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CASE REPORT

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Rituximab and pericardiectomy with waffle procedure in constrictive pericarditis due to IgG4-related disease: A case report

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Key Clinical Message

We should consider IgG4-related disease (IGRD) as one of the potential causes of constrictive pericarditis. In patients with constrictive pericarditis due to IGRD, the combination of surgical treatment and immunosuppressive therapy may be an effective strategy.

KEYWORDS

cardiac surgery, constrictive pericarditis, IgG4-related disease, rituximab

1 | INTRODUCTION

Constrictive pericarditis (CP) is a form of diastolic dysfunction resulting from a stiff pericardium and is often caused by factors such as trauma, inflammation, radiation, or cardiac surgery.[1] IgG4-related disease (IGRD) is a multiorgan fibroinflammatory condition that mimics many malignant, infectious, and inflammatory disorders.[2] Reports on CP caused by IGRD are limited.[3] This study reports a case of CP caused by IGRD and describes the successful treatment with pericardiectomy via the waffle procedure and rituximab administration to avoid long-term steroid use.

2 | CASE HISTORY

An 82-year-old man with chronic atrial fibrillation was previously admitted for heart failure (HF) with preserved ejection fraction 2 years before presentation at our hospital. His comorbidities were Type 2 diabetes mellitus, managed with oral antidiabetic agents, and exophthalmos of unknown cause. After discharge, his chronic HF status was stable at New York Heart Association functional class 2 upon receiving bisoprolol, losartan, edoxaban, spironolactone, and furosemide for 2 years. However, following this, clinical signs of right HF, including peripheral oedema and pleural effusion, were gradually found to worsen over the course of 3 months despite escalating doses of loop diuretics and use of empagliflozin in conjunction with loop diuretics and spironolactone during outpatient follow-up. Although he did not have any abdominal symptoms, total bilirubin increased from 0.9 to 1.7 mg/dL, γ-glutamyl transferase (γ-GTP) increased from 32 to 197 U/L and alkaline phosphatase (ALP) increased from 70 to 176 U/L. At the same time, he developed sialadenitis.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT

The patient's electrocardiogram showed chronic AF. Echocardiography revealed left ventricular (LV) ejection fraction of 50%, with dilation of both atria, septal bounce, and respiratory variation of E velocity in the LV inflow of 40.1%. These findings were consistent with CP. Despite worsening liver dysfunction, tricuspid regurgitation (TR) was mild and estimated right ventricular pressure was 27 mmHg. The inferior vena cava was dilatated without respiratory change. Computed tomography (CT) revealed partial pericardial calcifications (Figure 1). There was no dilatation and thickening of the aortic wall, and hydronephrosis was not detected by contrast enhanced CT. Therefore, we suspected worsening HF symptoms due to CP. He did not display an indication of infection. In addition, based on the lack of skin and muscular findings without elevation of anti-nucleotide antibody, anti-DNA antibody, P-anti-neutrophil cytoplasmic antibody (ANCA), C-ANCA, anti-ribonucleoprotein-1 (RNP-1) antibody, and C-reactive protein, he was not considered to have connective tissue or autoimmune diseases. The patient did not have a history of tuberculosis and the QuantiFERON-TB Gold test (Qiagen, Hilden, Germany) was negative. His IgG4 level was 1168 mg/dL. The minor salivary glands biopsy showed >10 IgG4+ cells per high powered field and the ratio of IgG4+/IgG-positive cells was nearly 40%.

Therefore, we suspected CP due to IGRD. The patient was diagnosed with CP via right heart catheterization (Figure 2), which showed equal right and LV end-diastolic pressures and a systolic area index of 2.5. The patient's right HF worsened, requiring intensified drug therapy. Therefore, surgical treatment was performed to relieve the symptoms of right HF and obtain pericardial tissue to clarify the pathology of CP. Off-pump total pericardiectomy was performed, involving resection of the anterior pericardium between the two phrenic nerves and the posterior pericardium overlying the diaphragm on both the left and right ventricles. Subsequently, the waffle procedure was performed (Figure 3). No complications occurred after operation, and oedema improved during hospitalization. On

