Interesting Cardiovascular Cases

I. Case 1: Erdheim-Chester Disease
   a. Pre-Test Question: Imaging features of Erdheim-Chester disease include which of the following?
      (A) Perivascular soft tissue infiltration
      (B) Perirenal soft tissue infiltration
      (C) Symmetric long bone sclerosis
      (D) Pulmonary interlobular septal thickening
      (E) All of the above
   b. Introduction: Erdheim-Chester disease is a rare multisystem disorder classified as a non-Langerhans cell Histiocytosis.
   c. Epidemiology: A strong male predominance is recognized for patients with Erdheim-Chester disease. The mean age at diagnosis is approximately 55 years, with a range of 16-80 years.
   d. Pathophysiology: Erdheim-Chester disease is a rare multisystem disorder characterized by tissue infiltration by foamy, lipid-laden histiocytes and macrophages, resulting in xanthomatous organ infiltration. Erdheim-Chester disease is distinguished from Langerhans cell Histiocytosis by the presence of a positive immunohistochemical reaction for CD68, and a negative reaction for CD1a, and staining for S-100 protein is also typically negative.
   e. Clinical Presentation: Patients with Erdheim-Chester disease may present with a number of symptoms, including bone pain due to skeletal involvement, diabetes insipidus, renal impairment due to obstruction, exophthalmos, ataxia, fatigue, cutaneous xanthomas (typically periorbital), and weight loss. Pulmonary involvement may produce symptoms such as dyspnea or cough. CNS symptoms, such as seizure, cerebellar and pyramidal syndromes, headaches, and neuropsychiatric disorders may occur. Deaths related to Erdheim-Chester disease are frequently related to cardiovascular involvement. The disease course is variable, with some patients presenting asymptptomatically and others suffering a more aggressive disease course.
   f. Imaging Findings:
      1. Skeletal: symmetric long bone sclerosis, commonly affecting the distal femoral metadiaphysis. Positive tracer uptake on bone scan is typical.
      2. CNS: Pituitary involvement may result in diabetes insipidus or other endocrine disturbances. The meninges may occasionally be involved.
3. **Cardiovascular:** Soft tissue infiltration within the heart, typically the right side, may be seen. Soft tissue infiltration within the atrioventricular groove may occur as well, and periaortic infiltration may occur. This infiltrative tissue may prominently enhance, particularly on MR with late gadolinium enhancement sequences. Pericardial thickening may also occur. The infiltrative tissue shows metabolic activity at FDG imaging.

4. **Thoracic:** Pulmonary involvement occurs in 14-23% of patients with Erdheim-Chester disease, presenting as pleural thickening or effusion. Lung parenchymal involvement typically manifests as smooth interlobular septal thickening and occasionally centrilobular nodules or areas of ground-glass opacity. Less commonly reported pulmonary findings include bronchial dilation, thin-walled cysts, and parenchymal consolidation.

5. **Retroperitoneum:** Retroperitoneal involvement occurs in at least 29% of patients, perhaps greater, with Erdheim-Chester disease, typically presenting as perirenal (often referred to as “hairy kidney”) and periaortic soft tissue infiltration. Adrenal enlargement may occur also.

g. **Differential Diagnosis:** Differential considerations for Erdheim-Chester disease, particularly when perivascular involvement is seen, include lymphoma, vasculitis, IgG4-related sclerosing disease, and possibly metastatic disease. Retroperitoneal involvement in Erdheim-Chester disease may be simulated by retroperitoneal fibrosis, although the latter often produces hydronephrosis and typically spares the posterior portion of the abdominal aorta. In contrast, retroperitoneal infiltration in Erdheim-Chester disease circumferentially encases the aorta, often does not involve the inferior vena cava, rarely produces hydronephrosis, and always spares the pelvic ureters. Cardiac involvement in Erdheim-Chester disease may resemble lymphoma or cardiac angiosarcoma, particularly when the right side of the heart is primarily affected.

h. **Diagnosis:** The diagnosis of Erdheim-Chester disease is usually based on tissue sampling showing the typical histopathological and immunohistochemical staining patterns. Ultrasound-guided biopsy of perirenal tissue may provide material sufficient for diagnosis in selected patients.

i. **Post-Test Question- Answer:** (E- all of the above).

