

Case report

Acute dilated cardiomyopathy in a patient with beriberi and cryoglobulinaemic vasculitis: an unusual potential complication of two rare disorders

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ABSTRACT

We report the case of a 45-year-old patient who presented with acute dilated cardiomyopathy. During admission the patient was consecutively diagnosed with cryoglobulinaemic vasculitis and beriberi. In both diseases, cardiac involvement may occur as dilated cardiomyopathy. Thiamin deficiency was the final cause for the severe cardiac manifestations (cardiac acute beriberi or Shoshin syndrome), which returned to normal after thiamin supplementation.

Introduction

Idiopathic or essential cryoglobulinaemic vasculitis (CV) has been defined as a primary (non-infectious) vasculitis with cryoglobulin immune deposits affecting small vessels and associated with serum cryoglobulins (1). Hepatitis C virus (HCV)-associated CV has been recently categorised as a vasculitis associated with probable etiology (1). Organs more frequently involved in CV are the skin, glomeruli, and peripheral nerves. Whereas type I cryoglobulins are often associated with lymphoproliferative and myelomatous diseases, types II and III (mixed) cryoglobulins are usually associated with HCV infection and autoimmune disorders, respectively, and less commonly with other infections or haematologic conditions (2). Classification criteria for HCV-positive and -negative CV have been recently developed (2). Traditionally, CV treatment has been based on glucocorticoids and other immunosuppressive agents, in addition to antiviral therapy in cases of associated-viral infections. However, rituximab, a targeted B-cell depletion therapy, has recently emerged as a efficient and safe treatment for CV

refractory to conventional therapies, either essential or HCV-related (3).

Cardiac involvement is uncommon in CV (4-6). The two main cardiac manifestations more frequently observed in CV consist of dilated cardiomyopathy (4) and myocardial ischaemia and/or infarction, caused by coronary vasculitis (7, 8). Several studies have reported the reversibility of dilated cardiomyopathy early after the initiation of corticosteroids and aggressive immunosuppressive therapy (4, 9, 10).

Beriberi disease refers to the deficiency of thiamine, or vitamin B1, a water-soluble vitamin found in a variety of foods, mainly red meat and whole grains cereals. Thiamine deficiency mainly results in neurological and cardiovascular dysfunction. Nervous system manifestations (also termed “dry beriberi”) include peripheral neuropathy and Wernicke-Korsakoff encephalopathy (11). Cardiovascular involvement (“wet beriberi”) may have a chronic course with peripheral vasodilatation, with salt and water retention leading to an oedematous and high cardiac output state (11). Wet beriberi may also have an acute or fulminant presentation (Shoshin beriberi), in which rapid cardiac insufficiency occurs and oedema may not be present. If no treatment is administered, death rapidly occurs, within hours or days (11).

To the best of our knowledge, we report the first association of beriberi and cryoglobulinaemic vasculitis in a middle-aged man presenting with acute dilated cardiomyopathy, which finally returned to normal after thiamine supplementation. Contributions of both rare diseases to the development of acute dilated cardiomyopathy are herein discussed.

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Case report

A 45-year-old man with no significant past medical history presented with vomiting, upper-right quadrant abdominal pain and generalised weakness lasting for two weeks. Physical examination was remarkable for a poor general condition and slight abdominal pain. Abnormal laboratory results included C-reactive protein 8.9 mg/dL, serum creatinine 1.4 mg/dL, GGT 95 UI/L and alkaline phosphatase 678 UI/L. An EKG showed sinus tachycardia and left ventricular hypertrophy changes. Forty-eight hours after admission, he was transferred to the Intensive Care Unit (ICU) because of sudden dyspnea and acute respiratory failure requiring intensive support with mechanical ventilation (day 0). High blood pressure was detected (190/120 mmHg) and was initially treated with several anti-hypertensive drugs. The EKG showed sinus rhythm with 60-70 bpm without changes with respect to the admission EKG. Chest x-ray revealed an enlarged cardiothoracic index with changes suggesting acute pulmonary oedema. A transthoracic echocardiography (TTE) displayed enlargement of the four cardiac chambers with severe systolic dysfunction [left ventricular ejection fraction (LVEF) <20%]. A chest CT angiography ruled out pulmonary thromboembolism. Troponin I levels were normal. Cardiac catheterisation showed normal coronary arteries. Cardiogenic shock next developed requiring vasoconstrictor and inotropic drugs, and an intra-aortic balloon pump placement, with satisfactory haemodynamic control. After extubation, at day +5, nasogastric enteral nutrition (Ensure Plus; Abbot) was administered (300 ml/day) during 4 days. At day +9, cardiac function had recovered to 50% LVEF.

Severe hypertensive and/or alcoholic cardiomyopathy, myocarditis or amyloid or glycogen-deposition diseases were considered as potential etiologies. An endomyocardial biopsy reported only normal myocardic fibres with non-specific interfibre oedema, with no signs of either inflammation or deposition disease. An electromyography found non-specific myopathic features. A muscle biopsy unexpectedly found a

non-necrotising vasculitis in a small-sized artery (Fig. 1A).

