Introduction

Immunoglobulin (Ig) G4-related diseases are a new concept and affect a variety of different organs. Organs that may be affected include the pancreas, bile duct, lacrimal glands, salivary glands, central nervous system, thyroid, lung, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, cardiovascular system, lymph nodes, skin, and breast. IgG4-related disease presents with a variety of symptoms according to the organ affected, and may be accompanied by serious complications such as organ dysfunction associated with IgG4-positive cell proliferation. IgG4-related cardiovascular diseases affect the coronary arteries, heart valves, myocardium, pericardium, aorta, and peripheral vasculature. Herein, we review IgG4-related cardiovascular diseases.

Methods

To search all relevant studies, articles were collected from the PubMed database using keywords such as “IgG4,” “cardiovascular disease,” “aortitis,” and “pericarditis.” Articles were identified that were published in English through to the end of 2016. All data were classified based on the field of study: coronary disease, valve disease, cardiac masses, or extra-cardiac lesions including the aorta and peripheral arteries. After screening the abstracts or full texts of these articles, 48 studies were selected for review.

Results

Coronary artery lesions

IgG4-related coronary artery lesions are stenotic lesions that are induced either by tumorous formation surrounding the coronary artery or periarterial soft tissue thickening along the coronary artery. Delgado-Garcia and colleagues presented a case of tumorous formation encasing the left anterior descending artery. Tumor resection and coronary bypass grafting relieved the myocardial ischemia. Treacy and colleagues reported three autopsy cases in which firm white whorled masses, ranging in diameter from 9 to 25 mm, surrounded both the right and left coronary arteries. Histologic sections showed a mixed inflammatory infiltrate extending from the media into the adventitia of each coronary artery. The infiltrate was composed predominantly of plasma cells and lymphocytes, with occasional neutrophils and eosinophils.

Tong and colleagues used computed tomography (CT) coronary angiography to investigate a 64-year-old man. Extensive soft tissue masses were identified in the epicardial space, encasing the triple coronary artery vessels and their branches with multiple segments of ectasia. They also used fluorine-18 fluorodeoxyglucose positron-emission tomography (FDG-PET) to identify moderately hypermetabolic perivascular soft tissue masses encasing the right and left coronary arteries and their branches. Treatment with prednisolone improved the patient’s condition, with a CT coronary angiogram obtained 5 months later showing reduced vascular/intimal thickening in the coronary arteries. Optical coherence tomography also identified circumferential intraluminal calcification at the site of aneurysmal dilation and at the stenotic site.

Valvular lesions

IgG4-related disease can also impair valve function. Infiltration of IgG4-positive plasma cells often disturbs
heart valve function, through stenosis and/or regurgitation. Besik and colleagues reported a case requiring both aortic and mitral valve replacement. Maleszewski and colleagues presented two cases affecting the aortic valve, and Yamauchi and colleagues reported a case with aortic regurgitation and heart block. IgG4 infiltration sometimes forms a swollen tumorous lesion on a valve leaflet, and in each report valve replacement was selected as the most appropriate treatment. Immunohistological analyses showed that IgG4-positive plasma cells were present in all four of these cases.

**Cardiac masses (myocardial lesions)**

Cardiac masses with elevated IgG4 serum levels were also reported, and were surgically or medically treated based on patients’ backgrounds. Kusunose and colleagues presented a case with an IgG4-related mass near the inferolateral wall of the left ventricle, and Kouzu and colleagues reported a case with a mass in the right ventricular outflow tract. CT, magnetic resonance imaging, echocardiography, IgG4-related extra-cardiac lesions, and pathologic findings were diagnostic modalities used for definitive diagnosis. Pathologically, IgG4-related tumors consist of spindle-shaped cells within a myxoid stroma. The stroma is infiltrated with lymphocytes, plasma cells, and eosinophils, and IgG4-positive plasma cells are abundant. Corticosteroid therapy was the first-line medical treatment, and tumor resection was also employed in each case.

**Pericardial lesions**

IgG4-positive plasma cells are also associated with pericardium. Matsumiya and colleagues detected IgG4-positive plasma cells in a biopsy specimen from a 50-year-old woman with a thickened pericardium. Clinical fever symptoms and elevated serum IgG4 were promptly resolved by administration of a moderate-dose glucocorticoid.

Mori and colleagues also reported a case with pericardial thickening. There were no pathologic findings, but serum IgG4 was elevated to 637 mg/dL. Administration of 30 mg prednisolone ameliorated progressive dyspnea, and the serum IgG4 level decreased to 205 mg/dL after 3 months.

Morita and colleagues presented a case with pericardial effusion. An open biopsy specimen from the pericardium revealed IgG4-positive plasma cells, and the patient was diagnosed as having an IgG4-related Mikulicz’s disease.

