Multimodality Imaging Evaluation of Coronary IgG4-Related Disease: A “Tumor-Like” Cardiac Lesion

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Abstract: Immunoglobulin G4-related disease (IgG4-RD) is a systemic immune-mediated fibro-inflammatory disorder. Coronary IgG4-RD has been scarcely reported and may present as “tumor-like” lesions. These pseudo-masses may be underdiagnosed mainly due to a vague clinical picture that can vary from complete lack of symptoms to acute coronary syndrome or sudden cardiac death. Early recognition of coronary IgG4-RD is essential to monitor disease activity and prevent life-threatening complications. We report a comprehensive non-invasive imaging evaluation of a patient affected by coronary IgG4-RD, which was diagnosed as an incidental finding during routine pre-laparoscopic cholecystectomy checkup. Non-invasive imaging revealed the presence of a peri-coronary soft-tissue mass that was stable at 12 months follow-up.

Keywords: autoimmune disease; IgG4-associated; IgG4-related disease; cardiac-gated imaging techniques; coronary artery disease; systemic vasculitis

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an emerging fibro-inflammatory condition with unknown etiology, characterized by lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, tumor-like lesions and elevated serum IgG4 concentrations in 60–70% of patients [1]. Recently, IgG4-RD has been recognized as a chronic immune-mediated systemic disease, usually affecting middle-aged to elderly patients, that can potentially encompass any organ system. Common presentations include type 1 autoimmune pancreatitis, Mikulicz syndrome, Riedel thyroiditis, sclerosing cholangitis, retroperitoneal fibrosis, interstitial nephritis, prostatitis and lung disease [2].

Periarteritis, with involvement of large-to-medium-sized vessels, may also be a manifestation of IgG4-RD as well as inflammatory aneurysm formation. More rarely, this condition has been reported to affect small-sized vessels such as coronary arteries, leading to potentially life-threatening complications, such as acute coronary syndrome or sudden cardiac death. Histopathologic assessment is considered the method of choice to confirm the diagnosis of IgG4-RD; however, it can be challenging to perform biopsy or to obtain surgical samples when this disease involves vital structures. In these cases, non-invasive imaging evaluation of coronary IgG4-RD may play a crucial role both for the diagnosis and management of this condition [1].
Since IgG4-RD involvement of coronary arteries has been scarcely described, our aim is to report multimodality non-invasive imaging findings of this rare entity and to present a review of the literature.

2. Case Presentation

A 63-year-old man came to our observation in May 2021 to perform a chest CT study for suspected pulmonary nodule previously detected on a chest X-ray during a routine pre-laparoscopic cholecystectomy checkup.

The patient was asymptomatic for angor and dyspnea. Past medical history was significant for multiple comorbidities including obesity, dyslipidemia, arterial hypertension, gouty arthritis, multi-district arthrosis, chronic renal failure, phlebopathy of the lower limbs with dyschromia and trophic ulcerations and multinodular thyroid goiter. The patient reported remote tobacco use, past episodes of chest pain and no history of coronary artery disease.

Chest CT did not reveal lung nodules but a peri-coronary “pseudotumor” as an incidental finding. Dual-energy coronary computed tomography angiography (DE-CCTA) was subsequently performed, and showed a soft-tissue mass within the anterior interventricular sulcus, which encased the distal tract of left main stem (LM), the proximal and the middle segment of the left anterior descending artery (LAD), the first diagonal (D1) and the proximal segment of the left circumflex artery (LCx), without causing any stenosis of the involved coronary segments and configuring the typical “pigs-in-a-blanket” sign (Figure 1). All coronary arteries did not show any intraluminal calcification or stenosis (i.e., Ca score = 0; CAD-RADS 1).

![Coronary CTA in a patient with coronary IgG4-RD. Axial maximum intensity projection (A) and curved multiplanar reconstructions (B,C) show the presence of a soft tissue (arrow) surrounding LM, LAD (A,B) and LCx (C) configuring the typical “pigs-in-a-blanket sign”.](image)

The pseudo-mass did not show early enhancement or iodine uptake during arterial phase but had a tenuous late-enhancement at delayed phase (Figure 2A,B).

Extended laboratory tests revealed mildly elevated IgG (1673 mg/dL—normal range: 700–1600 mg/dL) and IgG4 levels (138 mg/dL—normal range: 5–125 mg/dL) at turbidimetric assays, normal erythrocyte sedimentation rate, normal C-reactive protein levels, normocomplementemia, negative VDRL test and negative rheumatoid factor (RF) and antineutrophil cytoplasmic antibodies (ANCAs). Slightly high serum IgG4 levels raised suspicions of an immune-mediated disease.

