20, CD 10, BCL6, BCL2 positive
    • CD 21/35 and CD 23 positive FDC networks
    • Proliferation rate usually < 40%
    • Flow cytometry shows light chain restriction

  – Genetics
    • t(14;18) (BCL2)
Case 1

• FL grading
  – < 15 centroblasts / HPF – low grade
  – > 15 centroblasts / HPF = grade 3
    • 3a – centrocytes (small cells) present
    • 3b – centroblasts only

• *CD 20 immuno is a good way to identify if small B-cells are still present
Case 2

• 55 year old male. Lymphadenopathy. Previous FNA = NHL.
Case 2
Case 2
Case 2

CD 20

Cyclin D1
Case 2

SOX 11
Diagnosis

• Mantle cell lymphoma

  – Morphology
    • Architecture diffuse, mantle zone, nodular, other
    • Small centrocyte like cells, monomorphic
    • Large cell or blast morphology in pleomorphic variant
Case 2

• Mantle cell lymphoma
  – Phenotype
    • CD 20, CD 5, Cyclin d1, SOX11 positive
    • FMC7+, CD 200– on flow
  – Genetics
    • t (11;14) (cyclind1 / BCL1)
Case 2

• DDx
  – CLL/SLL
    • Small round lymphocytes, para-immunoblasts or proliferation centres frequent
    • CD 20, CD 5, CD 23, CD 200 positive
    • Cyclin d1, SOX11, FMC7 negative
    • Lacks t(11;14)
  – ‘Atypical CLL’ can be a dilemma
Case 3

• 50 year old male. ? Helicobacter gastritis.
Case 3

• Diagnosis:
  – Extranodal marginal zone lymphoma (MALT)

  – Morphology
    • Expansile/destructive mixed infiltrate including monocytoid B-cells and plasma cells
Case 3

• Phenotype
  – CD 20+, BCL2 over expressed, expanded and disrupted FDC networks
  – No other specific markers
  – Plasma cells frequently light chain restricted

• Frequently associated with chronic inflammation (eg H pylori gastritis)
Case 3

• Genetics
  – Multiple translocations including;
    • t(11;18), t(1;14), t(14;18) (MALT1), t(3;14)
Case 4

- 3 months tender subcutaneous nodules
- RUQ pain
- Gallstones
- On warfarin for atrial flutter, previous TIA + carotid endarterectomy
- Elevated amylase, lipase, CRP
- Ultrasound of SC nodule: fat necrosis
Gram, PAS-D, ZN – no organisms
Case 4

- Initial diagnosis: pancreatitis associated fat necrosis
- Actinomyces on micro – treated
- Ongoing raised CRP
- LDH continued to rise > 1000
- PET scan performed
Aorto-caval
Para-aortic
Retroperitoneal
Left Adrenal
(Lung)
Case 4

• “We think the patient has lymphoma. Could you please review the histology?”. 
Intravascular large B-cell lymphoma

- Classified as a variant of DLBCL in the 2017 WHO
- (Generally) extranodal large B-cell lymphoma characterised by preferential growth of lymphoma cells within vessels, particularly capillaries
- Larger vessels and arteries not involved
Intravascular large B-cell lymphoma

- Usually widely disseminated at presentation, but false negative staging (and biopsies) are common due to the usual lack of a tumour mass
- Lymph nodes may be involved in up to 15%
Intravascular large B-cell lymphoma

- Cells are large, have prominent nucleoli, and mitotic figures are common
- CD 20 positive, with frequent CD 5 (38%) and occasional CD 10 (13%).
- Majority non-germinal centre phenotype
- EBV, ALK negative
Intravascular large B-cell lymphoma

- Traditionally regarded as a very poor prognosis disease
- This is likely due to delayed diagnosis (i.e., frequently at autopsy in the past).
- With timely diagnosis and treatment, 3 year survival is now 60–81%.
- This patient is alive and disease free on follow up biopsies
Intravascular large B-cell lymphoma
Intravascular large B-cell lymphoma
Intravascular large B-cell lymphoma
Case 5

