Trainees’ session
AUTOPSY HISTOPATHOLOGY

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It’s all experience....and thinking

• No standard textbook
  – Online instead?
• No curriculum
• Autopsy practice encompasses ALL Medicine
  – ie every subspeciality
• Training opportunities variable+
• Can only see a small case mix prior to exams
• Learn on the job thereafter
4 generic histopathologies

1. what is the histopathology?
   - Is there a differential diagnosis?

2. What is the range of known causes of this?

3. In this particular case, which one most likely?

4. What other organ pathologies and/or tests would you want to confirm the diagnosis?
Case 1 – bone marrow

- 34 yr old Philippino nurse in UK
- No previous medical history
- Presented with ‘flu & vomiting.
- Rx Abx
- Then SOB and abdominal pain
- Became pancytopaenic
- H1N1 & legionella excluded
- D6 - ?septic shock, multi-organ failure
- Death – coronial autopsy
Case 1

- Blood cultures negative
- H1N1 – swab -ve
- Legionella - urine –ve

= severe sepsis but no focus of infection identified

- Autopsy
  - Major organs all grossly normal
  - Mediastinal nodes – mildly enlarged

- SLIDE: lumbar marrow
- H&E
- IHC [which antibody?]
Case 1

- Is the bone marrow?:
  1. Normal
  2. Leukaemia/lymphoma
  3. Obviously infected [visible agent]
  4. Hypercellular
  5. Haemophagocytic
  6. Hypocellular
Case 1

- Is the bone marrow?
  1. Normal
  2. Leukaemia/lymphoma
  3. Obviously infected [visible agent]
  4. Hypercellular
  5. Haemophagocytic
  6. Hypocellular

CD68 (PGM1) IHC
More macrophages
Larger
Gobbling up cells and nuclei
Normal CD68 in marrow
4 generic histopathologies

1. what is the histopathology?
2. haemophagocytosis
   - Is there a differential diagnosis? NO
3. What is the range of known causes of this?
   - Why does it happen?
4. In this particular case, which one most likely?
5. What other organ pathologies and/or tests would you want to confirm the diagnosis?
Haemophagocytosis

• Cytokine driven
• Macrophages in marrow, nodes, spleen etc engulf
  – Red blood cells
  – Neutrophils
  – Lymphocytes
  – Platelets

• Pan-cytopaenia
Haemophagocytic syndrome pathogenesis

- EBV infection with monoclonal T-lymphocyte expansion
- Sepsis or infection with intracellular organisms
- Apoptosis and end-organ damage
- Fever

- TNF-α
- sFasL
- IL-1
- TNF-α
- IFN-γ
- IL-1
- IL-6
- IL-18
- IL-2

- Hemophagocytosis with pancytopenia
HPS in bone marrow
Haemophagocytic syndrome

aka Haemophagocytic lymphohistiocytosis (HLH)

• 1979 first description
• Aetiology
  Familial - paediatric
  Secondary
  – Lymphomas – B & T
  – Infections – EBV, TB, HIV, leish, influenza, *bacterial sepsis*
  – Autoimmune disease
  – Heat stroke
  – etc
• High mortality
Hilar node 1
Hilar node 1 – grocott stain

• ?
Hilar node 1

- *Histoplasma capsulatum*
Hilar node 2

CD3
Diagnosis

• MOF
• Cytokine storm
• T-cell lymphoma – occult, not mass lesion
• Histoplasmosis – latent & irrelevant
Case 1 message

Small volume pathology can trigger big events, through cytokine amplification.

