From Clinic to Echocardiography to Microscope – The Multimodal Journey of a Rare Disease

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Abstract
Introduction: Constrictive pericarditis can be a systemic manifestation of immune-mediated diseases. A timely diagnosis followed by ethiologic workup is essential for improving patient prognosis.
Case presentation: A 67-year-old female patient who suffered multiple episodes of anasarca in the past two years was referred to our center for heart failure with preserved ejection fraction. She was previously investigated for autoimmune diseases based on persistent inflammatory syndrome and recurrent serositis. The physical exam showed systemic congestion, hepatomegaly, and jaundice. Sinus tachycardia and low voltage were observed on the ECG. Transthoracic echocardiography showed septal bounce, “annulus reversus” and “paradoxus”, thickened pericardium without effusion, and a dilated inferior vena cava. Cardiac catheterization was performed, revealing equalization of diastolic pressures and square root sign, confirming constriction. A partial pericardiectomy was performed. The histopathologic study showed polyclonal plasma cells with frequent IgG plasma cells and a IgG4/IgG ratio of 40%, considered a mark of the IgG4 disease as causal.
Conclusion: Multimodality imaging completed the clinical suspicion of constrictive pericarditis. Complex pathologic analysis of the pericardium led to considering a diagnosis of IgG4 disease, and the patient was referred to a tertiary center for diagnosis and adequate therapeutic management. Constrictive pericarditis can be an associated manifestation of IgG4-related diseases.

Keywords
constrictive pericarditis, IgG4 disease, rare disease, anasarca

Rezumat
Introducere: Pericardita constrictivă poate fi o manifestare a bolilor mediate imun.
Prezentare de caz: Pacientă de 67 de ani, cunoscută cu multiple episoade de anasarcă în ultimii 2 ani, este trimisă către centrul nostru cu diagnosticul de insuficiență cardiacă cu fracție de ejecție păstrată. A fost multiplu investigată anterior pentru un spectru de boli autoimune prin prisma asocierii dintre poliserozite și sindromul inflamator cronic. Examenul fizic actual evidențiază congestie sistemică, hepatomegalie cu tegumente și sclere icterice. Electrocardiograma obiectivează tahicardie sinusală și microvoltaj. Ecocardiografic, se observă sept interventricular sălțăreț, anulus reversus și paradoxus, cu diametru crescut al venei cave inferioare. Cateterismul cardiac confirmă suspiciunea de constricție prin obiectivarea interdependenței ventriculare și a semnului rădăcinii pătrate. Se efectuează pericardectomie parțială. Examenul histopatologic ulterior decelează plasmocite policlonale, cu frecvente celule IgG pozitive, raportul IgG4/IgG fiind 40%, ridicând suspiciunea cauzalității prin boala IgG4.
Concluzie: Imagistica multimodală a completat suspiciunea clinică de pericardită constrictivă. Analiza complexă patologică a pericardului a condus la diagnosticul de boală IgG4, pacienta fiind trimisă către un centru terțiar pentru definitivarea diagnosticului și stabilirea conduitei terapeutice adecvate. Pericardita constrictivă poate fi o manifestare cardiacă a bolii IgG4.

Cuvinte cheie
pericardită constrictivă, boală IgG4, boli rare, anasarcă

Introduction

Constrictive pericarditis is a highly symptomatic condition in which both cardiac filling and cardiac output are impaired due to ventricular interdependence. This leads to a significant degree of systemic and splanchnic congestion, with ascites, hepatomegaly and hepatic impairment occurring more frequently than in other forms of heart failure.[1] Signs of constriction, particularly septal bounce, “annulus reversus” and “paradoxus,” and hepatic vein diastolic flow reversal with expiration, should be actively searched in patients with heart failure with preserved ejection fraction (HFpEF) when the transthoracic echocardiography (TTE) exam fails to explain the degree of congestion as to evaluate constriction. IgG4-related disease (IgG4-RD) consists of a fibro-inflammatory condition, in which polyclonal plasma cells produce excessive amounts of IgG4, affecting multiple organs (e.g., salivary and lacrimal glands, pancreas, lymph nodes), including the pericardium.[2]

Case presentation

We present the case of a 67-year-old female patient with multiple episodes of pleural effusion, ascites, and lower limb edema since 2020, who was referred to our service for dyspnea on slight exertion.