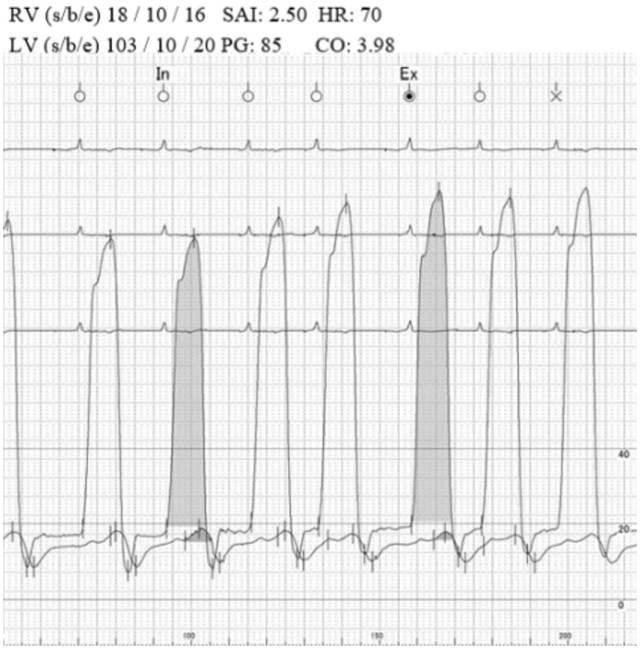

FIGURE 2 Findings of right heart catheterization before operation. Right and left ventricular end-diastolic pressures are equal. Both ventricular pressure curves are of a typical dip-and-plateau pattern. Systolic area index is 2.5, which is greater than the cutoff value (1.1) for diagnosis of constrictive pericarditis.

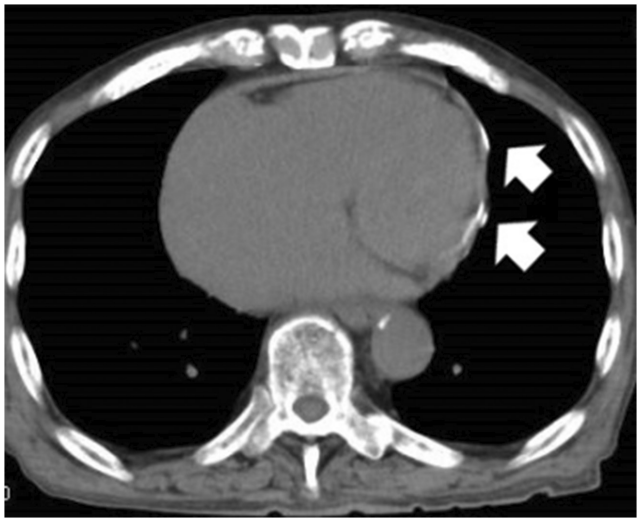

FIGURE 1 Computed tomography revealing partial calcification of the pericardium (white arrows).

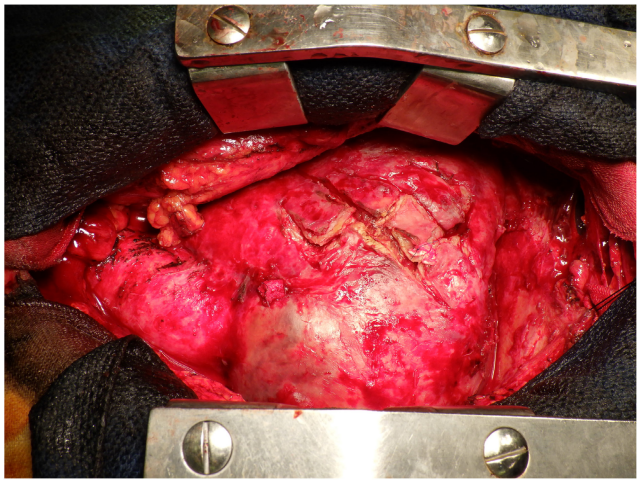

FIGURE 3 Pericardium has been removed and waffle procedure is performed.

histological examination of the pericardium, there were >10 IgG4+ cells per high powered field and the ratio of IgG4+/IgG-positive cells was >40%. Based on these findings, his final diagnosis was IGRD related CP (definite).[4]

Considering his old age, diabetes mellitus, and social solitude, a corticosteroid, which is the first-line immunosuppressive agent, was administered for only a short period of approximately 19 days. Instead of maintenance corticosteroids, rituximab (10 mg/kg) was administered once weekly for 4 weeks. As maintenance therapy, rituximab (10 mg/kg) was administrated every 6 months.

4 | OUTCOME AND FOLLOW-UP

After the IgG4 level decreased, the patient's ocular symptoms improved. Follow-up right heart catheterization at 6 months postoperatively revealed sustained hemodynamic improvement, with no clinical recurrence of CP for 18 months. Follow-up CT showed no recurrence of salivary gland swelling or new onset of nephrotic syndrome, and maintenance of improved exophthalmos was observed.

