Mesenchymal Tumours of the Upper GI Tract

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What I’ll do

• Minimise listing
• Anatomical divisions – how distally?
• Updates and practical pointers
• EUS-FNA (EUS-biopsy)
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• Minimise listing
• Anatomical divisions – how distally?
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Oesophagus

- Smooth muscle tumour (>> GIST)
- Sarcomatoid carcinoma

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Smooth muscle neoplasms

• Why distinguish from GIST?
  – Excision?
  – Imatinib?

• Immunohistochemistry
  – Beware ICCs
  – Other smooth muscle markers
Smooth muscle IHC markers

- Desmin and caldesmon
Smooth muscle IHC markers

- Desmin and caldesmon
- But PLAP and smoothelin are more specific.
A study of $\alpha_5$ chain of collagen IV, caldesmon, placental alkaline phosphatase and smoothelin as immunohistochemical markers of gastrointestinal smooth muscle neoplasms

Newton ACS Wong, Jenny Wingate, Richard Colling

Leiomyoma: 27/27
Leiomyosarcomas: 4/4 (focally reduced)
Angiomyolipoma: 1/5
DSCRT: 1/1
Smooth muscle IHC markers

• Sensitivity: 100% for all three markers

• Specificity:
  - Caldesmon 80%
  - PLAP 96%
  - Smoothelin 91%
Smooth muscle neoplasms

- In HIV/AIDS patients, EBV driven smooth muscle neoplasms:
  - less pleomorphism
  - low mitotic count
Sarcomatoid carcinoma

• May express DOG1 and/or CD117


CD117 expression in oesophageal carcinosarcoma: a potential diagnostic pitfall.

Martland GT¹, Goodman AJ, Shepherd NA.
EUS-biopsy

- GIST vs. smooth muscle neoplasm
- Physiological smooth muscle
EUS-biopsy

- GIST vs. smooth muscle neoplasm
- Physiological smooth muscle
- Other submucosal neoplasms
56 yr old woman with a GOJ tumour – normal mucosa. ?GIST. EUS-biopsied:
56 yr old woman with a GOJ tumour – normal mucosa. ?GIST. EUS-biopsied:
56 yr old woman with a GOJ tumour – normal mucosa. ?GIST. EUS-biopsied:

S100
Granular cell tumour
Stomach

- GIST
- Schwannoma
- IFP
- Glomus tumour
- Synovial sarcoma
- IMFT
- Plexiform fibromyxoma
• Is it a CD117 negative GIST?
  – Mainly epithelioid/mixed cell type
  – PDGFRA mutant
  – Gastric/omental

KIT-Negative Gastrointestinal Stromal Tumors
Proof of Concept and Therapeutic Implications

Fabiola Medeiros, MD, * Christopher L. Corless, MD, † Anette Duensing, MD, *
Jason L. Hornick, MD, PhD, * Andre M. Oliveira, MD, * Michael C. Heinrich, MD, †
Jonathan A. Fletcher, MD, *§ and Christopher D. M. Fletcher, MD, FRCPath*

CD117

DOG1

+ +

= CD117 neg GIST
Mutations of receptor tyrosine kinase (RTKs)

+ ‘D842V’ mutation $\Rightarrow$ CD117 neg GIST
Kinase Mutations in GISTs

Wild-type

PDGFRA
Exon 18
Exon 14
Exon 12
Exon 17
Exon 13

KIT
Exon 11
Exon 9

PDGFRA

KIT

Epithelioid/mixed cell type gastric GISTs

- **PDGFRA mutant**
  - Reduced CD117 expression
  - No age or gender association

- **Wild type**
  - Do express CD117
• Wild type
  – CD117 expression
  – Stomach
  – Children or young female adults
  – Multinodular/multifocal
  – Nodal and liver metastases
  – Poor response to imatinib
  – Better prognosis
Epithelioid/mixed cell type gastric GIST