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https://doi.org/10.2478/rjc-2023-0010

Table 1 - Previous investigations and medical history. GI – gastrointestinal; TTE – transthoracic echocardiography; LVEF – left ventricular ejection fraction; ESR – erythrocyte sedimentation rate; hs-CRP – high-sensitivity C-reactive protein; UNL – upper normal limit; ANA – antinuclear antibodies; dsDNA – double strand DNA antibody; CCP – cyclic citrullinated peptide antibodies; cANCA – diffuse staining antineutrophil cytoplasmic antibodies; pANCA – perinuclear staining antineutrophil antibodies; ADA- adenosine deaminase; LDH – lactate dehydrogenase; ACR – albumin creatinine ratio

March 2020	Ascites	Paracentesis with fluid analysis: transudate Upper and lower GI endoscopy: no abnormal findings Whole-body CT: mild pericardial effusion, small mediastinal nodules, non-specific small pulmonary nodules ECG: low voltage, otherwise normal TTE: LVEF 60%, grade I diastolic dysfunction, mild pericardial effusion, no significant valve disease
October 2020	Right pleural effusion Ascites	ESR: 83 mm/h; hs-CRP: 52 ng/ml IgG: 2402 mg/dl (UNL <1600 mg/dl); serum immunofixation (negative)
April 2021	Bilateral pleural effusion Ascites Arthralgia	ESR: 88 mm/h: hs-CRP: 45 ng/ml IgG: 2650 mg/dl (UNL <1600 mg/dl); serum immunofixation (negative) Rheumatoid factor, ANA, dsDNA, CCP, cANCA, pANCA antibodies (negative) Bone marrow biopsy: 15% lymphocites, 3% plasmocytes, otherwise normal
May 2021	Bilateral pleural effusion	QuantiFERON test: negative Pleural tap: exudate, ADA <39 U/L, glucose 111 mg/dl, LDH 81 U/L Pleural biopsy: no particular aspect
March 2022	Lower limb edema	24 h proteinuria: 355 mg ACR 90 mg/g
November 2022	NYHA class III	Referral to our clinic

Table 2 - TTE diastolic function assessment. Notice that the E/E' is abnormally low (annulus paradoxus) and that septal TDI velocities have higher values than the ones sampled from the lateral wall ("annulus reversus")

E	A	E/A	Septal E'	Lateral E'	E/E' (avg)	Septal S'	Lateral S'
70	55	1.3	12.9	9.9	6.14	8	6

Her medical history is extensive, as she has been investigated for systemic lupus erythematosus and various other autoimmune diseases, due to a persistent low grade inflammatory syndrome, elevated IgG, and recurrent serositis (Table 1). Furthermore, considering the recurrent pleural effusions, non-specific pulmonary nodules, history of weight loss (20 kg in 6 months), persistent cough, and geographical region, tuberculosis (TB) was suspected. Pleural tap was performed prior to the current presentation. The liquid analysis and pleural biopsy were not consistent with TB, while Quantiferron testing was negative. Meanwhile, the patient's blood pressure was 100/50 mmHg, her heart rate was 115 bpm, regular, and her heart sounds appeared muffled. Important pitting lower limb edema was seen bilaterally. The jugular veins were distended more prominently with inspiration. Oxygen saturation was 98% in room air, and respiratory rate was 17/min. The liver appeared enlarged 5 cm below the costal margin. Hepatojugular reflux was noted, as well as scleral jaundice. NTproBNP levels were checked, and were measured to be 420 pg/ml, which is strikingly low compared to the degree of congestion. Other abnormal blood tests included elevated total bilirubin (2.8 mg/dl) and elevated total serum proteins (8.6 g/dl) with elevated IgG and negative immunofixation. Albumin levels were normal, and the international normalized ratio (INR) was 1.4. The electrocardiograph (ECG) showed sinus tachycardia with low voltage. TTE was performed. The pericardium appeared thickened, especially adjacent to the right ventricular (RV) free wall (4.4 mm), without any fluid. The ejection fraction (EF) was preserved, without any significant valvular disease. Septal bounce was noted. Diastolic function was assessed with an E/A ratio of 1.3 (end-expiratory) and deceleration time of 133 ms. Changes in E and A waves with respiration were not feasible due to the poor acoustic window. The E/E' ratio is paradoxically low (6.14), while the septal TDI velocities are greater than the lateral ones, highly indicative of "annulus paradoxus" and "annulus reversus" (Table 2). The RV appeared normal, with a mild degree of tricuspid regurgitation. The systolic pulmonary artery pressure (sPAP) was estimated at 41 mmHg. The inferior vena cava was distended (30 mm) without respiratory collapse. Hepatic vein diastolic reversal with expiration is also noticeable with PW Doppler (Figure 1). The findings raised the suspicion of constrictive pericarditis. CT was performed to further assess and evaluate the pericardium. The maximum pericardial thickness was 5.9 mm anteriorly. Late enhancement was observed, suggesting ongoing inflammation. No calcium deposits or effusion were noted. Multiple mediastinal nodules were observed, with the biggest measuring 1.75 x 1.34 cm (Figure 2). Cardiac catheterization was performed to further confirm the constriction and to assess the coronary arteries. Cardiac index was estimated at 2.2l/m2/min. The square root sign, which indicates early rapid diastolic filling was present (Figure 3). Furthermore, the end-diastolic pressures ware elevated and similar in both ventricles (25 mmHg), confirming the ventricular interdependence (Figure 3). The coronary arteries are patent, without any significant lesions. Considering the clinical and imagistic findings, chronic constriction was confirmed, as the onset of the symptoms was two years prior.

Because the patient exhibited features of end-stage disease such as significant hepatic impairment with a Child-Pugh score of 9 and cachexia, partial pericardiectomy was planned. Anterior interphrenic pericardiectomy was performed with a favorable outcome. The patient was discharged three days after surgery with a lower level of NTproBNP (130 pg/ml, compared to 420 pg/ml). The removed

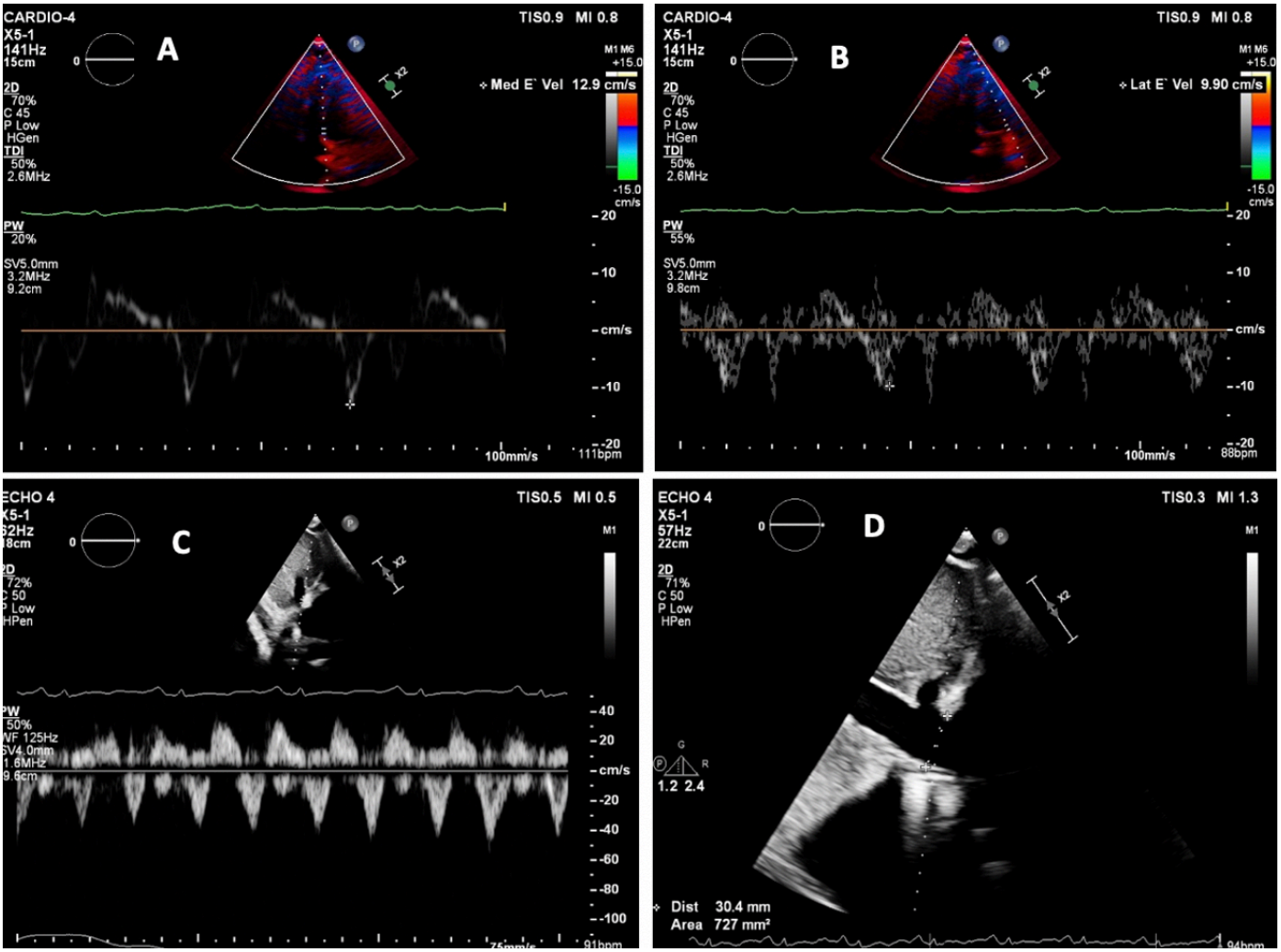

Figure 1 - Echocardiographic red flags. A, B: "Annulus paradoxus" with medial annular E' (12.9 cm/s) higher than lateral annular E' (9.9 cm/s); C: Hepatic vein PW Doppler profile with diastolic flow reversal; D: Dilated inferior vena cava (30 mm) with no respiratory variations

pericardium (Figure 4), along with a mediastinal lymph node were analyzed. Microscopy showed significant lymphoplasmacytic infiltration of the pericardium and frequent plasma cells in the lymph node. The plasma cells were polyclonal (kappa/lambda ratio of 3/1), and IgG was frequently positive. The IgG4/IgG ratio was 40%. According to the 2020 revised comprehensive diagnostic criteria for IgG4-RD, the patient meets the clinical and radiological criteria (nodules) as well as the pathological criteria, but the serum IgG4 levels could not be assessed.[3] Therefore, with 2/3 of the diagnostic criteria met, the diagnosis of IgG4-RD is probable.[3] The patient was referred to a tertiary center for definite diagnosis and appropriate management.

Discussion

The present case demonstrates the importance of clinical suspicion and the contribution of multimodality imaging and cardiac catheterization to diagnose constrictive pericarditis (CP). The diagnosis of constriction was delayed in our patient, being labeled as HFpEF. Echocardiographic signs of constriction should be actively searched for in patients with otherwise unexplainable congestion. Despite the poor acoustic window, several red flags for constriction were noticeable, such as "annulus reversus" and "paradoxus", distended inferior vena cava, and hepatic vein diastolic reversal. CT and/or CMR are indicated as second-level imaging techniques to assess calcifications, pericardial thickness, degree and extension of pericardial involvement (class I).[4] Furthermore, CT provides excellent anatomic assessment of the pericardium for the surgical planning of the pericardiectomy. Cardiac catheterization is indicated when the non-invasive diagnostic methods do not provide a definite diagnosis (class I) and should therefore be considered after CT/CMR are performed.[4] Importantly, NTproBNP levels can be discrepantly low compared to the degree of congestion in patients with CP, as there is no stretch on the myocardium in this instance.[5,6] Therefore, NTproBNP levels can be useful in differentiating CP from restrictive cardiomyopathy, as lower levels were reported in patients with CP.[6]