The patient did not have any signs or symptoms indicating skin, articular or neurological involvement. Vasculitis work-up revealed normal ESR (10 mm/h), urinalysis with no haematuria or red blood cells casts, proteinuria of 500 mg/day, low C4 complement fraction and slightly elevated rheumatoid factor (RF 26; normal range 0–15). Serum and urine immunofixation detected monoclonal IgM kappa gammopathy and free kappa light chains, respectively. Cryoglobulins were positive (cryocrit 1.25%). Serologies for HCV, HBV and HIV were negative. Peripheral blood immunophenotyping was normal. A thoracoabdominal CT scan did not reveal enlarged lymph nodes or splenomegaly. A kidney biopsy did not find any vasculitic changes. A liver biopsy showed hepatic steatosis with increased iron deposition, suggestive of alcohol consumption.

After cardiac function recovered, an essential type I cryoglobulinaemia with CV was diagnosed and at day +12, a single pulse of methylprednisolone of 1 gr followed by oral prednisone at 1 mg/kg/day was administered with initial improvement of the general condition.

Two weeks later, the patient presented again with acute dyspnea and was again transferred to the ICU. Hypertension and a severe high-output congestive heart failure (13 litres per minute) with normal central venous pressure and low systemic resistance were noted. A TTE revealed slight myocardial dilation with 60% LVEF. At this point, CRP levels were normal and nutritional parameters revealed low vitamin B1 levels (18 ng/mL; normal range 35–91 ng/mL) and vitamin B6 levels (<5 nmol; normal range 15–96 nmol/L). Other nutritional values were also low. The patient was questioned about dietary habits and admitted mild alcohol intake (only about 40 gr/day) and a diet poor in meat, cereals and fresh vegetables. Treatment included antihypertensive and diuretic drugs, as well as thiamine (100 mg/day) given intravenously for three days. Subsequently, cardiac output and haemodynamic situations progressively stabilised, and the

patient was transferred to a standard ward. Beriberi was then diagnosed and the endomyocardial biopsy was reevaluated at this point, in which changes of myocytolysis of moderate intensity were then suggested (Fig. 1B).

Ten days later, the patient developed a generalised vesicular eruption, rapidly followed by respiratory failure, haemoptysis and bilateral non-specific pulmonary infiltrates on the chest-CT. A cutaneous biopsy confirmed varicella-zoster virus. Again, in ICU, cardiac parameters were stable but the respiratory condition worsened requiring intubation and mechanical ventilation. At this point, no signs or symptoms of active cryoglobulinaemic vasculitis were present, RF was normal and cryoglobulins were undetectable. The patient presented several infectious complications, including *Staphylococcus aureus* and *Candida* septicemia, and a disseminated varicella-zoster virus infection, which finally led to a multiorgan dysfunction and death.

Necropsy revealed bilateral pulmonary condensations, with diffuse alveolar damage and intraparenchymal haemorrhage in inferior right lobe and both lobes in left lung. No signs of vasculitis in any of the territories evaluated were seen. Macroscopic cardiac evaluation only showed mild left ventricular hypertrophy with mild dilation, with complete microscopic recovery of the previous beriberi-related lesions (Fig. 1C).

Discussion

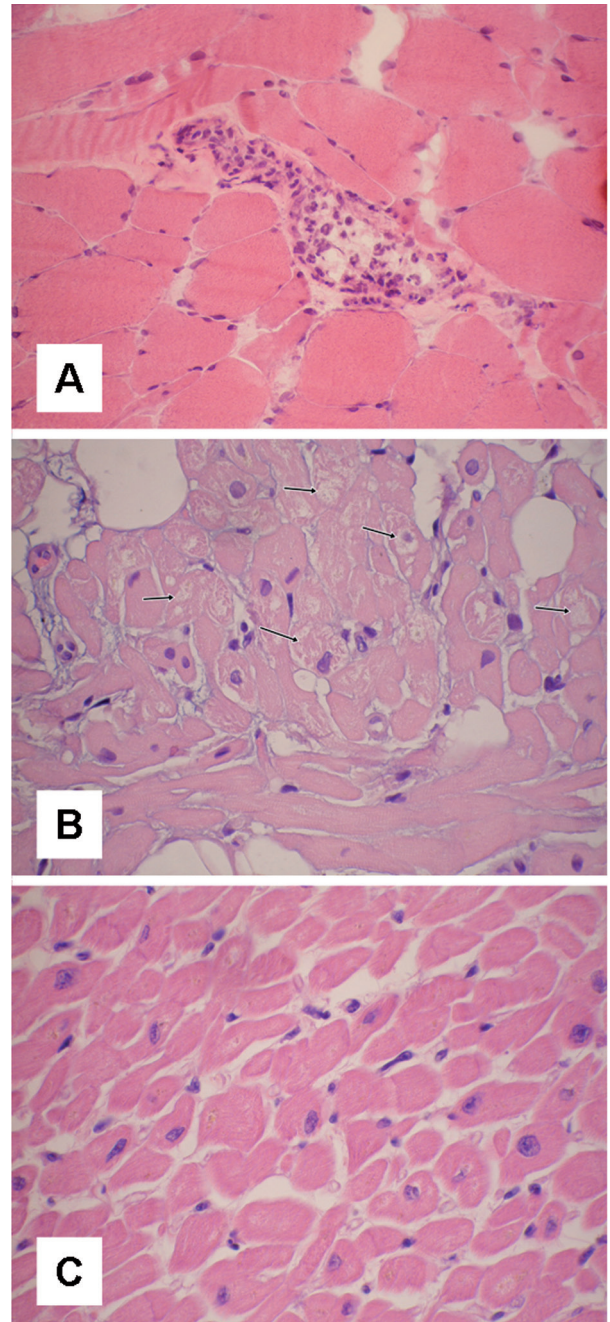
The vasculitides are a heterogeneous group of conditions characterised by blood vessel inflammation and necrosis. Essential CV is uncommon type of primary systemic vasculitis (3, 12). This has been confirmed in epidemiological population-based studies that disclosed a very low incidence, less than 4% of whole series of cases histologically confirmed as having a systemic vasculitis (13). Coexistence of essential type I CV and thiamine deficiency (beriberi disease) had not been previously reported. Acute heart dilatation with myocardial dysfunction was the presenting complication in a patient in whom both diseases were sequentially diagnosed.