Systemic inflammatory response syndrome (SIRS)
Two similar cases – “MOF/sepsis”

**F 24yrs**
- Phillipino nurse
- No medical history
- Unwell, abdo pain
- Progress to MOF
  - Liver
  - Lung
  - Kidney
- All imaging negative
- All microbiology negative
- Died on D8 of admission
- AUTOPSY – ENLARGED NODES IN MEDIASTINUM

**F 30yrs**
- African
- Recurrent joint pains – hands and knees
- Skin rash
- Seronegative for RhF etc
- Similar history to other..
- Died on D14 admission
- AUTOPSY- GROSSLY NEGATIVE
Diagnosis – f30yr

- Haemophagocytosis
- No lymphoma
- No sepsis

- ?
Diagnosis – f30yr

<table>
<thead>
<tr>
<th>Haemophagocytosis</th>
<th>DIFFERENTIAL DIAGNOsis OF MOF/SYSTEMIC SEPTIC SHOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymphoma</td>
<td>Sepsis</td>
</tr>
<tr>
<td>No sepsis</td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

? 

Vasculitis

Auto-immune disease
Diagnosis – f30yr

- Haemophagocytosis
- No lymphoma
- No sepsis
- ?
- Adult-onset Still’s disease [serogenative]
- Can trigger fatal cytokine storm
- Mimicking septic shock

DIFFERENTIAL DIAGNOSES OF MOF/SYSTEMIC SEPTIC SHOCK

- Sepsis
- Lymphoma
- Vasculitis
- Auto-immune disease
SIRS: Lung CD54 (ICAM-1) - upregulated by TNFa & HMGBP-1

‘Endothelial cell up-regulation = septic shock’ etc

M. Tsokos
Case 1 message

HPS in bone marrow can point to a range of critical pathogeneses.

If absent, probably no cytokine storm happening
Questions?
Case 2 - kidney

- 29 yr old female
- Pregnant to term. Discharged home
- D2 after normal VD – became ill
- Confusion and progressive renal failure
- D9 cardiac arrest
Case 2

- Relevant pre-mortem lab data
- Platelet count dropped
- Final = 10

- Autopsy
- Blotchy heart
- Kidneys looked normal
- Nil else to abnormal
4 generic histopathologies

1. what is the histopathology?
   - Is there a differential diagnosis? YES

2. What is the range of known causes of this?

3. In this particular case, which one most likely?

4. What other organ pathologies and/or tests would you want to confirm the diagnosis?
DD

• DIC
• Disseminated intravascular coagulation

• TTP
• Thrombotic thrombocytopenic purpura
Thrombotic microangiopathy (TMA)

- *Over-arching term*

- FIBRIN > platelets = disseminated intravascular coagulation (DIC)

- *Clotting factors abnormal*

- PLATELETS > fibrin = thrombotic thrombocytopenic purpura (TTP)

- *Clotting factors normal*
Case 2 - Kidney

CD61+ = platelets

Fibrin -ve
Disseminated intravascular coagulation (DIC)

- Most frequently seen in
  - Meningococcal infection
  - Strep pyogenes (group A)

- Fibrin & PLTs
DIC immuno-pattern

fibrin

CD61
Causes of TTP

• Reduced cleavage of vWF multimers

• Familial – mutation of ADAMTS-13 gene

• Acquired – auto-antibodies inhibit ADAMTS-13 function
  – **Pregnancy**
  – Drug therapy
  – SLE
  – Organ transplantation
  – Cancer
  – Surgery
  – HIV disease
  – HTLV-1 infection
  – E.coli 0157
TMA

- vWF
- FVIII
- fibrin
- PLT
- EC

ECs and other components are depicted within the TMA region.
TTP and related diseases

- TTP/HUS
- DIC
- APS/SLE
- HELLP/PET/Eclampsia
- Fatty liver of pregnancy
- Evan’s syndrome
- Heparin-induced thrombocytopenia
Schistocytes on blood film
Cerebral TMA - confusion
### DIC – related conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Any micro-organism</td>
</tr>
<tr>
<td>Trauma</td>
<td>Polytrauma</td>
</tr>
<tr>
<td></td>
<td>Neurotrauma</td>
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<tr>
<td></td>
<td>Fat embolism</td>
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<tr>
<td>Cancer</td>
<td>Solid tumours</td>
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<tr>
<td></td>
<td>MPD and LPD</td>
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<tr>
<td>Obstetric</td>
<td>Amniotic fluid embolism</td>
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<tr>
<td></td>
<td>Abruptio placentae</td>
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<tr>
<td>Organ destruction</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>Kasabach-Merrit syndrome</td>
</tr>
<tr>
<td></td>
<td>Large vascular aneurysm</td>
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<tr>
<td>Severe liver failure</td>
<td></td>
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<tr>
<td>Severe toxic or immunological reactions</td>
<td>Snake bite</td>
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<td></td>
<td>Recreational drugs</td>
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<tr>
<td></td>
<td>Transfusion reaction</td>
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<tr>
<td></td>
<td>Transplant rejection</td>
</tr>
</tbody>
</table>
Case 2

- Why did she die?