Cardiac MRI (CMR) was subsequently performed for a non-invasive characterization of the pseudo-mass. The lesion was isointense to myocardium in bSSFP cine-images, heterogeneously hypointense in T2-weighted sequences, and hypointense in T1-weighted sequences. The pseudo-mass did not present early enhancement during arterial first-pass...
perfusion imaging, but it showed late gadolinium enhancement (LGE), supporting the provisional diagnosis of a fibrotic/granulomatous lesion (Figure 3).

Figure 2. Dual-energy CCTA in a patient with coronary IgG4-RD. Axial iodine map reconstruction does not show any iodine uptake within the pseudo-mass (arrow) during the arterial phase (A), while there was a mild increase of iodine concentration during the delayed phase (B). Similarly, the low-dose PET-CT investigation acquired 60 min after the administration of 18F-FDG did not show a significant increase of the metabolic tracer (C).

Figure 3. CMR in patient with coronary IgG4-RD. Short axis images performed along the basal slice showing the peri-coronary pseudotumor encasing LAD during end-diastole (A) and end-systole (B). The lesion appeared isointense to myocardium in balanced steady-state free precession (bSSFP) sequence (A,B), hypointense in T1-weighted (C), and T2-weighted sequences with short-tau inversion recovery (STIR) (D). The pseudo-mass did not show any early enhancement during the arterial first-pass (E), but late gadolinium enhancement (LGE) was seen in the T1-weighed phase sensitive inversion recovery (PSIR) sequence (F).

In the suspicion of coronary IgG4-RD, the patient underwent a 18F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) scan, which did not show an increased FDG uptake of the cardiac pseudo-mass (Figure 2C).

In consideration of the complete absence of symptoms, the patency of coronary vessels and the good cardiac function, a biopsy was contraindicated because of the high procedural risk. Moreover, since the non-invasive imaging characteristics of the pseudo-mass were not consistent with active inflammation or malignancy, no surgical or pharmacological treatment was planned.

The patient underwent DE-CCTA follow-up studies at 6 months and 12 months, which demonstrated substantial stability of radiological findings and good clinical condition (Figure 4).
When this occurs, clinical presentation may vary from complete lack of symptoms to increased inflammatory aneurysms of large-to-middle-size vessels. Cardiovascular system involvement may manifest with arteritis or periarteritis and inflammatory aneurysms of large-to-middle-size vessels.

Coronary artery involvement (e.g., stenosis, aneurysm, and diffuse wall thickening) has rarely been reported in the literature, but over the past years its frequency has increased, probably due to the increasing availability of advanced cardiovascular imaging techniques. When this occurs, clinical presentation may vary from complete lack of symptoms to potentially fatal conditions such as acute coronary syndrome or sudden cardiac death [1].

Currently, IgG4-RD diagnosis is defined by the Comprehensive Diagnostic Criteria proposed in 2012 by Umehara et al. and revised in 2020, which refer to specific clinical, radiological, serological and pathological findings [4].

Serological findings imply detection of IgG4 serum levels > 135 mg/dL, which were considered critical for the diagnosis of IgG4-RD. Nonetheless, almost 30% of patients shows normal or mildly elevated IgG4 serum and their increase has shown to depend on the number of involved organs, and it is more common in case of pancreatic disease. Increased IgG4 concentration is also not specific for IgG4-RD, since other entities have also been associated with this laboratory finding (e.g., pancreatic adenocarcinoma, lymphoma, ANCA-associated vasculitis, asthma) [5,6].

Biopsy has always been considered the gold standard for the diagnosis of IgG4-RD, since it allows confirmation of the presence of the typical histological features characterized by lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells and storiform fibrosis [7]. According to the AHA/ACC/ESC guidelines, cardiac biopsy is considered the method of choice when diagnosis cannot be determined by non-invasive modalities or when tissue characterization can affect the therapy [8]. However, when lesions are adjacent to vital structures, performing a biopsy might not be an option.

In our case, the lack of clinical symptoms and the benignity of the lesion assessed by comprehensive multimodality imaging suggested a biopsy should not be performed in such a critical anatomical site. As matter of fact, 2019 ACR/EULAR IgG4-RD classification criteria do not require confirmation by biopsy when there is a strong suspicion of IgG4-RD by clinical, serological and radiological findings [9].