II. **Case 2: Takayasu arteritis**

i. **Pre-Test Question:** Which of the following statements regarding Takayasu arteritis is **true**?
(A) Takayasu arteritis is most commonly encountered in men over the age of 40
(B) Heavy, circumferential arterial calcification is a common feature of acute disease
(C) Mural wall thickening and enhancement are pathognomonic of acute disease
(D) Takayasu arteritis most commonly involves the aorta and its branches
(E) Most TA patients are diagnosed in the acute phase

ii. Introduction: Takayasu arteritis (TA) is an idiopathic, possibly autoimmune, inflammatory disorder primarily affecting the aorta and its major branch vessels, and occasionally the central pulmonary arteries.

iii. Epidemiology: TA may affect up to 6/1,000 patients worldwide, with the majority of cases found in Asian and African patients. TA is often discovered in the second decade of life, and is up to 10 times more common in women than men.

iv. Pathophysiology: TA is a panarteritis, with inflammation beginning within the vascular adventitia and then spreading to the media and intima. Perivascular cuffing with mononuclear inflammatory cell infiltration of the vasa vasorum is seen in the early phase, with inflammatory cell infiltration in the adventitia and media, with subsequent development of inflammation and granuloma formation. Fibrosis and calcification of the vessel wall follows later.

v. Clinical Presentation: TA has traditionally been divided into “pre-pulseless” (early, systemic) and “pulseless” (late, occlusive) stages. The diagnosis of TA during its early phase is frequently difficult, with symptoms including fatigue, fever, myalgias, arthralgias, and weight loss; such constitutional symptoms are common during the early phase. In the late / occlusive phase, various symptoms and clinical examination findings may be present, such as bruits, claudication, hypertension, and even end-organ damage, such as myocardial infarction, blindness, heart failure, mesenteric vascular insufficiency, and stroke. Aortic aneurysm and rupture is possible also. Late phase TA is sometimes further subdivided into a “classic pulseless” disease (Type 1), a mixed type (type 2), an atypical coarctation type (type 3), and a dilated type (type 4). The majority of patients present with late phase disease.

vi. Imaging:
1. Thoracic CT: During the early phase, arterial wall thickening and enhancement of the involved vessels is often seen. Unenhanced thoracic CT may show high attenuation vascular wall thickening. Stenoses may be seen in this stage. In patients with late stage TA, vascular stenosis and occlusions may occur, as may aneurysms, and heavy vascular wall calcification may be seen. Arterial phase CT may show the mural wall thickening to consist of a low attenuation, concentric, inner layer with an enhancing outer ring. Mural wall thickening and enhancement is often seen in the acute phase, but the fibrosis that occurs in the chronic phase may present with thickening and enhancement as well. Thoracic CT may show mosaic perfusion, due to the presence of pulmonary arteritis, and plexogenic arteriopathy inducing regional pulmonary hypoperfusion. Pulmonary embolism is also possible, which may result in pulmonary infarction and pleural effusion. Pulmonary consolidation and ground-glass opacity resulting from pulmonary hemorrhage may occur. An interstitial infiltrative appearance has been reported, as have nodular opacities, the latter presumably representing extravascular granulomatosis. Bronchiectasis is rare, but has been noted.

2. MRI: MRI findings in patients with TA include concentric vascular wall thickening which often shows intense enhancement following contrast administration, vascular stenosis, fusiform vascular dilation, and thickening of valve cusps. Perivascular signal abnormalities may be present as well. Nonspecific associated findings include pericardial fluid or signal alterations in the pericardium.

3. Angiography: Catheter angiography may show multifocal stenosis and / or aneurysms in patients with TA. Vascular stenosis tend to be long, tapered and smooth in character, and range from mild to severe, even with frank occlusions. Collateral vessel formation maybe prominent in the latter in circumstance. Catheter angiography has a limited role in TA diagnosis, as it is invasive, associated with a substantial radiation dose, can be difficult to perform in patients with stenosis, and does not depict the vessel wall well, and therefore cannot reliably distinguish between vascular narrowing due to acute mural inflammation or chronic transmural fibrosis. Furthermore, ischemic complications related to catheter angiography performed in patients with TA may occur. Several “types” of TA have been described on angiography:
   a. Type I: Localized to aorta and branches
b. Type II: Involvement of thoracoabdominal aorta, but sparing the arch

