Unusual Presentation of IgG4 Related Disease with Coronary Aneurysms

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Summary
IgG4-related systemic disease is characterized by high serum IgG4 concentrations, sclerosing inflammation containing numerous IgG4-positive plasmacytes, occurrence in multiple organs and good response to steroids. Although abdominal aneurysms in IgG4-related systemic disease are well described, there are only a few case reports of coronary artery involvement [1]. Recent studies have suggested that IgG4-related disease may underlie certain coronary artery abnormalities, such as coronary aneurysms, pseudo tumour, wall calcification, and intimal thickening.

Keywords: IgG4 disease; Coronary aneurysm

Background
This case demonstrated severe coronary artery involvement in IgG4-related disease. Although a rare entity, it is prudent to establish the state of the vascular system in this condition. Clinical diagnosis depends on serum IgG4 level, responsiveness to glucocorticoid therapy, and imaging studies to look for involvement of other organs that may be amenable to biopsy.

Case Presentation
A 70-year-old retired teacher was seen in the renal clinic in January 2014 with microscopic hematuria. He was an ex-smoker and had stopped smoking 30 years ago. His father was a coal miner who died at the age of 59 with lung disease. He was a known asthmatic which was well controlled and was diagnosed with mild aortic stenosis in 2012. He was under the care of a hematologist in 2013 for raised IgG paraproteinemia and was investigated with ANA, ANCA, and myeloma screening all of which were negative.

On examination, he weighed 76.9kg with a BMI of 26.2kg/m2, his pulse was regular with no radio femoral delay or carotid bruit. Blood pressure was within normal limits. Systemic examination was unremarkable apart from an ejection systolic murmur in the aortic area.
Investigations
Serum creatinine was 92micromol/l with a GFR of 71ml/min/m2; urine protein was negative. Hemoglobin was 140g/l. Immunoglobulin screen showed a raised IgG level of 33.2g/l, and normal IgM and IgA levels. Furthermore, free kappa and free lambda levels were high at 54.9 and 57.3 respectively, however, the kappa: lambda ratio was normal. Urine Bence Jones proteins and a bone marrow biopsy were normal. C3 and C4 levels were within normal range. IgG4 subclass levels were subsequently found to be elevated at 22.25g/l (< 1.3g/l).
A CT chest showed some bronchiectasis changes and a well-defined 4 cm right hilar mass closely associated with the upper lobe pulmonary artery. It also showed coronary artery aneurysms and a left subclavian artery aneurysm (Figure 1). The patient was referred to cardiology, however no further action was undertaken as he was asymptomatic.

Figure 1: CT scan of the chest showing coronary artery aneurysm.

He presented in January 2015 with two days history of epigastric and left side chest pain. His admission ECG showed slight ST depression in V3-V6, and his Troponin I was high at 2.67ug/l (0-0.03). Echocardiography showed hypokinetic inferior wall, basal and mid posterior regions, with overall mild/moderately impaired LV systolic function, mild diastolic dysfunction, and moderate aortic stenosis. He underwent coronary angiography which showed aneurysmal dilatation of the proximal segment of left anterior descending artery, a huge aneurysm of the left circumflex artery along the whole length, and total occlusion of the right coronary artery (Figure 2). He was further investigated with CT head and neck to check for other aneurysms, which showed a 23mm aneurysm at the proximal left subclavian artery near the aorta.
Figure 2: Coronary angiography which showed aneurysmal dilatation of the proximal segment of left anterior descending artery, a huge aneurysm of the left circumflex artery along the whole length, and total occlusion of the right coronary artery.

Treatment
Steroid therapy was commenced in May 2014 and stopped in February 2015 when he underwent Coronary Artery Bypass Graft (CABG) and tissue aortic valve replacement. Three venous grafts were placed to OM1, PDA, and LAD.

Outcome and Follow-Up
On follow up the he has had no further symptoms attributable to his IgG4 related disease, and his renal function is excellent (creatinine 94micromol/l and urine protein creatinine ratio of 17.4mg/mmol).

Discussion
IgG4-related disease was first proposed by Kamisawa et al. Based on immunohistochemical examination of the pancreas and other organs in patients with autoimmune pancreatitis [3]. The common features include tumor-like swelling of involved organs, a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells and a variable degree of fibrosis that has a characteristic “storiform” pattern. In addition, elevated serum concentrations of IgG4 are found in 60 to 70 percent of patients with IgG4-related disease [4,5]. Tissue biopsy is the gold standard for diagnosis of IgG4-related disease; however, imaging is an important part of work up. Arterial involvement is well known and usually involves large arteries such as the aorta and great vessels.
The involvement of small and medium sized arteries is rare [6]. Increased levels of serum and tissue IgG4 offer useful hints in diagnosing the condition [7]. Other findings may include peripheral eosinophilia, high IgE levels, and atopic manifestations. Serum IgG4 levels are increased (>1.3g/l) in 70% of the cases, and 61% of the patients have polyclonal hypergammaglobulinemia [7,8]. There is also a known co-relation between the level of IgG4 and the number of organs involved. IgG4 is usually seen in middle-aged to elderly men, but it is not entirely uncommon in other age groups.

Clinical symptoms can range from relatively mild to serious complications, including organ dysfunction due to the cellular infiltration and fibrosis, and symptoms of obstruction or compression because of organomegaly [9]. The pathogenesis of the IgG4-related disease remains poorly understood, although the leading theories point to an autoimmune or allergic mechanism. Current hypotheses include abnormal regulatory T cells that drive plasma cell differentiation, or an unknown antigen that elicits a robust Th2 immune response.

In addition to chronic organ damage caused by inflammation and fibrosis, there are also potential life-threatening vascular complications of IgG4-related disease [10]. In a meta-analysis done by Stone et al [11] the arch of the aorta was the most commonly involved portion of the thoracic aorta.

The optimal treatment for IgG4-related disease has not been established, but it responds well to steroids. According to international consensus, glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-related disease, unless contraindications to such treatment are present [11]. Following a successful course of induction therapy, certain patients benefit from maintenance therapy. Retreatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction [12]. The natural course of IgG4-related disease and prognosis is unclear. Although most patients improve with steroid therapy, untreated patients can succumb to irreversible multi-organ failure. Recognition and treatment of the disease is therefore very important. Relapses are common after stopping treatment and trials with Rituximab have given favorable results [13].

**Learning Points/Take Home Messages**

- This is a rare occurrence of IgG4 related disease in the coronary vasculature.
- Other imaging modalities along with serum IgG4 levels are important to establish IgG4 related disease.
- Glucocorticoid therapy is the first line agent to induce remission.

**REFERENCES**

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