Primary Cardiac Tumors Associated with Genetic Syndromes: A Comprehensive Review

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Disclosure

None
Goals and Objectives

- Highlight key clinical features of syndromes associated with cardiac tumors
- Review CT and MR imaging appearance of syndromic cardiac tumors
- Discuss the differences in tumor behavior and manifestation when cardiac tumors occur as part of a syndrome
- Review recommendations for surveillance
Cardiac tumors manifesting within the framework of a syndrome

- **Tuberous Sclerosis**
  - Benign tumors in brain, eyes, heart, kidneys, skin and lungs

- **Gorlin Syndrome**
  - Also known as nevoid basal cell carcinoma syndrome
  - Increases the risk of developing various cancerous and noncancerous tumors

- **Rhabdomyomas**

- **Fibroma**

- **Carney Complex**
  - Carney complex and its subsets LAMB and NAME syndrome comprise of lentiginosis (skin hyperpigmentation) and endocrine overactivity
  - Distinct from Carney triad

- **Myxomas**

- **Paraganglioma**
  - Carney triad, VHL, MEN2, NF1 and familial pheochromocytoma-paragangliomas
Tuberous Sclerosis and Rhabdomyomas

- **Tuberous sclerosis (TS):**
  - Autosomal dominant
  - Mutations in the tumor suppressor genes TSC1 (hamartin) and TSC2 (tuberin)
  - Leads to hamartomatous growths

Subependymal nodules

Skin manifestations (hypomelanotic macules, angiofibromas, cephalic fibrous plaques, shagreen patches, and ungual fibromas)

Renal angiomyolipomas

Lymphangioleiomyomatosis

Angiofibromas

MRI: T1 fat sat
Tuberous Sclerosis (TS) and Rhabdomyomas

- **Tuberous sclerosis (TS)**
- **Rhabdomyomas**
- **Can be the first manifestation of TS**
  May be detected on prenatal ultrasound

- **50% have rhabdomyomas**

- **40-90% occur in the setting of TS**

- **If multiple rhabdomyomas:**
  100% have TS
Rhabdomyomas: Imaging Appearance

- Echocardiography: main imaging modality and suffices in most cases
- MRI is a useful adjunct when diagnosis is unclear (e.g. large solitary tumor). Typical MR features include:
  - Intracavitary or intramyocardial mass
  - Homogeneous and follows signal intensity of myocardium on all MRI sequences
  - Minimal or no enhancement after gadolinium-based contrast agents
- MRI is also helpful in delineating the proximity of cardiac tumors to normal myocardium and the great vessels for pre-operative planning in symptomatic patients.

3 day old neonate with TS and a large rhabdomyoma involving the anterior septum leading to mild RVOT obstruction. MRI was requested for assessing 3D anatomy, hemodynamics and relationship to cardiac structures. No surgery was performed and the tumor spontaneously regressed.
Rhabdomyomas: MR Imaging Appearance

T1W: Isointense to myocardium
T2W with fat saturation: Isointense to mildly hyperintense
Post contrast (delayed imaging): Non-enhancing

1 day old neonate with a left ventricular cardiac tumor diagnosed on prenatal ultrasound. Cardiac MRI was requested for tissue characterization. The patient was asymptomatic, required no surgical treatment with spontaneous regression of the tumor.

Rhabdomyomas in TS: Management

- Majority regress in childhood (by 6 years of age)
- Usually no symptoms
- Surgery considered if symptomatic (heart failure, arrhythmias)
- Case reports of using rapamycin inhibitors (Everolimus)

3 day old neonate with TS and an intracavitary rhabdomyoma (*) in the left ventricle causing LVOT (arrow) obstruction. Given the degree of obstruction surgical removal was planned and MRI was requested for operative planning. Note additional rhabdomyoma in the right ventricle (curved arrow). Multiple rhabdomyomas are a feature of TS.
Rhabdomyomas in TS: Management

Cardiac rhabdomyomas are a major diagnostic criterion for the diagnosis of TS. TS ‘definite’ diagnosis requires two major or one major and two minor criteria.