c. Type III: Combined features of Types I and II

d. Type IV: Pulmonary arterial involvement

vii. Differential Diagnosis: The differential diagnosis for TA includes atherosclerosis, although the latter often presents in patients older than those typically affected by TA. Also, calcification related to atherosclerosis is limited to the vascular intima, whereas that of late-phase TA is transmural. Connective tissue disorders, such as Marfan’s and Ehlers-Danlos syndrome, may merit consideration, although these conditions do not typically manifest as vasculitis with systemic inflammation. Other causes of large vessel vasculitis should be considered as well, such as Giant cell arteritis (although this disorder usually does not affect patients under the age of 50), Behçet syndrome, Cogan syndrome, spondyloarthropathies, and systemic lupus erythematosus, although these disorders may be distinguished by their specific manifestations. Radiation-induced aortitis may produce stenoses that resemble those seen in TA. Other disorders that may produce perivascular infiltration resembling the wall thickening seen in TA include Erdheim-Chester disease and IgG4-related sclerosing disease. Very rarely, vascular or perivascular neoplasms, such as lymphoma or angiosarcoma, may simulate the vascular wall thickening seen in patients with TA. Diagnostic criteria for TA have been established by the American College of Rheumatology.

viii. Post-Test Question- Answer: (D- Takayasu arteritis most commonly involves the aorta and its branches).

III. Case 3: Hypertrophic cardiomyopathy with crypt formation

a. Pre-Test Question: Which of the following regarding hypertrophic cardiomyopathy (HCM) is correct?

(A) HCM is an uncommon disorder transmitted as an autosomal recessive trait
(B) The most commonly encountered morphologic variant of HCM is the mid-ventricular type
(C) A maximum LV wall thickness ≥ 30 mm is a predictor of sudden death
(D) Diffuse subendocardial delayed gadolinium enhancement is typical of HCM
(E) Mass-like HCM is differentiated from other causes of LV masses by low T2 signal intensity in HCM
b. *Introduction:* Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder which is a common cause of sudden death in young people. HCM has various phenotypical manifestations and a varied clinical course. HCM is defined as diffuse or segmental left ventricle (LV) hypertrophy with a non-dilated, hyperdynamic left ventricular chamber, in the absence of other cardiac or systemic disorders producing such findings.

c. *Pathophysiology:* HCM is an autosomal dominant trait, caused by mutations within sarcomere genes. HCM is characterized histopathologically by myocyte hypertrophy and disarray and interstitial fibrosis. Coronary arteriole dysplasia is also often present. Histological criteria for diagnosis require at least 5-10% of myocytes within the interventricular septum to show disarray - this can lead to false negative biopsies due to tissue sampling errors.

Various HCM phenotypes have been recognized, including an asymmetrical (septal) variant with or without left ventricular outflow tract obstruction (the most common pattern), an apical variant, a symmetric / concentric form, a mid-ventricular form, a “mass-like” variant and non-contiguous forms. The right ventricle may be involved in 71-33% of patients with HCM, usually at the apex or mid portion.

d. *Clinical Manifestations:* The prevalence of HCM may be as high as 1:500 individuals. Patients with HCM may be asymptomatic, with the disorder discovered incidentally. Many patients will present in adolescence or early adulthood, but some phenotypical expressions of HCM may not occur until well into adulthood. When symptoms are present, chest pain, dyspnea, syncope, or even sudden cardiac death may be encountered. The American College of Cardiology / European Society of Cardiology have established guidelines for sudden death risk stratification for HCM patients. The most commonly reported symptom is dyspnea on exertion, which is the result of impaired diastolic ventricular filling.

e. *Imaging:*
   
i. Echocardiography: Echocardiography is the mainstay for HCM patient evaluation, but is operator-dependent, may be limited by the available acoustic window, and may not optimally depict the endocardial surface of the anterolateral and apex of the LV, which can result in underestimation of the degree of LV hypertrophy.

   ii. MR:
      1. The asymmetric / septal variant often presents with wall thickening involving the anterior septum disproportionate to
the remaining myocardial musculature. 20-30% of these patients may have left ventricular outflow tract (LVOT) obstruction with a systolic pressure gradient across the LVOT. This gradient is caused by systolic anterior motion (SAM) of the mitral valve leaflets, which often also produces an asymmetric mitral regurgitant jet as well. SAM may be the result of a Venturi effect induced by the reduced LVOT diameter, or be the result of differing anatomical positions of the papillary muscles and mitral valve leaflets—the exact mechanism is debated. MR shows a low signal / signal void “jet” in the LVOT during systole. LVOT gradients can be estimated with phase-contrast MR, but are more accurately determined with Doppler echocardiography. Variations of septal HCM involvement include the “reverse-curve” and “sigmoid” morphologies. The former is seen in young patients and has a strong genetic and sudden death association, whereas the latter is seen in older patients, but is uncommonly associated with positive genetic testing.