  * Hint: heart was blotchy

- CNS & renal TMA are not acutely fatal
Heart – RV outside
Heart – horizontal slices
Heart – RV – acute necrosis
Heart – thrombi – TTP platelets
Case 2 message

‘DIC’ is more complicated than it might seem
Ruthless plug!

Google: ‘lucas autopsy sepsis’
InTech open access publication

Lancet this week – letters on Sepsis
Questions?
Case 3 – left ventricle

- 31 yr old female
- Nausea & vomiting, chest pain – unwell
- In A&E, cardiac echo = LV malfunction
- + 8 hours: cardiac arrest
- Resus, then arrest at 10 hours
Case 3

- Autopsy – negative
- Heart normal grossly – 255gm
- Toxicology screen negative
Case 3 – LV muscle
What do you see in the myofibres?
Case 3

Contraction band necroses
4 generic histopathologies

1. what is the histopathology?
   - Is there a differential diagnosis? NO
   - Is there more information on the slide? YES

2. What is the range of known causes of this?

3. In this particular case, which one most likely?

4. What other organ pathologies and/or tests would you want to confirm the diagnosis?
Case 3 – acute inflammation = duration of damage?
CBN and causation - 1

**Natural**
- Myocardial infarction
- Reperfusion injury
- Catecholamine heart
  - Phaeochromocytoma
  - ‘Takot subo’ cardiomyopathy
    - Sudden stress cardiac failure

**Iatrogenic**
- CPR per se (physical damage)
- Inotrope injection
  - Direct into heart
  - Into circulation
    - Cf catecholamine heart
- Endomyocardial biopsy
  - Forceps trauma
    - Cf massive external trauma
CBN and causation - 2

• .....and then there is COCAINE
• And other stimulant drugs
  – Ecstasy
  – Amphetamines etc
Case 3

= cocaine until proven otherwise

History of previous cocaine abuse
Family concurred with the diagnosis and verdict at inquest
Is Dr Steven Karch correct?

1. ‘In cocaine-related cardiac death, the blood level is of no consequence’; blood levels decline to zero within 24 hours; hair analysis is useful for chronology

2. ‘Cardiac fatality does not happen on first exposure: there is always previous damage [ie scarring] to see’
Cocaine & the heart

• Acute coronary artery spasm
• Chronic arteriosclerosis
  – Endothelial cell activation
• Acute adrenalin toxicity
  – Myofibre necrosis & scarring
• Acute hypertension
  – Cerebral haemorrhage
Another Case
Legal termination at 19/40 weeks

• 40 yr old
• Standard TOP (350ml amniotic fluid)

• GA – evacuation by suction and fragmentation; takes 10 mins

• Cardiac arrest 5 mins after procedure
• Could not re resuscitated
• Autopsy
Causes of death?

Nothing to see grossly

- Perforated uterus?
- VTE and PE?
- Amniotic fluid embolism?
- Sepsis?
- Intracerebral haemorrhage?
- Primary cardiac disease?
In the septum...
Another Case

- Heart – focal scars - ?causation
- Cocaine-related lesions?

- How to prove?
  - Blood screen
  - Hair analysis

- Blood cocaine = 1.4mg/L (!!)

