Diagnosis and Management of IgG4-Related Cardiovascular Lesions
What is the Next Step?

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(int Heart J 2018; 59: 909-910)

IgG4-related disease (IgG4-RD) is a fibroinflammatory disorder characterized by elevated serum IgG4 levels and tissue infiltration of IgG4-positive plasma cells. IgG4-RD can affect various organs, which may emerge simultaneously or metachronously. Systemic corticosteroids are generally effective in controlling disease activity; however, recurrent or refractory cases are also present. In Japan, IgG4-RD was specified as an intractable disease in 2017 (http://www.nanbyou.or.jp/entry/4505). IgG4-RD can be diagnosed using either comprehensive or organ-specific diagnostic criteria, the former of which can be applied regardless of the organs involved, but mandates both elevated serum IgG4 level and histopathological evidence of IgG4-positive cell infiltration in the indicated organ. The latter criteria are specifically set for organs, such as the pancreas, lacrimal and salivary glands, and kidney, and definitive diagnosis can also be made even when the histological findings cannot be obtained for the indicated organ.

It has become evident that the heart and large vessels can be potential targets of IgG4-RD. IgG4-related cardiovascular lesions present as various clinical features, such as pseudotumors, inflammatory aneurysm, periarteritis, and pericarditis. On the other hand, diagnosing IgG4-RD in the cardiovascular system may not always be straightforward, especially using the comprehensive diagnostic criteria, as tissue sampling from the heart and vessels may be associated with a considerable risk, leading to the under-recognition of IgG4-RD in the heart and vessels and inadequate evaluation what is the best treatment to this condition.

In this issue of the Journal, Yano, et al. reported a patient with right atrial mass that was diagnosed as an IgG4-related lesion. In this patient, the serum IgG4 level was markedly elevated (816 mg/dL), and IgG4-positive plasma cell infiltration was proved in intra-cardiac echo (ICE)-guided percutaneous transcatheter biopsy, which made the diagnosis reasonable. Storiform fibrosis or obstructive phlebitis, which are characteristic but not exclusive histological features of IgG4-RD, were absent in the biopsied specimens; however, the presence of these findings is known to differ according to the organs examined. Subsequent steroid therapy successfully reduced the right atrial mass volume and chest symptom of the patient and also decreased the serum IgG4 level.

In their paper, previous case reports describing 9 cases with histologically-proven myocardial involvement of IgG4-RD are summarized. In contrast to Yano, et al.'s case, IgG4-positive infiltration was shown in surgically resected samples (myocardium or cardiac valves) in most of these reported cases, and the serum IgG4 level was not elevated or measured in some cases. Therefore, some of these reported cases may not be diagnosed as definitive IgG4-related cardiac lesions according to the comprehensive diagnostic criteria in Japan. On the other hand, in some cases, IgG4-RD was diagnosed in other organs, such as the pancreas, lacrimal and submandibular glands, and retroperitoneum, in which myocardial involvement of IgG4-RD is more likely to occur. Two of these reported cases received medical treatment with predonisolone and rituximab after cardiothoracic surgery.

ICE-guided percutaneous transcatheter biopsy of the cardiac mass is an attractive alternative to open surgery for the diagnosis of IgG4-RD. However, what we should care about may not be really the technical issues but rather the clinical utility of diagnosing IgG4-RD in the cardiovascular system; in other words, “does it predict emergence of IgG4-RD in other organs?”, and “does steroid treatment ease symptoms, ameliorate pathophysiological abnormalities, or improve long-term outcome?” Yano, et al. have shed light on these questions in their case report. After diagnosing myocardial involvement in IgG4-RD, they started steroid treatment that led to an immediate reduction in the mass volume, a return to sinus rhythm, and relief of proptosis, which is presumably also caused by lacrimal involvement in IgG4-RD. Yano, et al.'s report suggested that IgG4-related cardiac lesions can be
treated by steroid therapy without surgical intervention, at least in some selected populations.

It may be questioned how the myocardial lesion can be suspected as a manifestation of IgG4-RD. The first clue may be other organ involvement. Other organ involvement is used as one of the diagnostic criteria in some organ-specific diagnosing criteria.\(^{10}\) To which extent does elevation in the serum IgG4 level makes the diagnosis of IgG4-RD probable? In Hamano, et al.’s study, serum IgG4 level above 135 mg/dL was shown to have high sensitivity and high specificity for identifying autoimmune pancreatitis, an IgG4-RD,\(^{13}\) among various pancreatic disorders. On the other hand, it was shown that more than 4% of individuals with some cardiovascular disorders had serum IgG4 levels above 135 mg/dL,\(^{11}\) indicating that high serum IgG4 levels, at least at this cut-off value, may not provide strong evidence for the observed cardiac lesion to be IgG4-related. The serum IgG4 level was highly elevated (816 mg/dL) in Yano, et al.'s case. Serum IgG4 levels generally show greater increase when multiple organs are involved.

Although steroid treatment is effective in IgG4-RD, it may be indicated when noxious symptoms, obstruction of involved organs, and anticipated organ dysfunction are present\(^{12,13}\) in cases with IgG4-related large vessel disease because steroid therapy might facilitate luminal dilatation of the large vessels\(^{14}\), leading to life-threatening events.\(^{15,16}\) In the next step, we should determine the subset of patients with myocardial involvement in IgG4-RD who will be benefited from steroid treatment, as the case reported by Yano, et al. has demonstrated.

**Disclosures**

**Conflicts of interest:** None.

**References**