2. The **apical HCM variant** primarily shows muscular hypertrophy at the LV apex. This variant is more commonly encountered in Asia patients, often affecting middle-aged men, but is increasingly recognized in the Western world. The apical HCM variant also enjoys a relatively better prognosis than other HCM forms, but is often complicated by hypertension.

3. **Symmetric / concentric HCM variant**: This HCM variant presents with diffuse, circumferential muscular hypertrophy, often with a small LV cavity that may completely obliterate during systole.

4. **Mid-ventricular HCM variant**: The muscular hypertrophy in the id-ventricular HCM variant is found in the middle third of the LV wall. Often the mid LV wall will completely appose during systole in patients with the mid-ventricular HCM variant, creating a “dumb-bell” configuration. Apical aneurysms may be present.

5. **Mass-like HCM**: Mass-like HCM results from focal, segmental myocyte disarray, creating a mass-like appearance within the myocardium. The mass-like area will follow normal myocardial signal on various sequences, unlike true masses (see Differential Diagnosis and Associations below).

6. **Non-contiguous HCM**: Non-contiguous HCM manifests as hypertrophic segments interspersed with normal myocardium, creating a “lumpy-bumpy” appearance. This HCM variant can be overlooked or underestimated at echocardiography.
7. LV “crypts”, defined as blind out-pouchings or pits, or “V-shaped” fissures extending into but confirmed by the myocardium, may be seen at SSFP or cine MR imaging in patients with HCM or “preclinical” HCM patients. These crypts may be most commonly involved at the LV and RV insertion points.

8. Maximum LV wall thickness ≥ 30 mm has been identified as a predictor of sudden death in HCM patients, as is LVOT obstruction.

9. Most patients with HCM have diastolic dysfunction. In some patients, in late-phase HCM, systolic dysfunction, with LV cavity dilation and wall thinning, may be seen. This situation has been referred to as the “burned-out” phase.

10. Delayed enhancement: Delayed myocardial enhancement is associated with myocardial fibrosis, and is a predictor of sudden cardiac death risk and possible progression to heart failure. Myocardial delayed enhancement (MDE) is seen in as many as 80% of HCM patients. MDE in HCM patients typically shows a patchy, mid-wall predilection, with multiple foci. The interventricular septum is also often involved, particularly the anteroseptal and basal segments. MDE also preferentially occurs at the anteroseptal and posteroseptal RV insertion points. The thicker the myocardium, in general, the more delayed enhancement may be seen. Areas of MDE may be encountered in areas of wall motion abnormality, and the presence of MDE has been correlated with the development of tachyarrhythmias. It has been reported that “relatively benign” MDE may be encountered at the RV free wall insertion point onto the interventricular septum. MDE in “burned-out” HCM may resemble ischemic MDE, although may deviate from recognized vascular territories.

iii. Perfusion: Perfusion imaging (particularly PET) may reveal defects and decreased myocardial blood flow in patients with HCM. This finding is an independent predictor of HCM-related mortality. Perfusion MR may provide similar data.

f. Clinical Course and Prognosis: HCM generally has a favorable course in asymptomatic or minimally symptomatic patients- the annual mortality in these patients is no greater than 1%. Even patients with LVOT gradients may do well for a number of years. In symptomatic patients deterioration is usually gradual, and symptoms may wax and wane. The prognosis is symptomatic patients is worse than asymptomatic patients, with the annual mortality exceeding 5%.

g. Diagnostic Criteria and Associations:
i. In general: end-diastolic LV wall thickness ≥15 mm.
   1. **Asymmetric / septal HCM variant:** Septal myocardial thickness ≥15 mm or ratio of septal wall thickness / inferior wall thickness at mid-ventricle > 1.5.
   2. **Apical HCM variant:** Absolute apical wall thickness ≥15 mm or apical / basal LV wall thickness ≥1.3 – 1.5. The appearance at end-systole on cross sectional imaging and angiography has often been described as “spade-like”. This configuration is often well seen in 2-chamber views. Subjective criteria include apical cavity obliteration and failure of progressive reduction in LV wall thickening towards the apex. Apical aneurysms may occur.
   3. **Symmetric / concentric HCM variant:** This HCM variant manifests as concentric left ventricular hypertrophy in the absence of a definable cause. The LV cavity is usually small. This form of HCM must be differentiated from competing causes of LV hypertrophy, including aortic stenosis, amyloidosis, other infiltrative cardiac diseases, hypertension, and athlete’s heart.
   4. **Mid-ventricular HCM variant:** This HCM variant is associated with ventricular dysrhythmias, systemic embolization, and myocardial necrosis.
   5. **Mass-like HCM:** Mass-like HCM must be distinguished from true intramyocardial masses. This is usually possible using steady-state free precession imaging, first-pass contrast-enhanced imaging and delayed enhancement techniques. Mass-like HCM will follow myocardial signal intensity on all these various sequences, and contractility through the mass-like region is maintained, whereas true masses show signal intensity that will differ from normal myocardium, and the abnormal area of thickening if often not contractile. Masses that may be confused with mass-like HCM, and vice-versa, include cardiac rhabdomyoma, lymphoma, and fibroma.