5 | DISCUSSION

In this case, we performed pericardiectomy and waffle procedure to reduce the recurrence of CP, given the high recurrence rate of IRGD.[5] Further, rituximab monotherapy was effective for IRGD. To our knowledge, there is no previous report of this treatment combination for CP due to IRGD.

Due to underdiagnosis of CP, this condition should be considered in patients presenting with symptoms of right HF and preserved ejection fraction. Invasive hemodynamic assessment has traditionally been the gold standard for diagnosis of CP. Distinguishing restrictive cardiomyopathy from CP remains a clinical challenge. Talreja et al. demonstrated that the systolic area index, the ratio of right ventricular to LV systolic area during inspiration and expiration assessed by right heart catheterization, was a reliable criterion for distinguishing CP from restrictive cardiomyopathy.[6]

In our patient, the systolic area index in the right heart catheter and the detection of pericardial calcification on CT proved to be valuable for the diagnosis of CP. Surgical pericardiectomy is a curative treatment for CP and can improve its prognosis, although the outcome also depends on the underlying etiology and preoperative functional class. However, the pericardiectomy technique remains controversial. Pericardiectomy is associated with high rates of complications and mortality,[7] and the resultant hemodynamic improvement may not be sustained in the long term. The waffle procedure is a grid incision in the residual epicardium, and when performed in addition to total pericardiectomy, can exhibit longer-lasting hemodynamic stability than can conventional total pericardiectomy alone.[8]

Only few reports of CP caused by IGRD are available in the literature. According to a previous study, IGRD can be classified into four homogeneous phenotypes.[2] The most common phenotype is pancreatohepatobiliary disease (31%), while retroperitoneal fibrosis with or without aortitis, which was the phenotype of our patient, accounts for approximately 25% of cases. Steroids are the first-line agents for the treatment of IGRD.[5] Although steroids achieve an initial response rate of >90%, the relapse rate of steroid therapy is approximately one in two patients.[5] In addition, even with a low dose of corticosteroids, long-term use may cause several serious adverse effects. Old age is associated with an increased rate of adverse effects associated with corticosteroid use. The frequency of rituximab administration in the treatment of patients with refractory IGRD has been increasing.[9] Some small-scale studies have suggested the efficacy of rituximab in inducing IGRD remission.[9,10] Gorecka et al. showed that rituximab, even without corticosteroids, was an effective treatment for pericardial effusion due to IGRD.[11] However, IGRD relapsed in approximately 40% of patients treated with rituximab, especially in those who did not receive maintenance therapy. Moreover, serious infections or hypogammaglobulinemia reportedly occurred in one-third of the patients.[12] As the efficacy of the addition of immunosuppressive agents on steroids is described in only small retrospective studies, further research was warranted.[5] In addition, according to a retrospective cohort study, rituximab might be superior to the combination of an immunosuppressive agent and steroid.[5]

Taken together, although rituximab is a second-line treatment option, the balance between its efficacy, risk of infection, and cost should be considered. In our case, we determined that steroids should not be maintained to avoid worsening of the patient's diabetes mellitus and because of his older age, severely decreased vision, and solitude.

CP due to IRGD is rare; our report suggests that the combination of the waffle procedure and rituximab was effective for the treatment of CP due to IRGD. Considering the high rate of recurrence of IRGD, this combination may be a feasible treatment option for patients with CP due to IRGD. Further research is warranted to evaluate this hypothesis.

6 | CONCLUSION

Herein, we described a case of CP caused by IGRD that was successfully treated with pericardiectomy with the

waffle procedure and rituximab administration to avoid worsening of diabetes mellitus due to long-term steroid use.

AUTHOR CONTRIBUTIONS

Toshitaka Okabe: Writing – original draft. **Taishi Kawahata:** Data curation; investigation. **Yui Koyanagi:** Data curation; investigation. **Yuki Ito:** Data curation; investigation. **Yuma Gibo:** Data curation; investigation. **Takeshi Okura:** Data curation; investigation. **Naoei Isomura:** Supervision. **Akihiro Nabuchi:** Supervision. **Hiroshi Okuyama:** Data curation; investigation; supervision. **Masahiko Ochiai:** Supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy of the patient.

ETHICS STATEMENT

Ethical approval was not sought as the report is from treatment results and not a trial.

CONSENT

The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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