- Case 5. 73 year old female. Left neck ? lymphoma.
Case 5
Case 5
Case 5

CD 20

CD 10
Case 5

BCL2

c-myc
Case 5

• FISH
  – Re-arrangement of c-myc, BCL2 and BCL6

C-myc dual colour break-apart FISH
Case 5

• Diagnosis:
  – ‘High grade B-cell lymphoma with myc and BCL2 and/or BCL6 rearrangements’
  – Usually referred to as ‘double hit’ or ‘triple hit’ lymphoma
Prognostic work up of DLBCL and friends

- DLBCL has historically not represented a disease entity, rather a grouping of aggressive B-cell NHL
- Prognosis as a result has been very variable, as has response to treatment
- Efforts have concentrated on stratifying DLBCL into prognostic and treatment responsive categories
DLBCL prognosis
DLBCL Prognosis

- Gene expression profiling identified better prognosis disease (Germinal centre phenotype) and poor prognosis disease (activated B-cell type and ‘other/unclassifiable’)

- Not suitable for day to day diagnostic work up
DLBCL Prognosis – Hans Algorithm
DLBCL prognosis

• There are reproducibility issues, but the Hans algorithm cell of origin method has become a standard to stratify DLBCL into germinal centre phenotype (better prognosis) and non-germinal centre phenotype (poorer prognosis)

• But - a subset of GCB type DLBCL was then identified with a dismal prognosis
The ‘double hit’

• Many of these poor prognosis GCB type DLBCL were noted on FISH to have re-arrangements of c-myc, BCL2 and/or BCL6, and were coined ‘double hit’ or ‘triple hit’ lymphoma

• To avoid FISH on every aggressive B-cell lymphoma, ICC has been adopted as triage
ICC triage in DLBCL

- (Almost) all double hit lymphomas are GCB type
- (Almost) all double hit lymphomas show >40% c-myc expression (ICC)
ICC triage in DLBCL

• So:
  – FISH on all aggressive B-cell lymphoma?
  – FISH on GCB type?
  – FISH on >40% c-myc ICC
  – FISH on GCB type with >40% c-myc ICC
    • All except the first risk occasional false negatives
    • Our approach is to FISH >40% c-myc ICC, if under 70
Finally – ICC double expressor

- It has also been noted that DLBCL with >50% BCL2 expression and > 40% c-myc expression (ICC) have an intermediate prognosis between ‘double hit’ and other DLBCL
- Most double hit lymphomas are double expressor, but most double expressor lymphomas are not double hit...
Case 6

- 55 year old male. Prior Allogeneic SCT, possible GvHD, also has EBV viraemia. Pan colitis with occasional raised areas that have adherent blood clots. Please assess for viral inclusion bodies and evidence of GvHd. Random colon biopsies.
Case 6
Case 6

CD 20

CD 79a

CD 3

PAX 5
Case 6

CD 30

EBV ISH
Case 6

- **Diagnosis:**
  - EBV associated DLBCL (monomorphic PTLD)

- **DDx:**
  - EBV positive mucocutaneous ulcer
    - Localised circumscribed ulceration without systemic disease
    - This patient was found to have widespread nodal and extranodal disease on PET
Case 6

• PTLD
  – Non destructive:
    • Plasmacytic hyperplasia, infectious mononucleosis, follicular hyperplasia
  – Polymorphic PTLD
    • Heterogenous population which effaces the architecture but does not meet the criteria for a specific lymphoma
Case 6

• PTLD
  – Monomorphic PTLD
    • Fulfil criteria for a specific B, plasma cell or T cell neoplasm
  – Classic Hodgkin lymphoma
Case 6

• This patient was treated with Rituximab, then recruited into a clinical trial of anti-EBV cytotoxic T lymphocytes with excellent (but incomplete) response
Case 7

• 61 year old female. Lymphadenopathy. Systemically unwell.
Case 7
Case 7
Case 7
Case 7