<table>
<thead>
<tr>
<th>Echocardiogram at the time of TS diagnosis</th>
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<tbody>
<tr>
<td>- If fetal rhabdomyoma(s) diagnosed, then serial observation and at least 1 postnatal echocardiogram.</td>
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<td>- Surveillance until regression demonstrated</td>
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<tr>
<th>Electrocardiogram at the time of diagnosis</th>
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<tr>
<td>- Surveillance studies every 3 to 5 years given risk of arrhythmias throughout life</td>
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<td>- Holter monitor as indicated for appropriate signs and symptoms</td>
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<th>Cardiology consultation at time of diagnosis</th>
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<tr>
<td>- Ongoing cardiology surveillance as indicated</td>
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<tr>
<td>- Medical and surgical intervention as indicated</td>
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<tr>
<td>- Referral to genetics and neurology when cardiology makes initial diagnosis</td>
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<tr>
<td>- Pediatric to adult transition plan with ongoing cardiology surveillance</td>
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</table>
Gorlin Syndrome and Fibromas

- Also known as nevoid basal cell carcinoma syndrome
- Autosomal dominant
- Diagnosis requires 2 major criteria or 1 major and 2 minor criteria
- Major criteria include: multiple or early onset basal cell carcinomas, odontogenic keratocysts of the jaw, three or more palmar or plantar pits, ectopic or early calcification of the falx, bifid, fused, or splayed ribs and family history of the syndrome
Gorlin Syndrome and Fibromas

Gorlin Syndrome

3-5% have fibromas

Cardiac fibromas

3-5% have Gorlin’s Syndrome

Cardiac fibromas are not a major diagnostic criteria
Fibromas: Imaging Appearance

- Typically involve the ventricular septum or free wall
- Solitary mass (in contrast to rhabdomyomas, which are often multiple)
- Calcification maybe present (and is a helpful differentiating feature from rhabdomyoma)
- MR appearance is distinctive:
  - Isointense to the myocardium on T1W
  - Heterogeneous & mildly hyperintense on T2W
  - No contrast enhancement on first pass perfusion (except rim)
  - Non-enhancing central core on delayed enhanced imaging with rim of enhancement
13 month old with amorphous calcifications in the heart anteriorly. These calcifications corresponded to a solitary right ventricular mass (proven fibroma). Calcifications exclude the possibility of a rhabdomyoma, the most common pediatric primary cardiac tumor. The MR appearance of this fibroma is shown on the subsequent slide.

Fibromas: Imaging Appearance

Pre-contrast imaging

RV fibroma (arrow) isointense on T1W

Heterogeneous and mildly hyperintense on T2W

Contrast imaging

First pass perfusion: No appreciable enhancement

Delayed enhancement: Non-enhancing central core with rim (arrow) enhancement

Fibroma in Gorlin Syndrome: Management

- Unlike rhabdomyomas, fibromas do not regress and require surgical resection.

- Patients meeting criteria for Gorlin Syndrome require imaging surveillance throughout life including annual brain MR (medulloblastoma), baseline echocardiography, panorex of jaw (keratocysts) and pelvic ultrasound (ovarian fibromas) at menarche.
Carney Complex and Myxomas

- Carney complex is distinct from Carney triad (discussed later)
- Autosomal dominant
- Mutation of protein kinase A
  - involved in regulation of metabolism, cell proliferation, differentiation and apoptosis
- Carney complex and its subsets **LAMB syndrome** (lentigines, atrial myxoma, blue nevi) and **NAME syndrome** (Nevi, Atrial myxoma, myxoid neurofibroma and ephelides) comprise of myxomas of the heart and skin, hyperpigmentation of the skin (lentiginosis) and endocrine overactivity
Carney Complex and Myxomas

Carney Complex

20-40% develop cardiac myxomas

Myxomas: Most common benign adult tumor

Only a small fraction (7-10%) occur in association with Carney Complex

Myxomas in young patients, multifocal or occurring in atypical locations are often in the setting of Carney Complex
Myxomas: Imaging Appearance

- Pedunculated ovoid or lobular mass with broad base attachment
- About 75% are located in the left atrium, 20% in the right atrium and 5% in one of the ventricles. In Carney complex, tumors may be multifocal or in atypical locations
- Mobile and may prolapse through the atrioventricular valve
- On CT myxomas are heterogeneously low in attenuation
- May have calcifications
- MRI:
  - Hypointense on T1W sequence
  - Hyperintense on T2W sequence
  - Heterogeneous enhancement
Myxomas: Imaging Appearance

Myxoma in a characteristic location (left atrium with attachment to interatrial septum). The mass is isointense on T1W imaging and prolapses through the mitral valve.

Note heterogeneous hyperintensity on T2W imaging.