• Wild type
  – Paediatric or ‘paediatric-like’ in adults
Epithelioid/mixed cell type gastric GIST

- Wild type
  - Paediatric or paediatric-like in adults
  - Could represent Carney triad (no known genetic basis) or Carney-Stratakis (inherited SDH gene mutation)
  - Loss of SDHB protein expression
• Wild type
  – CD117 expression
  – Stomach
  – Children or young female adults
  – Multinodular/multifocal
  – Nodal and liver metastases
  – Poor response to imatinib
  – Better prognosis
Gastric schwannoma

- GISTs ‘never’ show diffuse S100 positivity
- Peripheral lymphoid aggregates but ...
• CD117 and DOG1 diffusely +ve; S100 -ve
• KIT exon 11: c.1738_1752dup, p.(His580_Phe584dup)
Inflammatory fibroid polyp

• Up to $\frac{3}{4}$ may harbour PDGFRA mutations
58 yr old man with a previously excised gastric GIST. Scalp tumour excised:
58 yr old man with a previously excised gastric GIST. Scalp tumour excised:
58 yr old man with a previously excised gastric GIST. Scalp tumour excised:

- SMA
- CD117
DOG1 and CD34 negative
Wild type for KIT and PDGFRA

Collagen IV
DOG1 and CD34 negative
Wild type for \textit{KIT} and \textit{PDGFRA}

\textbf{Malignant gastric glomus tumour}
Glomus tumour

- Very uniform epithelioid cells with prominent cell membranes ... but GIST can too!
Glomus tumour

• Focal SMA positivity with prominent net-like collagen IV / laminin around cells ... but GIST can too (34%!)

• Lack of CD117, DOG1 and CD34 expressions
Abdominal monophasic synovial sarcoma is a morphological and immunohistochemical mimic of gastrointestinal stromal tumour

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Department of Histopathology, Bristol Royal Infirmary, Bristol, UK, \textsuperscript{1}Department of Pathology, Royal Liverpool University Hospital, Liverpool, UK, and \textsuperscript{2}Gloucestershire Cellular Pathology Laboratory, Cheltenham General Hospital, Cheltenham, UK
<table>
<thead>
<tr>
<th>Immunomarker†</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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<tbody>
<tr>
<td>CD117</td>
<td>+*</td>
<td>+*</td>
<td>+*</td>
<td>–</td>
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<tr>
<td>DOG1</td>
<td>+*</td>
<td>+</td>
<td>+*</td>
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<td>CD34</td>
<td>+</td>
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<td>Pancytokeratin</td>
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<td>CD56</td>
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<tr>
<td>Chromogranin</td>
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<td>Synaptophysin</td>
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<td>MMC‡</td>
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<tr>
<td>SMA</td>
<td>–</td>
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<td>–</td>
</tr>
<tr>
<td>Desmin</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>
1 yr old girl with a gastric mass.
• Desmin +
• SMA +/-
• CD117 -
• DOG1 -
• Pan CK -
Final diagnosis:
Inflammatory myofibroblastic tumour
Plexiform fibromyxoma

• aka ‘Plexiform angiomyxoid myofibroblastic tumour of the stomach (PAMTOTS)’; ‘fibroangiomyxoma’.
• 150 GISTs : 1 plexiform fibromyxoma.
• Young-middle aged adults of either sex.
• Non-syndromic.
• Gastric antrum; nowhere else in GIT.
Plexiform fibromyxoma (Miettinen et al. AJSP 2009; 33: 1624)
Plexiform fibromyxoma (Miettinen et al. AJSP 2009; 33: 1624)
Plexiform fibromyxoma

- **SMA+** (8/10 tested) and **CD10+/-** (1/3 tested).
- Negative for CD117, DOG1, CD34, desmin.
EUS-biopsy

