CAA (coronary artery aneurysm) as manifestation of CAV (cardiac allograft vasculopathy)

BACKGROUND: Coronary artery aneurysms are defined as dilated coronary arterial segments that are greater than 1.5 times the diameter of normal segments (1).

- The first postmortem case of coronary artery aneurysm (CAA) is described in 1761 by Morgagni.
- The histopathological features of CAA are based on the destruction of the media of the arterial wall, and this thinning of the media together with increased wall stress causes progressive dilatation of that segment of the coronary artery.
- The most common cause of CAA is atherosclerosis, which accounts for at least half of the coronary artery aneurysms diagnosed by pathology or angiography in adults (1).
- Other causes of coronary artery aneurysms include inflammation, trauma, coronary artery dissection, congenital conditions, infection, and iatrogenic manipulation of arteries such as percutaneous coronary interventions.

INCIDENCE: Aneurysms involving the left main coronary artery (LMCA) are rare (0.1%).

- In a study involving greater than 22,000 coronary angiograms, only 22 patients were found to have an aneurysm involving LMCA (2).
- These results are obtained from either post-mortem studies or angiography, and may underestimate the actual frequency by excluding asymptomatic patients.

DISTRIBUTION: The distribution of coronary artery aneurysms predominantly involves the proximal and middle segments of the right coronary artery followed by left anterior descending artery, left circumflex artery and left main artery CAA therefore may be asymptomatic or be the cause of angina, myocardial infarction, and sudden death due to thrombosis, coronary spasms, or impaired coronary flow reserve (3).

DISCUSSION: CAV becomes clinically apparent in up to 50% of cardiac transplant recipients within the first 5 years after transplant surgery.

- One of the main risk factors influencing graft loss and patient survival in post-transplant patients is CAV (4).
- CAV is a type of cardiovascular disease unique to transplant patients characterized in its early stages by intimal proliferation and in its later stages by luminal stenosis of epicardial branches, occlusion of smaller arteries, and myocardial infarction.
- Although CAV resembles atherosclerosis, there are important differences. For example, in CAV intimal proliferation is concentric and diffuse involving both proximal and distal portions of the coronary vasculature.
- In addition, calcification is uncommon and the elastic lamina remains intact. (4).
- The pathogenesis of CAV though unknown is thought to be multifactorial involving immune and non-immune factors
- Immunologic mechanisms include acute rejection and anti-HLA antibodies and non-immunologic mechanisms include donor age, hypertension, hyperlipidemia, pre-existing diabetes and side effects of immunosuppression such as post-transplant diabetes, nephrotoxicity, and cytomegalovirus (CMV) (5).
- The presentation of CAV is very subtle and it is imperative to identify individuals early in the disease process.
- Acute cellular rejection correlates and accounts for approximately 25% of the variance in CAV development in transplant recipients (6).
• The occurrence of ≥ 2 major rejection episodes has been significantly associated with an increased prevalence of CAV.
• In this patient, his first episode of rejection occurred 6 weeks after transplantation and his second episode occurred less than 5 months later.
• Individuals on immunosuppressive therapy are at risk for opportunistic diseases such as CMV, and the sequelae of CAV. Pathogens such as CMV can cause endothelial dysregulation and transplant arteriosclerosis.
• The incidence of CMV disease is 15-25% while primary infection or reactivation occurs in 50-70% of heart transplant patients.
• CMV may contribute to the vasculopathy observed in cardiac transplant patients by impairing the endothelia nitric oxide synthase pathway
• His catheterization at nineteen months indicated moderate vasculopathy with a large aneurysm of the LAD. The presence of a CAA in this patient is most likely secondary to multiple rejection episodes and is a rare presentation of CAV.

MANAGEMENT (surgical):
• The characteristic pattern of intimal thickening in CAV is diffuse and concentric, though many lesions are discrete and amenable to percutaneous intervention.
• Periprocedural angiographic success is defined as a decrease in luminal obstruction to <50% and restenosis is defined as ≥50% diameter stenosis on follow-up angiogram (7).
• Angioplasty may provide palliation for patients with focal stenoses of proximal or midvessel, but the published restenosis rate with percutaneous transluminal coronary angioplasty (PTCA) is as high as 55% at a mean of eight months whereas those treated with coronary stenting had restenosis of approximately 20% (8,9).
• Other percutaneous interventions including atherectomy and cutting balloon angioplasty have been evaluated but are also limited by high restenosis rate (9). Coronary artery bypass graft (CABG) is generally of limited use because of the diffuse concentric characteristics of CAV. In addition, procedural outcomes are often poor due to severe immunosuppression and multiple comorbidities such as diabetes, chronic renal failure and left ventricular dysfunction (10).

MANAGEMENT (medical):
• Once identified, there are various factors that guide therapeutic interventions.
• The size and location of CAA as well as coexistent obstructive CAD guide therapeutic measures. In evaluating both transplant and non-transplant patients with CAA, medical therapy should first be optimized.
• The usual coronary risk factors (elevated plasma cholesterol, diminished HDL, elevated triglycerides, cigarette smoking, hypertension, obesity, and diabetes) should be minimized and medical management optimized.
• Medical management includes statin therapy, smoking cessation, adequate blood pressure control, glycemic control, weight loss and behavioral modification including diet and exercise. For the transplant patient specifically, medical strategies can be used to minimize the immunologic risk of developing CAV.
• The calcineurin inhibitors (cyclosporine and tacrolimus) effectively prevent rejection, but do not prevent the development of CAV. Several mechanisms have been attributed for the lack of long-term success in prevention of CAV.
• First, neither calcineurin inhibitors nor purine synthesis inhibitors (azathioprine and mycophenolate mofetil) prevent intimal thickening in the first year post-transplant. In addition, calcineurin may only be partially inhibited by clinical doses of cyclosporine and this partial inhibition may initiate the immune rejection process (4).
• Newer immunosuppressant agents such as proliferation signal inhibitors have been shown to reduce acute rejection and have long-term efficacy against CAV.

CONCLUSION: CAV remains an ongoing obstacle to long-term success in cardiac transplant patients. The best approach to management of CAV is modification of underlying risk factors (hypertension, hyperlipidemia, diabetes) and optimization of immunosuppressive regimen.
Clinical trials have shown that proliferation signal inhibitors effectively reduce acute rejection and have long-term efficacy against CAV. Once CAV develops, the only definite treatment is re-transplantation, although the immunosuppressant rapamycin can limit disease progression.

Surgical procedures such as stenting and PTCA may offer benefits in the general population, but have high re-stenosis rates and limited benefits in transplant patients given the diffuse nature of CAV (4). A greater awareness and insight into immune and non-immune mechanisms are key components for therapeutic advances in the management of CAV.