Reminder of important clinical lesson

Heart transplantation in rapidly progressive end-stage heart failure associated with celiac disease

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Summary

Celiac disease is characterised by chronic immune-mediated malabsorption in genetically susceptible individuals induced by gluten proteins present in wheat, barley and rye. It occurs in adults and children at rates approaching 1% of the population. Cardiomyopathy associated with celiac disease is infrequent. The authors present here a first case of a severe progressive dilated cardiomyopathy that required heart transplantation in young woman with celiac disease.

BACKGROUND

Correct diagnosis and proper therapy to celiac disease could diminish the incidence of associated dilated cardiomyopathy (DCM), and hence, reduce comorbidities and further therapy expenses.

CASE PRESENTATION

A 24-year-old woman was admitted to our hospital with congestive heart failure class IV of the New York Heart Association classification with rapid progression during the past 45 days. Fourteen pack/years of cigarette smoking and a history of dyspnoea on exertion since 2 months were present. No histories of flu-like symptoms in the past 3 months or alcohol intake were present. Two spontaneous abortions, as well as one preterm birth were known. Chronic diarrhoea during the last 3 months led to the clinical diagnosis of celiac disease. Familial history was negative.

At admission, signs of biventricular heart failure could be clinically assessed. She was 151 cm tall and weighed 44 kg. Heart rate was 92 beats per minute, blood pressure 90/60 mm Hg and respiratory rate 18 breaths per minute. Clinical examination revealed raised jugular venous pressure, displaced apex and bilateral pedal oedema. Laboratory data showed severe anaemia with haematocrit of 27%, haemoglobin of 7.7 g/dl, red blood cell count 3.9 M/ μ l, white cell count 7.5 M/ μ l and thrombocytopenia 50 000/ μ l; further values show glucose 720 mg/l, renal failure urea 27 mg/l, creatinine 7.4 mg/l, disturbance of the haemostasis with prothrombin time 28.4%, kaolin partial thromboplastin time 50 s and antiphospholipid antibodies were negative. Furthermore, high circulating d-dimers >10 000, hypoproteinaemia albumin 3.2 g/l, total proteins 5.2 g/l, elevated liver enzyme levels, glutamic oxaloacetic transaminase 559 μ l, glutamic pyruvic transaminase 621 μ kat/l, γ -glutamyltransferase 43 μ kat/l, alkaline phosphatase 226

μ kat/l, cardiac troponin I 0.02 ng/ml, normal CPK-MB 42 μ l, elevated antitransglutaminase antibodies >200 U/ml and normal levels of blood gases and electrolytes were found. Negative results were found for antinuclear factors, anti-DNA antibody, antiextractable nuclear antigens antibody, antineutrophilic cytoplasmic antibodies, HIV, syphilis and Chagas.

The 12-lead ECG showed sinus rhythm, left axis deviation, complete right bundle branch block and frequent multifocal premature ventricular contractions. Cardiothoracic ratio was 61% on chest roentgenogram (figure 1A). A 24-h Holter recording revealed complex ventricular arrhythmias with couplets, triplets and self-limited runs of ventricular tachycardia (figure 1B). Echocardiography showed left and right ventricular dilatation with severe impairment of systolic function and restrictive filling pattern. Left ventricular ejection fraction calculated with the modified biplane Simpson's rule was 24% and severe pulmonary hypertension, with pulmonary artery systolic pressure of 70 mm Hg was present.

The patient was initially treated with intravenous furosemide 20 mg twice a day, a daily oral administration of spironolactone 25 mg and digoxin 0.25 mg, subcutaneous enoxaparin 50 mg twice a day, as well as acenocoumarol 2 mg daily.

In the meantime, endoscopy with duodenal biopsy and additional laboratory assessment were conducted. Celiac disease with positive antigliadin and endomysial antibodies was confirmed.

Invasive haemodynamic examination conducted in a tertiary healthcare centre confirmed echocardiographic findings, with elevated left ventricular end-diastolic pressure 34 mm Hg, moderate pulmonary hypertension 60/45/25 mm Hg, pulmonary vascular resistance 14 Wood units, no evidence of pulmonary embolism and normal coronary arteries. A rapid progression of the clinical status led to

the decision to place the patient on a high-urgency transplantation list. Heart transplantation could be conducted successfully 4 days later. After an uncomplicated postoperative period, the patient was discharged with the following post-transplant medications: tacrolimus 10 mg three times daily, mycophenolate mofetil 1000 mg two times daily and prednisone 20 mg four times daily.

