Current Research Findings from the UK Paws GIST Clinic

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GIST

Mutations in KIT/PDGFRA (85%)  Wild-Type GIST (15%)

SDH deficient

Germline mutation:
-SDHA
-SDHB
-SDHC
-SDHD

SDHC epi-mutation

SDH preserved

-NF1
-BRAF

Other
Genotype of SDH deficient UK PAWS GIST WT GIST cohort

- SDHA: 10 cases
- SDHB: 2 cases
- SDHC: 2 cases
- SDHD: 1 case
- SDHC epimutation: 4 cases
Synchronous tumours with SDH deficient GIST

26% of SDH deficient GIST cohort had synchronous tumors
Histological characteristics of wt GIST

SDH preserved
- Spindle cell histology from small bowel GIST
- Typically small bowel

SDH deficient
- Mixed epithelioid histology from gastric GIST
- Typically gastric

Gross specimen of gastric wt GIST
SDH deficient GIST

- Young age at presentation
- Primary tumour is typically gastric in location
- Histology is epithelioid or mixed epithelioid
- High rates of metastases
- *SDHA* is the most common *SDHx* gene implicated in SDH deficient GIST
- Most common variant is *SDHA* c.91C>T p.(Arg31Ter)
- Important to remember genetics may not always be the answer in wt GIST, high frequency of *SDHC* epi-mutations in this cohort
Diagnostic algorithm for SDH deficient wt GIST:

- **KIT and PDGFRA**
  - WT GIST GIST

- **Histology review and SDHB IH**
  - Germline genetic testing*
    - No Pathogenic germline variant detected
      - Preserved SDHB IH expression
      - Testing complete/Research studies
    - Pathogenic germline variant detected

- **MRI neck and skull base +/- MRI abdomen and pelvis**
  - Plasma metanephrines + 3MT

- **Loss of SDHB IH expression**
  - SDHC promoter methylation analysis of tumour
    - Methylation >10%
      - Confirm low SDHC mRNA expression
      - Somatic mutation testing
    - Methylation <10%
      - Testing complete/Research studies

* = SDHA, SDHB, SDHB, SDHD, SDHAF2, NF1, MAX, TMEM127, KIT, PDGFRA, VHL
Identify new functional assessment tools to identify SDH deficiency

• Ex-vivo metabolomics
Targeted metabolomics profiling for succinate
2. Evaluate new translational biomarkers for diagnosis, surveillance and to monitor response to therapeutic intervention in SDH deficient disease.
In-vivo metabolomics using MRI spectroscopy ($^1$H-MRS)
Monitoring biological response to treatment

37 year old female
Metastatic PPGL, *SDHB c.268C>T*
Treatment with Lu$^{177}$ PRRT

<table>
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<tr>
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<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Reference range</th>
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<td>1193</td>
<td>&lt;1000 pmol/l</td>
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3. Developing diagnostic tests for clinical utility to identify potential therapeutic targets
- Technique which can be applied to paraffin embedded samples
- Cost effective and time efficient
- Pyrosequencing technique
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PATIENTS