The role of cardiovascular imaging modalities in the evaluation of IgG4-related cardiovascular disease

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Immunoglobulin 4-related disease (IgG4-related disease) is a systemic inflammatory disease characterized by an increase in serum levels of IgG4 and by fibrosclerosis, lymphocytic infiltration and IgG4-positive plasma cells. Assay of serum IgG4 levels and biopsy of involved organs are necessary for diagnosis. The disease usually responds to treatment with corticosteroids and/or immunosuppressive medication.
IgG4-related cardiovascular disease (IgG4-RCVD) disease manifests as cardiac pseudotumors, inflammatory periaortitis, coronary arteritis and/or pericarditis and severely affects patient prognosis. Various imaging techniques have been successfully used for early disease detection and follow-up of CVD.

Echocardiography and vascular ultrasound are the most commonly used non-invasive, non-radiating imaging techniques. Periaortitis/periarteritis and coronary artery aneurysms can be assessed by Computed Tomography (CT). In active periarterial or coronary artery inflammation, ^{18}FDG-PET will show FDG uptake at the area of the lesion. Cardiovascular Magnetic Resonance (CMR) can offer an integrated imaging of aorta, coronary arteries and the heart, assessment of disease acuity, extent of fibrosis and guide further treatment. However, multimodality imaging may be necessary in cases with multifocal CV involvement.The aim of this article is to describe this rare disease and present the role of cardiovascular imaging modalities in diagnosis, risk stratification and treatment of patients.

Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibrotic inflammatory disease, that presents with lymphocytic infiltration, IgG4-positive plasma cells, simultaneous development of fibrosis, and usually elevated serum levels of IgG4 [1, 2]. Early diagnosis is rather difficult, due to non-specific symptoms and may be diagnosed by organ dysfunction [3, 4].

CLINICAL MANIFESTATIONS AND TREATMENT OF IGG4-RELATED CARDIOVASCULAR DISEASE

The clinical presentation of IgG4-related cardiovascular disease (IgG4-RCVD) is characterized by symptoms including one or more organs or organ failure. It may involve various organs such as the pancreas (Autoimmune Pancreatitis-AIP), lacrimal glands (Mikulicz's disease), retroperitoneum (retroperitoneal fibrosis), aorta (aortic aneurysm and aortitis) and heart (constrictive pericarditis and pseudotumors around the coronary arteries). Multiple organ involvement may coexist during the evolution of the disease [5] and malignancies were reported in 7.4% of IgG4-RD patients [6].

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DIAGNOSTIC CRITERIA FOR IGG4-RD

These include (1) serum IgG4 concentration >135 mg/dl, and (2) >40% of IgG-positive plasma cells being IgG4-positive and >10 cells/high powered field in biopsy samples.
The treatment of IgG4-RCVD usually requires higher doses of corticosteroids than IgG4-related extra-cardiovascular disorders, with the ideal dose of medication and surgical intervention being tailored to individual patient needs [5].

HOW CAN CARDIOVASCULAR IMAGING TECHNIQUES DIAGNOSE IGG4-RCVD?

1.Echocardiography and Ultrasonography

Echocardiography gives reliable information about pericardial anatomy /function, valvular integrity, wall motion changes and ventricular function. Transthoracic Echocardiography

(TTE) and/or Transoesophageal Echocardiography (TEE) enable early and accurate diagnosis and severity assessment of valvular involvement. TTE can also detect complex and irregular masses, adherent to the endocardial surface of any cardiac chamber or great vessels and TEE can offer more details about their anatomy and pathophysiology. Echocardiography is ideal for the detection of pericardial lesions and cardiac pseudotumors [7, 8]. Contrast enhanced ultrasound (CEUS) can demonstrate abundant contrast enhancement in the periaortic tissue [9] and be used for post-surgery monitoring of IgG4 patients, due to their capability to reliable identify vascular leak [10]. By assessing flow-velocity, Continuous Doppler Ultrasound (CDUS), can evaluate flow characteristics before lumen changes detectable on angiography take place [11]. However, echocardiography, although inexpensive and widely available, remains an operator-dependent technique, limited by acoustic window and its inability to perform tissue characterisation [12].

2. Multisclice Computed Tomography.

Periaortitis and periarteritis can be detected by CT as a non-smooth soft tissue thickening around the aorta and various arteries [13]. Besides luminal narrowing of the coronary arteries, marked circumferential periarterial thickening around the coronary arteries with enhancement at the point of stenosis is the typical finding of vasculitis [14]. The CT limitations are the need for iodinated contrast administration and radiation exposure. Although CT is most effective in the assessment of the aorta and its proximal branches, it is relatively limited in distal aortic branches [15]. CT is also valuable to detect pericardial effusions and thickening with or without calcification [16].

3. Cardiovascular Magnetic Resonance (CMR) Imaging

Due to its capability to perform function evaluation and tissue characterization without radiation, CMR has a very promising role in the evaluation of IgG4-RCVD [17]. It can also assess disease activity and response to treatment. Although there are no studies regarding CMR use in IgG4-related cardiovascular disease, CMR has been successfully used to determine disease activity in Takayasu arteritis (TA) [18]. The use of paramagnetic contrast agent has significantly increased the diagnostic capacity of Magnetic Resonance Angiography (MRA) to differentiate between active and inactive TA [19]. Finally, whole-body MRA combined with vessel wall imaging provides a more detailed evaluation of disease extent and activity in TA [20].

4. Cardiac catheterization

This provides the final assessment of constrictive pericarditis [21, 22] and coronary artery lesions [23]. However, it is invasive and is not indicated for repetitive evaluation.

5. Positron Emission Tomography.

In IgG4-RCVD, FDG-PET shows FDG uptake at the lesion with active periarterial inflammation [24]. FDG-PET is the most useful technique for identifying biopsy sites and evaluating treatment efficacy [24].

6. PET-CT and PET/MRI.

These modalities have been already used for assessment of aortic involvement in great vessel vasculitides [25]. However, the multifocal nature of IgG4-RCVD may necessitate a combination of multimodality imaging [26, 27].

CONCLUSIONS.

CV imaging of IgG4-RCVD facilitates early diagnosis and treatment assessment. Echocardiography / US and multislice CT are the most commonly used techniques for this purpose. Wider adoption of CMR promises an integrated non-invasive, non-radiating assessment of cardiovascular anatomy, function, disease activity and fibrosis extent. However, the multifocal presentation of IgG4-RCVD may necessitate a multimodality imaging approach.

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