

# Difficult diagnosis of cardiac haemochromatosis: a case report

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## Background

Primary iron overload cardiomyopathy is an important and potentially preventable cause of heart failure (HF), usually manifesting in the 4–5th decade of life. Patients may be asymptomatic early in the disease with hidden progression of cardiac dysfunction. The challenge of timely detection is an awareness of this systemic disorder and an adequate degree of clinical vigilance.

## Case summary

A 48-year-old man was referred to the university clinic due to the episode of atrial fibrillation. The specific features of bronze skin and yellow eyes together with a combination of syndromes (cardiomyopathy, cirrhosis, ascites and portal hypertension, diabetes mellitus, and chronic kidney disease) stimulated the testing of iron metabolism markers, which were far above the normal range. Echocardiography and cardiac magnetic resonance (CMR) showed the dilatation of all cardiac cavities and biventricular systolic dysfunction. CMR T2\* mapping was consistent with the diagnosis of myocardial and hepatic siderosis. Hereditary Type I haemochromatosis was confirmed by a genetic test. After 6 months of standard HF treatment, chelation therapy with deferiprone and regular phlebotomies imaging tests showed a reduction of ventricular and atrial volumes, an improvement in the cardiac systolic function and a decrease of iron accumulation.

## Discussion

In this case, complicating syndromes were detected earlier than underlying disease of primary haemochromatosis. Cardiac haemochromatosis should be considered in any patient with unexplained HF, especially in the case of a positive family history, abnormal liver enzymes, endocrinopathies, or evidence of involvement of other organ systems. Screening for systemic iron overload with transferrin saturation and serum ferritin is the first step. Further non-invasive imaging tests should be done to confirm organ involvement.

## Keywords

Case report • Haemochromatosis • Iron overload • Cardiac • Cardiomyopathy • Hereditary • Cirrhosis

## Learning points

- Haemochromatosis is an important specific cause of heart failure, and it's often asymptomatic until the middle age, at which point iron levels finally exceed the storage capacity of cells and tissue damage occurs.
- Physicians should remember the red flags of this disease: combination of bronze skin, diabetes, cirrhosis, arthritis, and cardiomyopathy.
- Cardiac magnetic resonance with measurement of T2\* relaxation time is superior to other diagnostic modalities since it allows not only to detect but also to quantify myocardial iron overload.

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## Introduction

Cardiac haemochromatosis is an important and potentially preventable cause of heart failure (HF). However, this condition is often diagnosed in the latter stages of the disease, when complications may have already developed. Iron deposition in the heart often causes arrhythmias and progressive systolic dysfunction. This usually manifests itself in the form of dilated cardiomyopathy with low left ventricular ejection fraction (LVEF), which can be reversible only if it is diagnosed and treated in its early stages. This unique genetic condition is often asymptomatic until the middle age, at which point iron levels finally exceed the storage capacity of cells and tissue is damaged, resulting in cirrhosis, hypogonadism, diabetes, arthropathy, cardiomyopathy, and skin pigmentation. In this case, we discuss the difficulties of differential diagnosis of cardiac haemochromatosis and the effect of specific and HF treatment.

## Timeline

The start of the disease (2013)	Typical symptoms and signs of heart failure (HF), biventricular dilative cardiomyopathy.
Clinical manifestation	Cirrhosis (Child B class) with hepatosplenomegaly, ascites and portal hypertension, diabetes mellitus with diabetic foot, chronic kidney disease, and HF.
Clinical presentation (2017)	Patient was referred to hospital due to the episode of atrial fibrillation. Objectively: bronze-shaded skin, telangiectasia on the shoulders, and slightly yellowish eyes. Electrocardiogram: atrial fibrillation, decreased voltage on the main limbs leads. Iron metabolism markers: serum ferritin, transferrin saturation, and iron level above the normal range. Echocardiography: the dilatation of all cardiac cavities and biventricular systolic dysfunction. Cardiac magnetic resonance: left ventricular ejection fraction (LVEF) 28%, right ventricular ejection fraction (RVEF) 20%, reduced T2* relaxation times in the myocardium, and liver to 8.8 and 2.5 ms, respectively.
Confirmation	Genetic test confirmed hereditary type I haemochromatosis.
6 months after treatment	Cardiac magnetic resonance: the reduction of ventricular and atrial volumes, LVEF 52%, RVEF 50%, as well as positive dynamics of T2* relaxation times: 10.5 ms and 3.2 ms in the myocardium and liver, respectively.