Pathological examination of explanted heart revealed an organ that weighted 295 g, with no significant stenosis of coronary vessels and white spotty areas localised predominantly at the subendocardium (figure 2A). Microscopy showed irregular cardiomyocyte hypertrophy with multinucleation and fibre elongation, focal interstitial fibrosis, inflammatory cell accumulation, mono- and polymorphonuclear cells, with scarce myocardial damage,

moderate-to-severe endocardial fibrosis (figure 2B), as well as amyloid deposits located at the subendocardium and subepicardium that could be seen by characteristic yellow-green birefringence under crossed polarisation with Congo red dye.

The patient shows an excellent follow-up with definite clinical improvement. She has gained weight and is keeping strictly with immunosuppressive medication and staying on a strict gluten-free diet.

DISCUSSION

A possible immunological type of DCM associated with celiac disease was reported several times in the literature.¹ Cases that showed regression of ventricular dysfunction and dilatation under gluten-free diet were also published.²⁻⁴

Figure 1 (A) Posteroanterior chest radiograph showing an extreme enlarged heart, with a clearly raised cardiothoracic ratio. (B) 24-h Holter ECG shows complex ventricular arrhythmias with couplets, triplets and self-limited runs of ventricular tachycardia.

Figure 2 (A) Macroscopy of the explanted heart revealed an organ that weighted 295 g, with no significant stenosis of coronary vessels and white spotty areas localised predominantly at the subendocardium. (B) Microscopy showing irregular myocardial hypertrophy, with wide sectors with loss of myocardial fibres, inflammatory infiltrates predominantly monocytic and intensive fibrosis ((A) H&E $\times 100$). Interstitial myocardial oedema and inflammatory infiltrate predominantly mononuclear ((B) H&E $\times 100$). Inflammatory infiltrate predominantly lymphocytic with focal myocyte damage ((C) H&E $\times 400$). Myocardial inflammatory infiltrate with lymphocytes, neutrophils and eosinophils ((D) H&E $\times 400$). Myocardium with hypertrophic fibres and anisodiametry, with enlarged and irregular nucleus, and polyploidy, with a pale perinuclear halo ((E) H&E $\times 400$). Dense and intense fibrosis in extended myocardial regions, irregular myocardial hypertrophy and vacuolated degenerative changes ((F) Masson's trichrome stain $\times 100$).

Several mechanisms have been proposed for the development of cardiomyopathy in celiac disease. Nutritional deficiencies occur secondary to chronic malabsorption, with decrease in serum total carnitine levels compared to levels in patients with isolated DCM.⁵ Increased systemic absorption of various luminal antigens and infectious agents could cause myocardial damage secondary to immune-mediated mechanisms.⁶ Cross-reactivity immune response against antigens present in both small intestine and myocardium could also cause myocardial damage.^{4-5 7}

There are divergent opinions concerning the causative association of DCM and celiac disease. A study that investigated celiac disease in patients with cardiomyopathy and their relatives concluded that celiac disease seems to be associated, but not co-segregated, with DCM in familial cases.⁸ Results from another study indicate that the prevalence of celiac disease in patients with DCM is similar to that reported for the general population, which seems to contradict cause-specific relationship.⁹ In our case, a very short period of clinical symptoms could have purely arisen by chance, given only 3 months of clinical apparent symptoms of celiac disease and a prevalence of tTG antibodies in the range of 1 in 200–300 in otherwise healthy persons.

Association of DCM and celiac disease may occur in approximately 1–5% of the patients.¹ Because myocardial compromise can be detected in subclinical stages with tissue Doppler echocardiography,¹⁰ early assessment of cardiac function should be recommended. On one hand, compliant treatment for celiac disease would improve cardiac function,^{4-5 7} on the other hand, patients with severe clinical forms of celiac disease without consistent therapy would possibly constitute the candidates to develop myocardial compromise. This is another issue that also remains to be proven.

Learning points

- DCM may be associated to celiac disease.
- Myocardial compromise in celiac disease can be detected in subclinical stages with tissue Doppler echocardiography.
- Compliant treatment for celiac disease may probably improve cardiac function.

Competing interests None.

Patient consent Obtained.

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