Post-contrast delayed enhanced imaging demonstrates heterogeneous enhancement.
Myxomas in Carney Complex: Presentation and Management

- Patients may be asymptomatic
- Usually a local complication leads to symptoms requiring further diagnostic tests. Most common complications are embolism, intracardiac obstruction, 'myxoma disease' (fever, arthralgias, polymyositis, weight loss and hypergammaglobulinaemia)
- Surgical removal of tumor is recommended
- Patients with Carney complex can be challenging:
  - May develop additional sites of myxoma formation
  - Higher recurrence rate than sporadic myxomas
Syndromes associated with cardiac paragangliomas

- Paragangliomas may occur sporadically or in the context of a syndrome
- Numerous syndromes are associated with paragangliomas:
  - Multiple Endocrine Neoplasia 2 (MEN2)
  - Von Hippel Lindau (VHL)
  - Neurofibromatosis Type 1 (NF1)
  - Carney Triad
    - Coexistence of three types of neoplasms including gastric gastrointestinal stromal tumors (GIST), pulmonary chondroma and extra-adrenal paraganglioma
- Hereditary paraganglioma syndrome
  - 4 subtypes
  - Result from mutations in one of three subunits of the succinate dehydrogenase (SDH) gene
Terminology: Paraganglioma or pheochromocytoma

- Paraganglia are cells of neural crest origin
- Two types:
  - Located in the adrenal medulla (secrete epinephrine and norepinephrine)
  - Found outside the adrenal glands or extra-adrenal paraganglia
- Pheochromocytoma refers to a tumor of the sympathetic paraganglia located within the adrenal medulla
- Morphologically identical lesion located outside the adrenal medulla is known as a paraganglioma
Syndromes associated with cardiac paragangliomas

- **Paragangliomas**
  - 25-50% occur in syndromes
    - In children 69% occur in syndromes
    - If metastatic disease is present in a pediatric patient, 87.5% will be related to a germline mutation

- **Multicentric tumors, young age, and family history** suggest a syndromic form
Paragangliomas: Imaging Appearance

- Usually intrapericardial occurring at sites of paraganglia
  - Atria
    - Left atrium is the most commonly reported site
  - Root of great vessels
- Characterized by avid contrast enhancement on CT and MR
- Can be heterogeneous due to hemorrhage or cystic degeneration
- MR imaging features:
  - Isointense to hypointense on T1W imaging
  - Hyperintense on T2W imaging
  - Avid enhancement with rim enhancement on delayed images

40 year old with episodic headaches and sweating found to have a paraganglioma in the right AV groove. Because of the avid enhancement, the lesion can easily be overlooked and mistaken for blood pool.
The same patient (as previous slide) underwent cardiac MR. Genetic analysis revealed a mutation in succinate dehydrogenase which may be seen in setting of hereditary paraganglioma syndrome.
Syndromic Paragangliomas: Management

• Can be hormonally active with excess catecholamine secretion. These functional tumors require treatment for catecholamine excess (alpha and beta blockers)

• Surgery
  - The tumor receives its blood supply from coronary arteries: risk of life threatening hemorrhage

• Patients < 45 years of age, with multiple tumors, extra-adrenal paragangliomas, family history or malignant paragangliomas should be considered for genetic screening
  - Given the large number of genes associated with paragangliomas testing can be prioritized based on additional clinical factors
  - Comprehensive screening panels available
## Summary

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<tr>
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<th>Tuberous Sclerosis</th>
<th>Gorlin Syndrome</th>
<th>Carney Complex</th>
<th>VHL, MEN2, others</th>
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<tr>
<td>Associated Cardiac Tumor</td>
<td>Rhabdomyomas common manifestation</td>
<td>Fibromas occur in a low percent of cases</td>
<td>Myxomas</td>
<td>Paragangliomas</td>
</tr>
<tr>
<td>Imaging Appearance</td>
<td>Intracavitary or intramural mass following signal intensity of the myocardium</td>
<td>Isointense on T1W and heterogeneous on T2W images</td>
<td>Mobile, pedunculated mass hypointense on T1W and hyperintense on T2W</td>
<td>Mass occurring at the root of the great vessels or atria</td>
</tr>
<tr>
<td>Non-enhancing Multiple tumors</td>
<td>Non-enhancing central core</td>
<td>Heterogeneous enhancement</td>
<td>Heterogeneous enhancement</td>
<td>Hyper-enhancement</td>
</tr>
<tr>
<td>May contain calcifications</td>
<td></td>
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<td>Atypical locations, multifocal tumors or young patients</td>
<td></td>
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<td>Treatment</td>
<td>Spontaneously resolve</td>
<td>Surgical excision</td>
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<td>Surgical excision</td>
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</table>


Thank You

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