CV is a systemic vasculitis affecting small, and less frequently medium-sized vessels, in which purpura is the most frequent presentation. However, some cases (as the present case) may have involvement of other territories (*e.g.* muscles, peripheral nerves, kidneys, gastrointestinal tract, lungs or central nervous system) without cutaneous vasculitis (14). Cardiac manifestations are uncommon in CV, and by far, these are more frequently seen in HCV-related CV (4) than in essential CV (5, 6). In a recent series of 165 patients with HCV-related CV (4), 4% of them had cardiac manifestations, mainly thoracic pain and congestive heart failure, and the common alteration in cardiac imaging was a dilated cardiomyopathy (4). Several studies have reported reversibility of the dilated heart early after the initiation of high doses of corticosteroids and other aggressive immunosuppressive therapy (4), including plasmapheresis (9) and rituximab (10, 15). In addition, small- and medium-sized coronary vasculitis leading to myocardial ischaemia, infarction and/or segmental left ventricular dysfunction has been found from 22% (7) to 55% (8) of CV patients at necropsy. However, myocardial infarction clinically apparent has been reported in only about 8% of patients (8, 16).

In the present case, the reversibility of myocardial dilatation and dysfunction after thiamin supplementation previous to the addition of glucocorticoid therapy, together with the absence of acute or chronic changes of cardiac vasculitis in the endomyocardial biopsy and at necropsy examination reasonably excluded this etiology.

Beriberi heart disease is characterised by oedema, low peripheral (arteriolar) vascular resistance, accelerated circulation and high output cardiac failure, cardiomegaly, and/or thiamine dietary deficiency (11, 17, 18). Although beriberi is very rarely reported in developed countries nowadays, when present, it is usually associated with chronic alcoholism, fat diets, long-term starvation, long-term peritoneal dialysis or sustained intravenous fluid administration with high glucose concentration (17). The diagnosis is de-

Fig. 1A: Muscle biopsy showing leukocytic infiltration of a small-vessel wall. **B:** Endomyocardial biopsy showing extensive changes of myocytolysis of moderate intensity (arrows). **C:** Heart (autopsy): Complete recovery of lesions. (All figures H&E x40).



finitively confirmed with the dramatic improvement of signs and symptoms after thiamine administration. Of note, systemic vascular resistance returns to normal within two weeks of thiamine therapy (19). However, the exact mechanisms through which thiamine deficiency leads to the characteristic cardiovascular abnormalities, such as depression of myocardial contractility and heart failure, are not well known (20, 21). Although there is no conclusive data about the effects of thiamine deficiency on the heart, the histological

hallmarks of myocardial involvement are muscle necrosis and colliquative myocytolysis (11), which were detected in the myocardial biopsy. Such lesions resolved after treatment and no signs of cardiac beriberi were detected at cardiac necropsy.

The patient acknowledged mild to moderate alcohol intake and a diet poor in thiamine content. Low thiamine levels (checked during the first admission in ICU) oriented to a cardiac acute beriberi (Shoshin syndrome), which could be confirmed after recovery with

thiamine supplementation contained in the enteral nutrition, since the patient initially received 0.780 mg/day for 4 days during his first admission for congestive heart failure. In the second ICU admission, high output cardiac failure was milder and treated with full doses of thiamine (1 gr/day for 3 days) and was followed by a complete recovery. Whether the initial abdominal symptoms were caused by congestive heart failure, cryoglobulinaemic vasculitis or abdominal beriberi (22) will remain unknown since all conditions were finally resolved.

As a conclusion, the young patient reported here suffered from two debilitating conditions, a deficient nutritional status causing a cardiac beriberi and a concomitant systemic vasculitis, for which he received glucocorticoids, and finally died from a serious opportunistic infection.

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