Pericardial involvement in IgG4-RD has been described in the literature.[7,8] However, as the pericardium did not exhibit did not exhibit

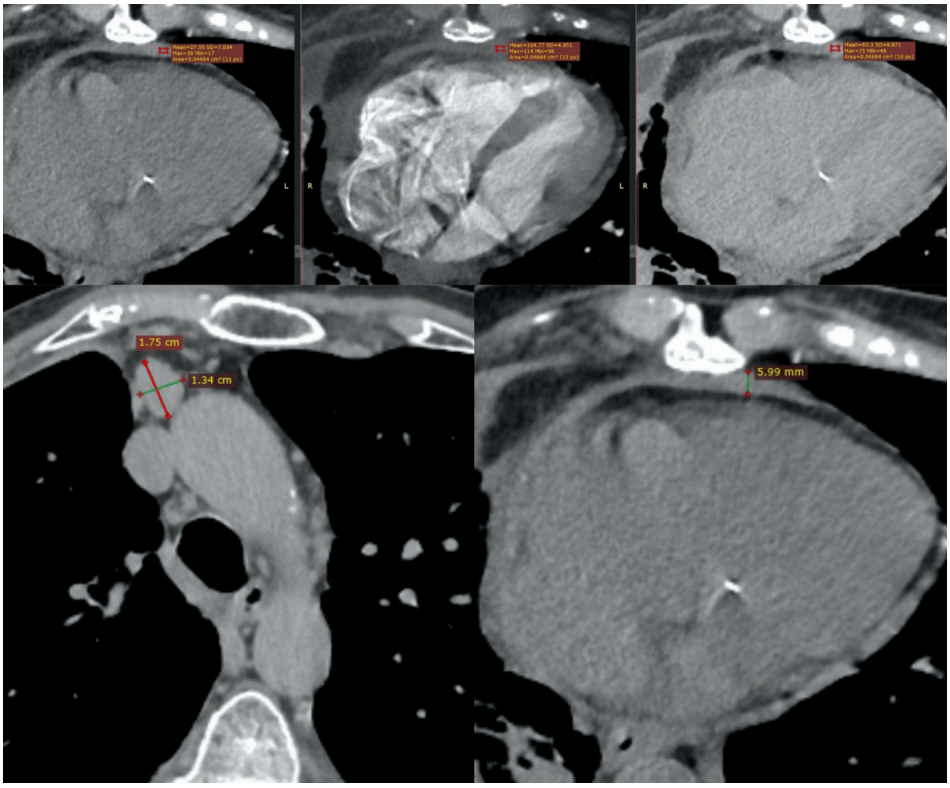

Figure 2 - CT findings. Notice the thickened pericardium and lymph node

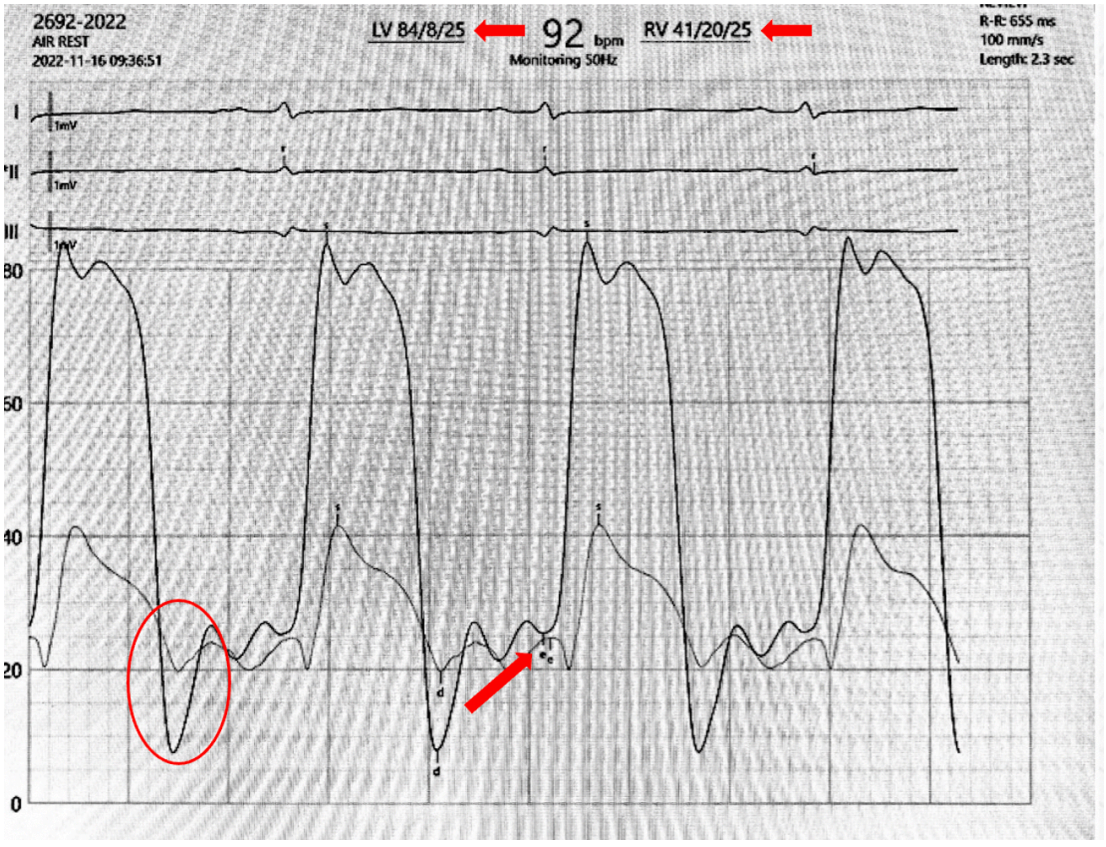