- Lipoma
EUS-biopsy
EUS-biopsy
EUS-biopsy
EUS-biopsy
EUS-biopsy

Pancreatic heterotopia

Trypsin
Small intestine

- GIST
- Inflam. fibroid polyp
- Reactive nodular fibrous pseudotumour
GIST

- KIT exon 9 mutant (relative resistance to imatinib)
Reactive Nodular Fibrous Pseudotumor of the Gastrointestinal Tract and Mesentery
A Clinicopathologic Study of Five Cases

Rhonda K. Yantiss, M.D., G. Petur Nielsen, M.D., Gregory Y. Lauwers, M.D., and Andrew E. Rosenberg, M.D.

Although the majority of mesenchymal lesions of the gastrointestinal tract are neoplastic in nature, nonneoplastic reactive processes may involve the gastrointestinal tract and mesentery, causing diagnostic confusion with more aggressive neoplasms, such as fibromatosis or gastrointestinal stromal tumors. In this study, we report a series of fibroinflammatory lesions of the gastrointestinal tract that we think represent a relatively cohesive group of tumors and describe the clinical and pathologic features of this entity, which we have termed “reactive nodular fibrous pseudotumor.” The tumors affected five patients (four male and one female patient) who ranged in age from 48 to 71 years (mean 56 years). Two patients presented with acute abdominal pain without a significant past medical history, two had incidental lesions discovered during evaluation for other medical conditions, and one was found to have an abdominal mass. Three patients had a history of abdominal surgery. The tumors were multiple in three patients and solitary in two patients. Four patients had no residual disease following surgical resection (mean follow-up 16.3 months) and one patient who had an incomplete surgical resection had stable disease at 26 months. In summary, we report a series of distinct intraabdominal fibroinflammatory pseudotumors that we have collectively termed “reactive nodular fibrous pseudotumors.” These lesions are uncommon and may infiltrate the bowel wall, thereby mimicking primary bowel neoplasms or intraabdominal fibromatosis. Recognition of these nonneoplastic lesions is important, as they pursue a benign clinical course, but may be confused with other mesenchymal neoplasms that require more aggressive treatment.

Key Words: Reactive nodular fibrous pseudotumor—Fibroinflammatory tumor—Fibromatosis—Sclerosing mesenteritis—Mesentery—Gastrointestinal tract—Differential diagnosis.

RNFP

- Hx of intra-abdominal injury.
- Well circumscribed.
- Serosal/subserosal.
- (Myo)fibroblastic.
- Keloidal / collagen bundles.
- Chronic inflammation.
Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract

David L. Stockman, MD,* Markku Miettinen, MD,† Saul Suster, MD,* Dominic Spagnolo, MBBS, FRCPA, MD,‡§ Hugo Domínguez-Malagon, MD,∥ Jason L. Hornick, MD, PhD,¶ Volkan Adsay, MD,# Pauline M. Chou, MD, PhD,** Benhur Amanuel, MBBS, FRCPA,‡§ Peter VanTuinen, PhD,* and Eduardo V. Zambrano, MD*
GNET

• Clear cell sarcoma-like tumours of the GIT (CCSLTGT)
• NOT to be confused with clear cell sarcoma of soft parts.
• Small bowel >> Stomach and large bowel
GNET

- **S100+**  **SOX10+**
- Variably **CD56 +** and/or **synaptophysin +**
- Negative for **Melan-A**, **HMB45**, **tyrosinase**, **CD117**, **DOG1**, **desmin**, **SMA**.

- **EWS gene rearrangements** (13 of 14 cases)
EWS/CREB1 fusion
Peri-tumoral tissue
MDM2 FISH
Dedifferentiated liposarcoma

- Older male
- Mesenteric/retroperitoneal.
- Consider if pleomorphic cells with no specific immunophenotype.
- **MDM2 amplification** (FISH).
Summary

• Love mesenchymal neoplasms
• Schmooze your local sarcoma pathologist
• Embrace EUS-biopsies