h. **Differential Diagnosis:** The differential diagnosis of HCM includes left ventricular hypertrophy from other causes, such as hypertensive heart disease or aortic stenosis. Left ventricular mass may also be increased in athlete’s heart. Typically delayed enhancement is not seen in such patients, although a period of de-conditioning may be required to differentiate athlete’s heart from HCM. With this approach, athlete’s heart will show a decrease in LV mass, whereas HCM will not change. Restrictive cardiomyopathy, such as sarcoidosis and amyloidosis, should be differentiated from HCM. Focal intramyocardial masses (fibroma, rhabdomyoma, lymphoma) or intracavitary thrombus closely
applied to the LV wall should be differentiated from the mass-like HCM variant.

i. Post-Test Question- Answer: (C- A maximum LV wall thickness ≥ 30 mm has been identified as a predictor of sudden death in HCM patients).

IV. **Case 4: Cardiac fibroma**

a. **Pre-Test Question:** Cardiac MRI features of cardiac fibromas include which of the following?
   (A) Focal intramyocardial mass within the LV
   (B) Lesion calcification
   (C) Low T2 signal intensity within the lesion
   (D) Prominent enhancement on delayed enhancement imaging
   (E) All of the above

b. *Introduction:* Cardiac fibroma consists of fibroblasts contained within areas of collagen. Fibromas may be neoplastic in nature, although some have regarded fibromas as hamartomatous proliferations rather than true neoplasms.

c. *Epidemiology:* Fibromas often affect children, and may even occur in utero. The mean age of presentation is 13 years, with one-third presenting in patients under the age of 1. Males and females are equally affected. Fibromas are the second most common tumor to affect the heart in children, behind rhabdomyoma.

d. *Pathophysiology:* Cardiac fibromas are firm masses located within the myocardial wall, almost always the ventricles. These lesions, unlike most cardiac neoplasms, typically do not undergo necrosis, cystic change, or hemorrhage.

e. *Clinical Presentation:* Cardiac fibromas may present with arrhythmias, and may even produce sudden death. Some patients with cardiac fibroma may present with cardiac failure, syncope, cyanosis, or chest pain. About one-third of cardiac fibromas may be detected asymptptomatically. Cardiac fibromas may be associated with Gorlin syndrome (also known as basal cell nevus syndrome), consisting of odontogenic keratocysts of the mandible, rib and vertebral anomalies, intracranial calcifications, a distinct facies, basal cell malignancies, and an increased risk for neoplasia in multiple organ systems.

f. *Imaging:*

   i. Echocardiography: Fibromas often appear as solitary, hyperechoic, hypocontractile, intramyocardial masses. These lesions may be mistaken for hypertrophic cardiomyopathy.
ii. CT: Cardiac fibromas often appear as homogenous masses of soft tissue attenuation at CT. The lesion may appear infiltrative or circumscribed. Calcification may occur (unlike rhabdomyoma).

iii. MRI: Due to the dense, fibrous nature of the lesion, cardiac fibromas often show homogeneous hypointense signal on T2-weighted sequences (unlike rhabdomyoma, which often shows increased T2 signal). Fibromas are often nearly isointense on T1-weighted imaging. Cardiac fibromas often show little or no contrast early enhancement, although reports of homogeneous and heterogeneous enhancement patterns, as well as peripheral enhancement, have been described. When enhancement occurs, it is typically seen on delayed enhancement imaging rather than at first-pass imaging, and may be quite prominent. Cardiac fibromas are usually located within the ventricles, particularly the left, either arising from the interventricular septum or lateral free wall. An atrial location may be rarely encountered in patients with Gardner syndrome.

g. Differential Diagnosis: The main differential diagnostic consideration for cardiac fibroma presenting in the pediatric patient is cardiac rhabdomyoma. Focal presentations of hypertrophic cardiomyopathy can resemble cardiac fibroma.

Post-Test Question- Answer: (E- all of the above).

References: