

Dilated Cardiomyopathy

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Abstract

A 78-years-old man is admitted to our hospital on October 2009 with low extremity swelling and bilateral pleural effusion.

The patient was diagnosed a pancreatic carcinoma on July of the same year, which was operated with pancreatoduodenectomy, and refers to have chronic diarrhea since the operation. The patient's weight is 59 kg and height 1.67 m (BMI 21.2 kg/m²). Serum albumin is lowered to 21 g/l (nv 35-50). The diagnosis of anasarca following malabsorption with malnutrition is made and the patient is treated with pancreatic enzymes, opioids and diuretics, leading to significant improvement of the symptoms.

One month after discharge, he is readmitted to the hospital because of the recurrence of the previous symptoms. Further investigation by echocardiography reveals a dilated cardiomyopathy, in a patient without previous history of heart disease.

Dilated cardiomyopathy can be caused by a variety of disorders. The most frequent causes are coronary artery disease, infectious myocarditis, deposition diseases such as Hemochromatosis and Amyloidosis, and medications, in particular chemotherapeutic agents or recreational drugs like alcohol and cocaine.

The patient has no evidence suggesting one of the frequent causes of dilated cardiomyopathy. On medical history he has however a pancreatic malignancy with recent uncontrolled diarrhea, causing malabsorption and malnutrition.

Multiple nutritional deficiencies have been reported to be involved in heart failure and for some of them replacement therapy results in improvement in cardiac function.

In our case, zinc deficiency is diagnosed and treated, together with carnitine and multivitamin supplementation.

The combination of classical heart failure therapy and nutritional supplementations leads in this case to a more positive course than usually observed in similar patients, with a conserved quality of life and no more need of hospitalization at one year of follow-up.

Key words

dilated cardiomyopathy, heart failure, micronutrient deficiency, vitamins deficiency

History and findings

A 78-years-old man is admitted to our hospital on October 2009 with low extremity swelling and weakness. The symptoms started two to three weeks prior to admission and are gradually increasing. The patient was diagnosed a pancreatic carcinoma on July of the same year, which was operated with pancreatoduodenectomy. He is also known for a previous prostatic carcinoma, in remission after radiotherapy and hormone therapy.

On admission, he has normal vital parameters. His weight is 59 kg and height 1.67 m (BMI 21.2 kg/m²). Clinical examination reveals symmetric swelling of the lower extremities; heart auscultation is normal, with regular rhythm and no murmurs; thorax examination reveals dullness to percussion and diminished breath sounds on both lung bases. Abdominal and remaining clinical examination don't show other pathological findings.

Chest X-ray confirms the presence of bilateral pleural effusion, without signs of pulmonary edema. The laboratory analysis show a mild normocytic-normochromic anemia (hb 11.1 g/dl, nv 14.0-18.0) with normal vitamin B12, folic acid and ferritin. On serum chemistry profile, potassium is diminished to 2.6 mmol/l (nv 3.5-5.0), liver function tests are elevated to 2-to-3-fold the upper limit of normal by unaltered INR (1.1) and renal function is conserved. Serum albumin is lowered to 21 g/l (nv 35-50). An abdominal CT scan reveals the presence of pancreatic tumor recurrence in the upper retroperitoneal space, without liver metastases.

On further anamnesis, the patient refers to have chronic diarrhea since the operation, despite of pancreatic enzyme replacement and loperamide therapy. Although the appetite is maintained, the patient lost 15 kg body weight since the identification of pancreatic carcinoma.

The diagnosis of malnutrition with anasarca following malabsorption is made; further laboratory analysis reveal a deficiency of vitamins A and D, which are promptly substituted.

The malabsorption is linked to the chronic diarrhea, and the patient is treated with opioids, in combination with higher doses of pancreatic enzymes and a trial of antibiotic treatment for an empiric diagnosis of bacterial overgrowth. A loop diuretic is associated to reduce the amount of edema. The patient's conditions improve significantly and he is discharged home after 30 days of hospital stay.

On December 2009 the patient is rehospitalized because of the recurrence of similar symptoms.

The clinical examination reveals again a constellation of fluid overload, with low extremities swelling and bilateral pleural effusion.

The patient has no more diarrhea, the weight has stabilized (50 kg, BMI 17.9 kg/m²) since demission and the albumin is now 30 g/l (nv 35-50).

Therefore, we extend the investigations executing an echocardiography: left ventricular dilatation is observed, with severe systolic (ejection fraction of 25%, nv >60%) and diastolic dysfunctions, without valvular dysfunctions.

Summarizing, our 78year old tumor patient, without relevant cardiac history, develops a symptomatic dilated cardiomyopathy of unknown origin.