Seo, Yanagi, and Matsuzaki each presented cases with IgG4-related constrictive pericarditis. In three of the cases, results from pericardium specimens were consistent with IgG4-related disease. All patients were treated with pericardiectomy, and in some cases this was followed by corticosteroid therapy (Seo and Yanagi cases only).

**Aortic lesions**

IgG4-related inflammatory changes can cause different morphologic changes in the aorta. Lindsay and colleagues presented a case with periaortitis. An abdominal CT scan revealed periaortic soft tissue surrounding the abdominal aorta from below the level of the renal arteries. This soft tissue extended to include the proximal half of each common iliac artery. No calcification or aneurysmal changes were observed. A biopsy of the periaortic mass detected plasma cells and other inflammatory cells, and immunohistochemistry demonstrated that more than 50% of the plasma cells were positive for IgG4. Periaortitis can progress to aortic rupture. Ikeda and Kasashima reported a case of IgG4-related periaortitis that was complicated by aortic rupture during and after corticosteroid therapy. Patients with IgG4-related aortitis were older than those with Takayasu’s arteritis or Behcet’s aortitis, and were more likely to be male than those with Takayasu’s arteritis.

Aneurysmal changes can also occur. Nuñez Fernández and colleagues described a case of aneurysmal dilatation of the ascending aorta. Diagnosis of IgG4-related aneurysmal change is by immunohistochemistry, with greater than 50% IgG4-positive cells and an IgG4/IgG cell ratio greater than 0.4. Colombier and colleagues reported a similar case with an asymptomatic ascending aortic aneurysm and thickening of the aortic wall. A case of abdominal aortic aneurysm associated with a coronary artery aneurysm and periarteritis was also presented, and it was proposed that periaortic inflammatory change might precede aortoduodenal fistula formation.

**Peripheral artery lesions**

IgG4-positive plasma cells have also been detected in peripheral arteries. These include the renal, splenic, femoral, and carotid arteries. A case of small-vessel systemic vasculitis involving muscle tissue was also reported. Most of the morphologic changes in these cases are aneurysmal changes.
Discussion

Modalities used for IgG4-related disease diagnosis include high-serum IgG4 levels and positive immunohistochemical results. However, Inokuchi and colleagues found that even in the presence of histological findings consistent with IgG4-related disease, serum IgG4 levels may not elevated.\textsuperscript{15} Aqaimy and colleagues also reported 15 cases of aortic aneurysms that were immunohistologically confirmed as IgG4-related, yet had serologically normal IgG4 levels.\textsuperscript{46} Therefore, several subtypes may be recognized as “incomplete forms” of IgG4-related diseases in the future. When atypical morphologic features are encountered, IgG4-related cardiovascular diseases should be further differentiated. Serological studies combined with immunohistological examination can confirm the diagnosis.

As a diagnostic tool for IgG4-related vascular diseases, FDG-PET/CT might play a great role. Yabusaki and colleagues concluded that the entire aorta and major branches can be involved with more than twofold higher FDG uptake than the venous background pool, and with wall thickening.\textsuperscript{47} Settepani and colleagues mentioned that the images showed increased tracer uptake in the ascending aorta,\textsuperscript{48} and Mavrogeni and colleagues thought that FDG-PET would show FDG uptake in the area of IgG4-related soft tissue thickening with active inflammation around arteries including coronary arteries.\textsuperscript{49} However, it is unclear whether FDG-PET/CT is useful as a diagnostic tool for other IgG4-related valvular, myocardial, and pericardial lesions.

Many investigators have reported cases of coronary artery lesions followed by pericardial and aortic ones, and the incidences of myocardial and valvular lesions are low among IgG4-related cardiovascular diseases.

Treatments for IgG4-related cardiovascular diseases do not differ from those of non-IgG4-related ones. However, corticosteroid therapy with or without surgical intervention can lead to excellent outcomes. Mizushima and colleagues highlighted three aspects relating to corticosteroid therapy and clinical course in IgG4-related vascular diseases: 1) the possibility of latent existence and progression, 2) the efficacy of corticosteroid therapy in preventing new aneurysm formation in patients without luminal dilatation, and 3) the possibility that a small proportion of patients may actually develop luminal dilatation.\textsuperscript{50} The therapeutic corticosteroid dosage required to treat IgG4-related diseases differs case-by-case, and Tajima and colleagues have suggested that treatment of IgG4-related cardiovascular diseases might require higher doses of corticosteroids than other IgG4-related diseases.\textsuperscript{51}

IgG4-related diseases can involve any organs. Therefore, it is important to survey for extra-cardiovascular lesions when IgG4-related cardiovascular disease is suspected. In the absence of immunohistological confirmation, clinical features in other organs may help to arrive at a definitive diagnosis of IgG4-related cardiovascular disease.

Conclusion

IgG4-related cardiovascular diseases involve the coronary arteries, heart valves, myocardium, pericardium, aorta, and peripheral arteries. Corticosteroid therapy with or without surgical intervention can lead to excellent outcomes.

Disclosure Statement

None declared.

References