Ki67

c-myc
Case 7

• Diagnosis:
  – T-cell/ histiocyte rich large B-cell lymphoma
  – Subtype of DLBCL

• Usually presents with high stage disease, B-symptoms, and has a poor prognosis
Case 8

- 63 year old male. ? transformation of CTCL.
Case 8
Case 8

CD 3

CD 4

CD 8

CD 7
Mycosis fungoides

• Clinical features are essential to the diagnosis
  – Progressive patches, plaques and eventually tumours, frequently on sun protected skin
Mycosis Fungoides

• Morphology
  – Initially subtle; band like infiltrate with mildly atypical small to medium lymphocytes showing epidermotropism
  – alignment along the basal epidermis with ‘haloing’
  – Pautrier microabcesses lovely but not that common
Mycosis fungoides

• Morphology
  – Large cell transformation defined as presence of > 25% large cells
  – May or may not be CD 30 positive
Mycosis fungoides
Mycosis fungoides

- Initial diagnosis frequently takes:
  - Multiple biopsies over a significant time frame
  - Clinical correlation
  - PCR for TCR gene rearrangements from several sites / times showing the same monoclonal band

- Little is lost clinically by this delay (currently)
Case 9

• 61 year old male. Suspected lymphoma, 2 weeks history of fever, night sweats, worsening lymphadenopathy proven radiologically and pancytopenia.
Case 9
Case 9

CD 3

CD 2

CD 30

Granzyme B
Case 9

ALK
Case 9

• Diagnosis:
  – Anaplastic large cell lymphoma, ALK negative
  – CD30+ PTCL with typical morphology and CD4+ cytotoxic phenotype

• ALK+ ALCL usually presents in younger people, and has a better prognosis; ALK negative still has a better prognosis than PTCL NOS
Case 10

• 28 year old female. Incisional biopsy left arm and back. Subcutaneous diffuse nodules left arm, right breast, lower back, right facial swelling. ?Fat necrosis/ Dercum disease/ Lipoma. Subcutaneous lump. Multiple subcutaneous large, firm lumps of unclear origin. Associated with malaise and headaches with fevers. Diagnostic dilemma.
Dercum Disease?

• Adiposis dolorosa, also known as Dercum disease or Anders disease, is a rare condition characterized by generalized obesity and fatty tumors in the adipose tissue. The tumours are normally painful and found in multiples on the extremities.

• Dercum disease was first described at Jefferson Medical College by neurologist Francis Xavier Dercum in 1892.

• Wikipedia
Francis Xavier Dercum
Case 10
Case 10
Case 10

CD 3

CD 8
Case 10

Granzyme B

BF-1
Case 10

• Diagnosis:
  – Subcutaneous panniculitis-like T-cell lymphoma

• Alpha/beta subtype PTCL presenting as subcutaneous infiltrates

• Prognosis is good relative to other PTCL
SPTCL

- **Morphology:**
  - Medium to large hyperchromatic cells ring individual adipocytes, histiocytes in background

- **Phenotype:**
  - CD 3, CD 8, BF1, cytotoxic marker positive
SPTCL

• DDx
  – Lupus panniculitis
    • Polymorphous infiltrate including B-cells
  – Primary cutaneous gamma delta T-cell lymphoma
    • Often involves dermis
    • CD 56, TCRgamma/delta, cytotoxic marker positive
    • BF1 negative, frequently double negative (CD4-/8-)

Case 11

• 31 year old male. Left neck node. ? TB.
Case 11

PAX 5

CD 20
Case 11

• Diagnosis:
  – Classical Hodgkin lymphoma
Hodgkin Lymphoma

• Hodgkin Reed Sternberg Cells
  – Classic (at least two nuclei / lobes with prominent eosinophilic nucleoli)
  – Mononuclear
  – Mummified (pyknotic nuclei)
  – Lacunar (surrounding retraction, common in NS)
  – Popcorn (multilobate, vesicular, common in NLPHL)
HRS cells
“My brain can’t deal with this. Let’s get something to eat”