Figure 4. One-year follow-up CCTA in patient with coronary IgG4-RD. Axial maximum intensity projection (A) and curved multiplanar reconstructions of LAD (B) and LCx (C) performed along the same planes of Figure 1. CCTA images show a substantial morpho-volumetric stability of the cardiac pseudo-mass after 12 months (arrow), with the typical “pigs-in-a-blanket sign”.

3. Discussion

IgG4-RD is a systemic immune-mediated inflammatory disease typically associated with high serum IgG4 concentration and IgG4+ plasma cell infiltration that can involve several organs. The most common sites are the pancreas, salivary glands, retroperitoneal organs, and liver [1,3].

Cardiovascular system involvement may manifest with arteritis or periarteritis and inflammatory aneurysms of large-to-middle-size vessels.

Coronary artery involvement (e.g., stenosis, aneurysm, and diffuse wall thickening) has rarely been reported in the literature, but over the past years its frequency has increased, probably due to the increasing availability of advanced cardiovascular imaging techniques. When this occurs, clinical presentation may vary from complete lack of symptoms to potentially fatal conditions such as acute coronary syndrome or sudden cardiac death [1].

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In our case, coronary CTA allowed for the direct visualization of the soft-tissue mass completely encasing the coronary vessels without causing their luminal narrowing. This finding configures the typical “pigs-in-a-blanket” sign, which is considered to be specific for coronary IgG4-RD [6].

Table 1 summarizes the clinical presentation and the diagnostic workflow of coronary IgG4-RD in all cases reported in the scientific literature, and it emphasizes the increasing role that CCTA has for its diagnosis.

Dual-energy CCTA also provides additional parameters for non-invasive characterization of cardiac lesions [10–15]. In our case, it allowed for direct quantification of iodine concentration within the cardiac pseudotumor, both during arterial first-pass and at delayed phase, showing concordant results with CMR.

CMR findings in coronary IgG4-RD have been scarcely described (Table 1), despite this technique representing the gold standard for non-invasive tissue characterization of cardiac masses [16,17]. CMR has been also used to provide information about disease activity and to guide treatment in vasculitis, such as in Takayasu arteritis [18]. In our case, low signal intensity on both T1- and T2-weighted sequences, together with the absence of early gadolinium enhancement and positive LGE, reflected the fibrotic or granulomatous nature of the lesion.

Conversely, in case of active perivascular inflammation, increased iodine density during arterial first-pass in DECT or increased signal intensity in T2-weighted sequences and early gadolinium enhancement in CMR would have been expected findings [19]. Moreover, active perivascular inflammation may have led to clinical symptoms such as chest pain or to acute coronary syndrome.

18F-FDG PET/CT represents a remarkable tool to evaluate a systemic inflammatory disease and to highlight IgG4-RD localization for guiding the biopsy, or to monitor treatment response [20]. Its main advantage is to provide metabolic information of the whole body in a single scan. In our case, 18F-FDG PET/CT did not show increased 18F-FDG uptake, suggesting a quiescent phase of coronary IgG4-RD, which was confirmed by follow-up CCTA examinations.

The first-line therapy in patients with symptomatic active IgG4-RD is glucocorticoids, which are extensively used for remission induction and disease relapse, but they can also be used for maintenance therapy. Steroid-sparing agents can also be used for remission maintenance when long-term therapies expose patients to glucocorticoid toxicities. A “watchful waiting” strategy is also suitable in asymptomatic patients and in case of highly fibrotic inactive lesions that are weakly responsive to pharmacologic treatments. In our case, the lack of clinical symptoms, together with laboratory and imaging findings, excluded the presence of active inflammation, and the patient did not require any pharmacological treatment. Moreover, in these patients, the risk/benefit balance may not encourage any therapeutic courses [21].