Cause of death:
- 1a. Acute cardiac failure
- 1b. Termination of pregnancy and cocaine-related cardiac damage
Case 3 message

CBNs – look for them
Is it the LAS responsible?
Cocaine: the commonest cause of chest pain in London males <35 yrs old

Health warning: CPR obscures the underlying pathology and causation
Questions?
Case 4 - cerebellum

• 23 yr old male
• Symptomatic Huntington’s chorea
• No previous seizures

• Found collapsed in the bath at home.
• Taken to hospital
• Never regained consciousness
• D3: died in liver and multi-organ failure
Case 4

• Autopsy
• Brain – slight atrophy
• Cerebellum normal grossly
• Liver abnormal - but not relevant to case

• Cerebral histopathology = Huntington’s disease
What are you seeing in the PJC\textsubscript{s} and dentate nucleus?
What are you seeing in the PJC's and dentate nucleus?

Normal neurones
Red neurone change
Dark neurones
4 generic histopathologies

1. What is the histopathology?
   - Is there a differential diagnosis? Not really
2. What is the range of known causes of this?
3. In this particular case, which one most likely?
4. What other organ pathologies and/or tests would you want to confirm the diagnosis?
Differential aetiological diagnosis of cerebellum RNC

1. Hypoxia-ischaemia
2. Hypoglycaemia
3. Hyperglycaemia
4. Hyperthermia
5. Hypothermia
6. Hyponatraemia
Differential aetiological diagnosis of cerebellum RNC

1. Hypoxia-ischaemia
2. Hypoglycaemia – (insulin effect)
3. Hyperglycaemia
4. Hyperthermia
5. Hypothermia
6. Hyponatraemia
## Sorting out RNC

<table>
<thead>
<tr>
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<th>Hypoxia-ischaemia</th>
<th>Hypoglycaemia</th>
<th>Hyperthermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex - gross</td>
<td>Watershed</td>
<td>Uniform</td>
<td>-</td>
</tr>
<tr>
<td>Cortical layers</td>
<td>Middle laminae</td>
<td>Superficial laminae</td>
<td>If prolonged</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>CA1&gt;CA3 Dentate only if severe</td>
<td>CA1 dentate</td>
<td>If prolonged</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Watershed – PJC &amp; dentate nuclei</td>
<td>Absent</td>
<td>PJC &amp; dentate</td>
</tr>
<tr>
<td>Brain stem</td>
<td>Can be involved</td>
<td>Absent</td>
<td>If prolonged</td>
</tr>
</tbody>
</table>

Greenfield Neuropathology 2008
RNC

• Global = HIE
• Watershed areas
• First stage of laminar infarction of cortex

• Most sensitive sites for autopsy sampling:
  – Hippocampus CA1-4 area
  – Cerebellum – dentate nucleus and Purkinje cells
RNC chronological sequence

• ‘Dark neurone change’ – ambiguous state
• Obvious RNC: about 10 hours +
  – Pyknotic nucleus
  – Hypereosinophilic cytoplasm
• = Irreversible injury
• Microglial and astrocytic reaction: 3-5 days+
• Cell vanishes
• Surrounding neuropil implodes (infarction)
Hyperthermia brain damage

• Malignant hyperthermia
• High fevers
• External hyperthermia injury (heat stroke)
• Etc

• Survivors may have **cerebellar ataxia** and atrophy on imaging
<table>
<thead>
<tr>
<th>Case 4 – much debate; tetchy inquest</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hot bath</td>
</tr>
<tr>
<td>• Let out before LAS arrived</td>
</tr>
<tr>
<td>• <strong>Body temperature = 42 deg C</strong></td>
</tr>
<tr>
<td>• Liver pathology odd, but probably due to heat stroke or shock</td>
</tr>
<tr>
<td>• Cerebellar RNC a clue</td>
</tr>
<tr>
<td>• Neuropathologists’ view:</td>
</tr>
<tr>
<td>• No obvious diagnosis</td>
</tr>
<tr>
<td>• RNC not necessarily due to hyperthermia</td>
</tr>
<tr>
<td>• Could be part of MOF</td>
</tr>
</tbody>
</table>
Case 4 message

RNC usually from HIE
Provides a minimum timing of critical event

Also a possible clue for alternative pathogenesis
Questions?
Thank you for asking me to present this material