CARNEY’S TRIAD
Just when you thought Pheochromocytoma was rare...
WHAT IS CARNEY’S TRIAD?

- Discovered by pathologist Dr. Aidan Carney of the Mayo Clinic in 1977.

- It is an extremely rare syndrome with around 100 cases reported worldwide.

- In general, three main tumors comprise the triad:
  - Extra-adrenal Paragangliomas
  - Gastrointestinal Stromal Tumors (GIST)
  - Pulmonary Chondromas

- The triad is now known as a novel form of Multiple Endocrine Neoplasia (MEN) which is a genetic condition with a female predilection.

- Some other tumor types associated with Carney Triad are:
  - Pheochromocytomas
  - Esophageal leiomyomas
  - Adrenocortical adenomas
DIAGNOSING CARNEY’S TRIAD

- The genetic mutation (if any) or abnormality remains unknown.
  - Although evidence shows recurrent losses at chromosome 1, not every case has this loss, so it cannot be determined as the cause.

- To be diagnosed, a patient must present at least two of the three tumor types.
  - The different lesions do not need to be present at the same time.
  - Years may separate the appearance between the different tumors, making it that much harder to diagnose.

- Carney Triad has been reported in all races and several countries.
  - Predominantly affects younger females.
    - More often than not GIST is the first tumor appearing in the late teen years.
CARNEY’S TUMORS- GIST

- GIST - (most common tumor in the triad) is a rare sarcoma cancer which affects the digestive tract or nearby structures within the abdomen.
- The most frequent site for the primary tumor of GIST is formed in between the muscle layers of the stomach from the interstitial cells of Cajal (ICC).
  - Where the tumor originates is important as it differentiates a sarcoma cancer from a carcinoma cancer.
    - Sarcoma cancer is one of the four major cancer types. The tumors are derived from connective tissues, bones, and muscle.
    - Where as Carcinoma cancer, which holds the most common cancer types, (i.e. breast, colon, lung, and prostate cancers) is derived from epithelial cells.
CARNEY TRIAD - GIST

- There are different types of GIST mutations:
  - Kit
  - PDGFRA
  - “Wild Type” - when no mutation is found
    - Carney Triad cases have the wild type GIST.

- Young patients, especially young females, with Wild Type GIST, should be screened the rest of their lives for the other Carney Triad tumors as a precaution.

- GIST in Carney cases is clinically, pathologically, and behaviorally different from sporadic GIST.
  - Carney GIST are usually slow growing compared to the aggressive sporadic GIST.
  - Triad GISTs typically grow from within the wall of the stomach into the stomach, in contrast to most GISTs that grow from within the wall outward into the abdomen.
  - Carney patients with metastatic GIST have a better prognosis and live many years after the spread.

- There is nearly a 50% chance that GIST in Carney cases will metastasize.
GIST - TREATMENT

- NIH and Mayo differ on their treatment styles for Carney Triad patients when GIST is found only in the stomach:
  
  - Mayo Clinic desires full removal of the stomach to stop the spread of GIST. Their theory is that GIST starts in the lining of the stomach and is contained there. If removed before the cells spread, they believe that GIST will not appear elsewhere.

  - NIH theory counters that there have been cases of patients with GIST who had their entire stomach removed and later formed GIST in their intestines, esophagus, and/or liver. NIH believes surgical removal of the tumors and chemotherapy drugs are the best treatment of GIST.
    - Gleevec and Sutent are the two most common drugs used, although a new series of chemo drugs are in trial stages.
CARNEY’S TUMORS- PULMONARY CHONDROMA

- Pulmonary Chondroma – is a cartilaginous benign lung tumor.

- Often mistaken as metastases from GIST.

- Usually asymptomatic, often multiple and medium sized. None of the Chondroma tumors in the Carney cases metastasized.

- Pulmonary Chondromas appear on x-rays due to the calcification of the tumors, and they look like a deadly lung cancer. However, there are no known fatalities due to Chondroma tumors in Carney patients.
PULMONARY CHONDROMA TREATMENT

More often than not, Pulmonary Chondromas are left alone but growth rate is monitored.

When the tumor grows too large and impedes breathing, surgical resection is the only option.

Doctors wait as long as possible because surgical resection often leads to the removal of a lobe of the lung.
CARNEY'S TUMORS - PARAGANGLIOMA

- Paragangliomas are the least common of the three main tumors for Carney Triad.
  - Most are functioning tumors, and the majority of those secrete, but are not limited to, Norepinephrine.
    - Epinephrine and Dopamine can also be secreted.
  - Pheochromocytoma has also been reported in at least 5 different cases.

