A 43 year old male presents with abdominal complaints. An axial CT reveals ....
Diagnosis: Gastrointestinal Stromal Tumor

Location: stomach
Size: 12 cm
Mitotic count: 10 mitoses / 50 high power fields
Risk Assessment: High risk of aggressive behavior

C-kit
Definitions

Mutation
Any change in the DNA of a cell

Next Generation Sequencing
A technology that rapidly determines the sequence of molecules that compose DNA
3 billion base pairs in each human cell
Organized into 23 pairs of chromosomes
15-70 trillion cells in human body
1 billion cells in a 1cm GIST
Human Cell

- Mitochondria
- DNA
- C-Kit
Mutations

Deletion

Substitution
Mutations
Mutations
Mutations in GIST

- CKIT: 75-80%
- PDGFRA: 10-15%
- SDH-A,B,C,D: 6%
- BRAF: 2%<1%
- KRAS: 10-15%
- NF1: 6%
- PRKAR1B-BRAF: 2%<1%
- FGFR1 fusions: 2%<1%
- ETV6-NTRK3: 2%<1%
C-KIT

Protein – cell surface receptor - tyrosine kinase

Chromosome 4

Development of heme stem cells, germ cells, mast cells, melanocytes, interstitial cells of Cajal

Cell survival

Cell proliferation

Cell adhesion

Cell differentiation and maturation
Gastrointestinal Stromal Tumors

Inactive KIT or PDGFRα → Active KIT or PDGFRα

Ligand binding → Oncogenic mutations

Signalling

KIT

Exon 9 (11%)
Exon 11 (67.5%)
Exon 13 (0.9%)
Exon 17 (0.5%)
Gastrointestinal Stromal Tumors

Kit mutations - worse prognosis than PDGFRα mutations
- deletions in exon 11 most aggressive
- exon 9 mutations associated with intestinal location and more aggressive course

PDGFRα exon 14 and 18 mutations - gastric origin, epithelioid morphology and favorable outcome
C-Kit and PDGFRa Negative GIST Account for 12% of GIST

epithelioid/stomach

BRAF
NRAS
KRAS
ETV6-NTRK3
FGFR1 fusions

loss of function mutation – succinate dehydrogenase & IGFR amplification
Human Cell

Mitochondria

Complex II

Inter membrane Space

Inner Mitochondrial Membrane

Matrix

SDHC

SDHD

Q→QH₂

Heme

[Fe-S]

SDHB

SDHA

FAD

FADH₂

Succinate

Fumarate

C-Kit
Succinate Dehydrogenase Deficient GIST

Most frequent wild type $KIT/PDGFR\alpha$-GIST

Mutation results in buildup of succinate

Leads to aberrant DNA methylation and dysfunction

Component of Carney Stratakis syndrome (gastric GIST and paraganglioma) and Carney triad (gastric GIST, paraganglioma, pulmonary chondroma)

Affects young females (<20yrs), multiple, plexiform architecture, high rate of metastases, long survival

Not responsive to tyrosine kinase inhibitors
Succinate Dehydrogenase Deficient GIST - Epimutant
Progression of Molecular Aberrations in GIST

Benign

Additional CKIT and PDGFRA mutations

Resistance to Drugs

Malignant

CKIT

PDGFRA

BRAF

SDH

Chromosome 14, 14q Loss or monosomy

Chromosome 8q 17q Gains

Chromosome 1p, 9p, 11p 10, 13q, 15q, 22q Loss
Mutational Analysis in Gastrointestinal Stromal Tumor

All tumors that are intermediate or high risk should be tested.
Mutation identification provides information on prognosis, responsiveness to tyrosine kinase inhibitors, genetic transformation over time, tumors associated with syndromes, and targets for therapy.
GIST – Treatment Effect