Figure 3 - Cardiac catheterization. Notice the square root sign (oval) and ventricular interdependence (arrow)

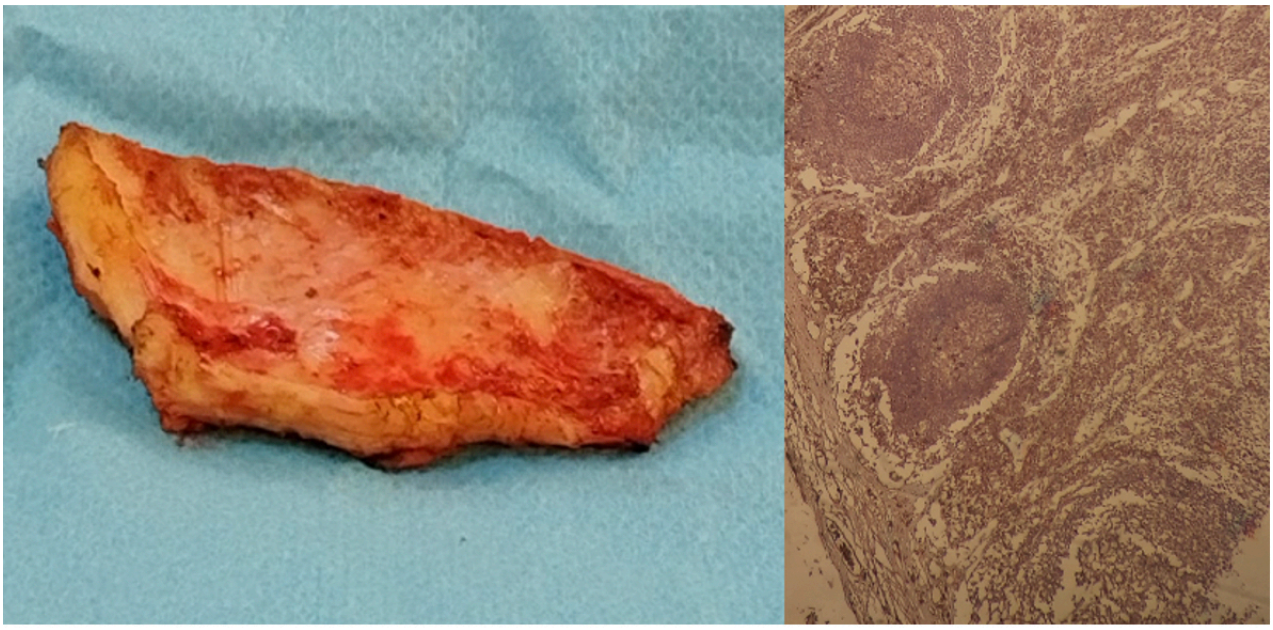

Figure 4 - Removed pericardium and lymph node microscopy. Notice the frequent IgG producing plasma cells