Differential diagnosis

Dilated cardiomyopathy can be caused by a variety of disorders. The most frequent causes are coronary artery disease, infectious myocarditis, deposition diseases such as Hemochromatosis and Amyloidosis, and medications, in particular chemotherapeutic agents or recreational drugs like alcohol and cocaine (see table1).

In about 50% of cases, however, no etiology can be found and the cardiomyopathy is deemed idiopathic.

Table1: Main causes of dilated cardiomyopathy.

ischemic

infectious disease: virus: Coxsackievirus, Cytomegalovirus, HIV
 bacterial: Streptococci – rheumatic fever, Typhoid fever, Lyme disease

deposition diseases: Hemochromatosis, Amyloidosis

medications: chemotherapeutic agents: Anthracyclines, Cyclophosphamide, Trastuzumab
 antiretroviral drugs: Zidovudine, Didanosine, Zalcitabine
 Phenothiazines

toxins: Ethanol, Cocaine, Amphetamines
 Lead, Carbon monoxide

immunologic diseases: Systemic lupus, Scleroderma, Giant cell arteritis
 Sarcoidosis, Autoimmune myocarditis

endocrinologic disorders: Thyroid hormone excess or deficiency, Growth hormone excess or
 deficiency, Pheochromocytoma

nutritional deficiencies: Thiamine, Coenzyme Q10, Carnitine, Selenium, Zinc

genetic disease: Duchenne's muscular dystrophy, Myotonic dystrophy
 Familial cardiomyopathies

idiopathic

The patient has no previous cardiologic history, ECG is normal and he performed a normal cardiac stress test last year. We therefore consider an ischemic origin of the dilated cardiomyopathy as unlikely and decide not to execute a coronary angiography, in a patient with a poor prognosis due to the malignant disease.

An infectious cause of the cardiomyopathy seems to be unlikely, in the absence of elevated myocardial enzymes and with a C-reactive protein (CRP) only slightly elevated to 17 mg/l (nv <5). Despite of the diagnosis of two tumors, the patient did not receive any chemotherapeutic agent known to cause cardiomyopathy, and he also doesn't use recreational drugs.

The clinical history and the examination reveal no evidence for a systemic immunologic disease; echocardiography images (without thickening of the heart wall or altered muscular texture) and

blood chemistry give no clues for a deposition disease like Hemochromatosis (ferritin 295.7 ug/l, nv 15.0-300.0) or Amyloidosis (protein electrophoresis without monoclonal bands). Thyroid hormone values are also found to be within the normal range (TSH 1.690 mIU/l, nv 0.400-4.000).

The patient has no evidence suggesting one of the frequent causes of dilated cardiomyopathy. On medical history he has however a pancreatic malignancy with recent uncontrolled diarrhea, causing malabsorption and malnutrition.

Several nutritional deficiencies have been reported in patients with dilated cardiomyopathy, and some of them are involved in the pathogenesis of heart failure¹⁻⁴ (see table2).

Table 2: nutritional deficiencies involved in cardiomyopathy.

vitamins: thiamine (vit B1), coenzyme Q10, riboflavin (vit B2), pyridoxine (vit B6), vitamin D

amino acids: carnitine, taurine

trace minerals: selenium, zinc

Thiamine plays an important role in carbohydrate energy metabolism, particularly for the oxidative phosphorylation, and is therefore crucial for myocardial energy production. Thiamine is stored in very small quantities, and the loop diuretics, often used in heart failure, cause increased urinary loss, endangering the patients for a deficit²⁻⁵.

The cardiomyopathy following thiamine deficiency is known as “wet beri beri”, a combination of heart failure, vasodilatation and capillary leak, which is reversible by vitamin supplementation. There is also some evidence that thiamine supplementation can improve cardiac function in patients with chronic heart failure receiving loop diuretics^{6, 7}.

Coenzyme Q10 (CoQ10) is critical for the transport of electrons through the initial portion of the mitochondrial respiratory chain and is an important antioxidant. It is synthesized within the human cells, by a pathway including HMG-CoA-reductase, which is inhibited by lipid-lowering drugs (statins), frequently used in heart failure patients. Significantly reduced CoQ10 levels are well documented in heart failure patients, but despite promising results of supplementation in animal models, the role of CoQ10 therapy in patients with heart failure is not yet defined^{2-4, 8}.

Vitamin D is one of the most important factors in the regulation of calcium metabolism, which is known to be impaired in patients with chronic heart failure. Even though the role of vitamin D deficiency in heart failure is not yet entirely understood, a low vitamin D status is frequently found in patients with congestive heart failure and may therefore be a contributing pathogenic factor⁹.