Table 1. Literature review of non-invasive/invasive multimodality imaging of coronary pseudomasses in IgG4-RD.

| Coronary Arteries Involved | Clinical Presentation                  | TTE | CCTA | CMR | PET-CT | IVUS/OCT | Biopsy |
|----------------------------|---------------------------------------|-----|------|-----|--------|----------|--------|
| Matsumoto (2008) [22]      | RCA                                   |     | X    | X   |        | X        |        |
| Ikutomi (2011) [23]        | RCA                                   |     |      |     |        | X        |        |
| Tanigawa (2011) [24]       | RCA, LCX                              |     |      | X   |        |          |        |
| Kusumoto (2012) [25]       | RCA, LAD                              |     | X    |     |        |          | X      |
| Urabe (2012) [26]          | RCA, LCX                              |     | X    |     |        | X        |        |
| Kan-o (2013) [27]          | RCA, LM                               |     | X    |     |        |          |        |
| Baruah (2014) [28]         | LAD, LCX                              |     | X    |     |        | X        |        |
| Guo (2015) [29]            | RCA, LM, LAD, LCX                     |     | X    |     |        | X        |        |
| Hourai (2016) [30]         | RCA, LAD                              |     | X    |     |        | X        |        |
| Keraliya (2016) [31]       | RCA, LM, LAD, LCX                     |     | X    |     |        | X        |        |
Table 1. Cont.

| Coronary Arteries Involved | Clinical Presentation | TTE | CCTA | CMR | PET-CT | IVUS/OCT | Biopsy |
|---------------------------|-----------------------|-----|------|-----|--------|----------|--------|
| Ito (2016) [32]           | LAD, LCX, D1, D2      | Chest pain | X    |     |        |          |        |
| Nishimura (2016) [33]     | RCA                   | No symptoms | X    | X   |        |          |        |
| Kanzaki (2017) [34]       | LCX                   | No symptoms | X    |     |        |          |        |
| Komiya (2017) [35]        | RCA, LAD              | No symptoms | X    | X   |        |          |        |
| Sakamoto (2017) [36]      | LAD                   | Palpitations |     |     |        |          |        |
| Rokutanda (2017) [37]     | LAD                   | Chest pain | X    |     |        |          |        |
| Matsuda (2018) [38]       | LAD, LCX              | No symptoms | X    |     |        |          |        |
| Huang (2018) [20]         | LAD, LCX              | No symptoms | X    |     |        |          |        |
| Okuyama (2019) [39]       | RCA, LM, LAD          | Acute coronary syndrome | X    |     |        |          |        |
| Koseki (2019) [40]        | RCA, LAD, LCX         | No symptoms | X    |     |        |          |        |
| De la Fuente (2019) [41]  | RCA                   | No symptoms | X    |     |        |          |        |
| Ansari-Gilani (2020) [42] | RCA, LAD, LCX         | Acute coronary syndrome | X and TEE |     |        |          |        |
| Nakamura (2020) [3]       | RCA, LAD              | No symptoms | X    | X   |        |          |        |
| Vasudevan (2021) [43]     | LAD, LCX              | No symptoms | X    |     |        |          |        |
| Kubota (2021) [44]        | RCA, LAD              | No symptoms | X    | X   |        |          |        |
| Lee (2021) [45]           | LAD                   | No symptoms | X    | X   |        |          |        |
| Yardimci (2021) [46]      | RCA, LAD, LCX         | Chest pain | X    |     |        |          |        |
| Yamaura (2022) [47]       | RCA, LAD, LCX         | Chest pain, dyspnea | X    |     |        |          |        |
| Maeda (2022) [48]         | RCA, LAD, LCX         | Chest pain, fatigue | X    |     |        |          |        |
| Liu (2022) [49]           | LAD                   | Dyspnea, cough, fever | X    |     |        |          |        |
| Ratwatte (2022) [50]      | LAD, LCX              | Acute coronary syndrome | X    |     |        |          |        |
| Karmally (2022) [51]      | RCA, LAD              | Dyspnea, cough | X    |     |        |          |        |
| Current Case (2022)       | LM, LAD, LCX, D1      | No symptoms | X    | X   |        |          |        |

TTE: Transthoracic Echocardiogram; TEE: Transesophageal Echocardiogram; CCTA: Coronary Computed Tomography Angiography; CMR: Cardiovascular Magnetic Resonance; PET-CT: Positron Emission Tomography/Computed Tomography; IVUS: Intravascular Ultrasound; OCT: Optical Coherence Tomography; LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main coronary artery; D1: diagonal 1; D2: diagonal 2; RCA: right coronary artery.

4. Conclusions

Coronary IgG4-RD diagnosis is a rare and potentially fatal condition whose diagnosis is generally challenging. Non-invasive multimodality imaging plays a pivotal role for its diagnosis, since performing a biopsy might not always be an option due to the critical location of these lesions. Finally, non-invasive imaging is crucial to monitor disease activity and guide treatment.

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