IgG4 producing cells, other differential diagnosis should be sought, including diseases like: HHV8-negative Multicentric Castleman's Disease, perforating collagenosis, or lymphoproliferative disorders or autoimmune diseases, such as Wegener's polyangiitis, Churg-Strauss disease, or Sjogren's syndrome, which could be formally excluded based on the absence of the specific autoantibodies.[9] Therefore, referring the patient to a tertiary center was crucial for definite diagnosis. If IgG4-RD is confirmed after exclusion of other diagnoses, corticosteroids are the first line of treatment and the preferred induction treatment. High doses of corticosteroids should be considered in urgent situations, such as inflammatory aortic aneurysms which pose the risk for dissection.[10] Biologic therapy with rituximab or methotrexate can be used in specific cases, combined with corticosteroids or as corticosteroid sparing agents.[10] Medical therapy is recommended in patients with chronic constriction, while specific therapies, such as antituberculosis drugs, are also recommended to prevent progression to constriction in specific cases.[4] Despite the fact the patient comes from a TB endemic region, there are no pericardial calcifications, and the pleural fluid and biopsy done before did not show any suggestive findings for TB. Anti-inflammatory therapy should be attempted in cases with transient or newly diagnosed constriction with concomitant evidence of pericardial inflammation (CRP elevation/pericardial enhancement on CT) (class IIb indication).[4] However, the benefit is improbable considering the long duration of constriction. A similar case report showed the limited benefit of corticosteroids in reversing constriction in the setting of IgG4-RD.[8] Surgery is the accepted standard of treatment in patients with chronic constrictive pericarditis who have persistent and prominent symptoms (NYHA class III or IV), such as in our case.[4] Nevertheless, patients with end-stage CP derive little or no benefit from the surgery, and the operative risk is inordinately high.[4] Our patient exhibits some end-stage disease manifestations. She has a history of weight loss of more than >5% in 6 months, losing 20 kg and currently weighing 57 kg (BMI 22.27 kg/m2). The hepatic impairment is secondary to congestion, with a Child-Pugh score of 9 (class B). Survival after radical pericardiectomy in patients with a Child-Pugh score ≥7 (B or C) was reported to be significantly worse than in patients with Child-Pugh A.[4]

Conclusion

Clinical suspicion can be completed by multimodality imaging and cardiac catheterization to diagnose constrictive pericarditis, leading to a correcting treatment. CP should be suspected in any patient with long-term unexplained congestion. Complex pathologic analysis of the pericardium led to considering a diagnosis of IgG4 disease, and the patient was referred to a tertiary center for diagnosis and adequate therapeutic management. CP can be an associated manifestation of IgG4-RD. Rare diseases should be known by physicians as we may encounter them under more common appearances.

Abbreviations

ACR – albumin creatinine ratio
ADA- adenosine deaminase
ANA – antinuclear antibodies
cANCA – diffuse staining antineutrophil cytoplasmic antibodies
CCP – cyclic citrullinated peptide antibodies
CP – constrictive pericarditis
dsDNA – double strand DNA antibody
ECG – electrocardiography
ESR – erythrocyte sedimentation rate

GI – gastrointestinal
HFpEF – heart failure with preserved ejection fraction
hs-CRP – high-sensitivity C-reactive protein
IgG4-RD – IgG4-related disease
LDH – lactate dehydrogenase
LVEF – left ventricular ejection fraction
pANCA – perinuclear staining antineutrophil antibodies
PW – pulsed wave
sPAP – systolic pulmonary artery pressure
TB – tuberculosis
TTE – transthoracic echocardiography
UNL – upper normal limit

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