Carnitine is an amino-acid derivative and plays an essential role in the transport of long-chain fatty acids from the cytoplasm into the mitochondrial matrix; it is also involved in the activation of pyruvate dehydrogenase, improving glucose oxidation. It is therefore an essential substrate for the energy production of the heart muscle. Genetically determined Carnitine deficiency is associated with the development of cardiomyopathy and skeletal muscle dysfunction, which can be ameliorated with Carnitine replacement; Carnitine deficiency may also be acquired and up to 50% of the patients with heart failure exhibit a marked Carnitine depletion^{2-4, 10, 11}.

The administration of L-carnitine has been reported to result in hemodynamic improvement and an overall benefit in the functional capacity of patients with myocardial dysfunction¹²⁻¹⁴.

Taurine is an amino acid not involved in protein synthesis. It is an important factor for the modulation of cellular calcium levels and is found in particularly high concentrations in the heart,

where intracellular calcium plays a vital role in myocyte energy production. Calcium is also the principal biochemical coupler for muscle function: impaired reuptake of calcium into the sarcoplasmic reticulum adversely affects diastolic relaxation, whereas calcium release by the sarcoplasmic reticulum is a principal determinant of systolic function.

Cardiac Taurine concentrations are reduced in heart disease and Taurine depletion has been shown to render the heart more susceptible to ischemic damage and to decrease contractile force. Despite this, evidence of benefit of taurine administration in humans is lacking, since studies in patients with congestive heart failure have been very limited and uncontrolled²⁻⁴.

Selenium deficiency has been associated with a specific form of dilated cardiomyopathy, named Keshan disease, which is reported in geographical areas where selenium is rare (i.e. China, New Zealand) and as consequence of selenium deficiency following bariatric surgery or total parenteral nutrition. The disease is reversible after selenium supplementation¹⁵⁻¹⁷.

Selenium is an essential part of the enzyme glutathione peroxidase, which catalyses active oxygen species thereby protecting cardiac myocytes from the toxic effect of free radicals.

Zinc is involved in almost all metabolic pathways, acting as co-factor of more than 300 enzymes and having a role in the metabolism of RNA and DNA, in signal transduction and in gene expression¹⁸. Reduced serum Zinc has been associated with the appearance of a dilated cardiomyopathy, and furthermore urinary Zinc excretion is increased in response to treatment with angiotensin converting enzyme inhibitors, which are a basic medication in heart insufficiency patients.

Further investigations, treatment and course

The diagnostic workup of our patient reveals an elevated level of thiamine (561 nmol/l, nv 66-200) and a normal value for plasma selenium (0.93 umol/l, nv 0.89-1.90), while Zinc deficiency is diagnosed (plasma level 6.9 umol/l, nv 9.2-18.4).

Vitamin D is not measured, in view of the fact that is supplemented since the previous hospitalization.

Carnitine is not measured, because we could not clarify which test is reliable and if there is a correlation between blood values and tissue carnitine concentration (the parameter used in available studies).

As therapeutic intervention, nutritional supplementation of Zinc 20 mg/d for 30 days, Carnitine 2 g/d and a multivitamin preparation (Supradyn 1/d) are associated to the classical heart failure therapy (an ATII-inhibitor, Telmisartan 40 mg/d; low dose of beta-blocker, Atenolol 25 mg/d and diuretics, Torasemide 10 mg/d and Spironolactone 100 mg/d).

In the course, the patient is treated with ambulatory palliative chemotherapy with Gemcitabine for the previously described tumor recurrence in retroperitoneal space. He has only occasional episodes of leg swelling, which need an adaptation of the diuretic therapy, and is no more hospitalized.

Unfortunately no examination of the cardiac function has been performed in the follow-up.

Almost one year after the two hospitalizations, he is living at home with a satisfying quality of life, has a maintained nutritional state, only occasional diarrhea and the weight is stabilized at 49 kg (50 kg at demission on December 2009).

Conclusions and learning points

Several nutritional deficits, involving vitamins, amino acids and trace minerals, play an important role in the development or worsening of heart failure. At present, there is good evidence of their central functional role in the heart metabolism and of the presence of nutritional deficiency in heart failure patients.

The evidence regarding the beneficial consequences of nutritional supplementation in heart failure remains weak and mainly based on animal models or small studies. The awareness to the topic is poor, hence this therapeutic option is not even mentioned in the actual guidelines of the international society of cardiology (American Heart Association, European Society of Cardiology)^{19, 20}. In our patient, the combination of classical heart failure therapy and nutritional supplementations led to a more positive course than usually observed in similar patients, with a conserved quality of life and no more need of hospitalization at one year of follow-up.

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