- Locations for Carney Triad Paraganglioma are anywhere along the sympathetic and parasympathetic nervous system.
  - Some major organs along the sympathetic and parasympathetic nervous system are:
    - brain, eyes, trachea and bronchi, heart, liver, gallbladder, stomach, kidney, colon, and bladder.
LOCATING PARAGANGLIOMA

- After testing biochemically positive for Paraganglioma, a number of scans can be done in order to locate it.
  - Most common are MIBG, Octreotide, PET, MRI, and CT.
PARAGANGLIOMA TREATMENT

- For functioning tumors primary concern is the stabilization of blood pressure and heart rate with:
  - Alpha/Beta blockers
  - Calcium channel blockers
  - ACE inhibitors
- Surgical removal remains the only cure.
- In non-operable areas a handful of Chemo/Radiation treatments are available:
  - 131MIBG
  - CDV
  - Y-90
  - Sutent
  - Octreotide
- The choice between the treatments weigh in on genetics, how the tumors react to scans, and the treatment itself.
CARNEY TRIAD - NON-FAMILIAL

- In the early stages of Carney Triad, doctors believed it was not a germline mutation (meaning it is not passed on to the next generation).
  - But then a number of cases started to show a combination of GIST and Paraganglioma within families.
  - The statistic changed to a 50-50 chance of it being familial, and at one point doctors believed that both parents needed the unknown Carney Triad mutation in order for it to be passed down.
  - They referred the familial Carney Triad as Carney Dyad, due to only the two tumors being present.

- When Dr. Carney teamed up with Dr. Stratakis, they discovered SDH germline mutations in those who had familial Carney. They diagnosed those patients with Carney-Stratakis (sometimes known as Carney-Stratakis Dyad) and it is now registered as a completely different disease. Thus, Carney Triad remains as a non-familial syndrome.
CARNEY STRATAKIS

Dr. Carney and Dr. Stratakis teamed up in 2001 to research the familial Carney cases and noticed two major differences.

- In the familial cases no Pulmonary Chondroma were present.
- There was an equal ratio of male to female.

Some major findings:

- A portion of Carney Triad cases may have some SDH chromosomal losses, but not mutations. Where Carney Stratakis show SDH mutations.
- First indication that SDHC can cause paragangliomas in the abdomen. (Before it was believed SDHC only caused paragangliomas in the head and neck)
SUCCINATE DEHYDROGENASE (SDH)

- The SDH role in Carney.
  - Doctors used clues from familial paragangliomas and their relation to the SDH genes to see how they related to the Carney cases.
  - What surprised them was SDHB, SDHC, and SDHD showed germline mutations in those with familial Carney.

- These mutations result in the loss of normal function of the SDH protein.
  - SDH genes are considered to be tumor suppressor genes.
  - When they are missing or non-functional, the person will be at higher risk of developing tumors.
SDH... CONTINUED

- Three different studies are starting to show a common element of Carney’s Triad and Carney-Stratakis with the loss of some part of the SDH protein.
  - Through mutations that make it familial. (Carney-Stratakis)
  - Or some other unknown means (Carney’s Triad and sporadic pediatric GIST.)

- However, there are always exceptions.
  - Some Carney patients do not show any evidence of loss or mutation of the SDH protein
  - There is even one patient that has the SDHB mutation and has pulmonary chondroma and paraganglioma, but no GIST.
## DIFFERENCES IN TRIAD AND STRATAKIS

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<tr>
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<th>Carney Triad</th>
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<tr>
<td>GISTs</td>
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<tr>
<td>Chromosomal loss in SDH</td>
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*Chart information taken from [www.gistsupport.org]*
CARNEY TRIAD- SOURCES

Informative Sources:

- http://jco.ascopubs.org/content/22/10/2029.full.pdf
- http://atlasgeneticsoncology.org/Kprones/CarneyTriadID10132.html
- http://jtcsc.ptsnetjournals.org/cgi/content/full/121/5/1011
- http://jcem.endojournals.org/cgi/content/abstract/92/8/2938
- http://journals.lww.com/ajsp/Abstract/2010/01000/Gastric_Stromal_Tumors_in_Carney_Triad_Are.7.aspx
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*Disclaimer: The information contained in this presentation is for general information purposes only and is subject to change.*