## Case presentation

A 48-year-old man was referred to the Vilnius University Hospital Santaros Klinikos due to atrial fibrillation with a rapid ventricular

response, which was subsequently restored to sinus rhythm by using DC cardioversion. Of note, his electrocardiography ([Figure 1](#)) additionally showed decreased voltage in the limb leads and non-specific repolarization abnormalities. He presented with typical symptoms and objective signs of HF, and it was known from medical history that a previous echocardiography (done in 2013) had shown biventricular dilatation and impaired left ventricular (LV) function. Despite complaining of increasing weakness, fatigue, shortness of breath, and abdominal volume, the patient did not take any cardiac medication before index hospitalization. Transthoracic echocardiography confirmed significant ventricular dilatation and systolic dysfunction (LVEF 27%) with severe reduction of global and regional longitudinal strain ([Figure 2](#)). Ischaemic origin of HF was excluded during the initial workup by invasive angiography, family history was negative. Past medical history was significant for the following conditions: cirrhosis (Child B class) with hepatosplenomegaly, ascites and portal hypertension, diabetes mellitus with diabetic foot, and chronic kidney disease.

Importantly, a subsequent more careful inspection revealed bronze-shaded skin, telangiectasia on the shoulders and abdomen, and slightly yellowish eyes. These special features combined with concomitant cirrhosis, diabetes, and cardiomyopathy stimulated the testing of iron metabolism markers. Laboratory tests' results consistent with iron overload and their dynamic changes after treatment are presented in the [Table 1](#).

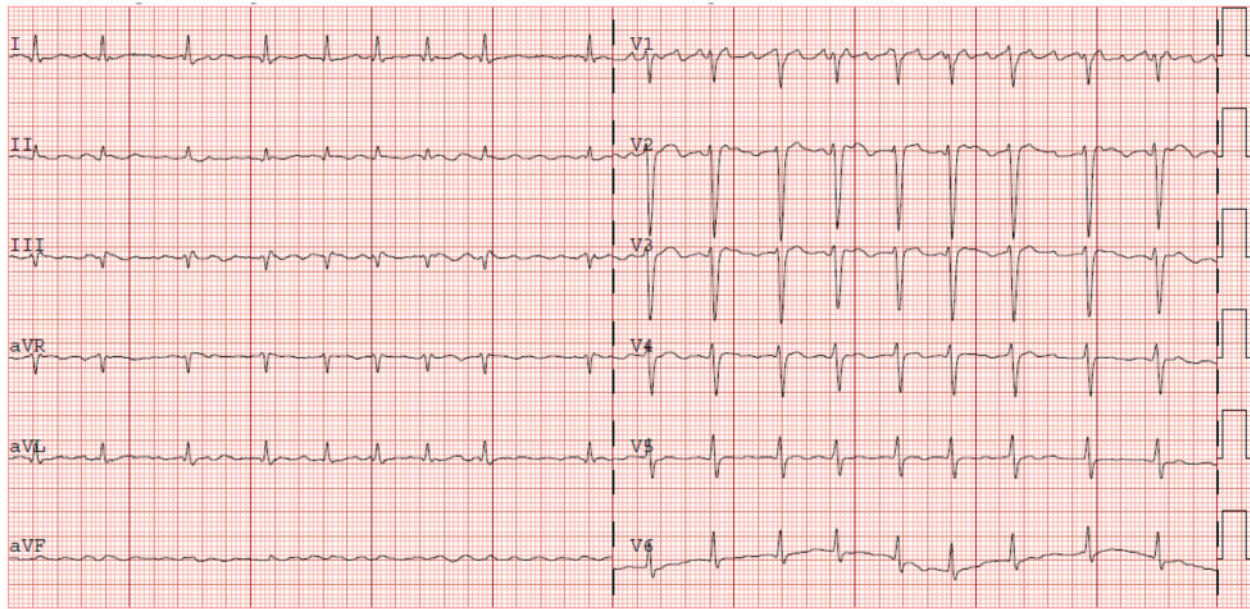
In order to detect the iron accumulation in the heart cardiac magnetic resonance (CMR) was performed on a 1.5 T scanner (Siemens Avanto, Erlangen, Germany) with measurement of T2\* relaxation time of the heart and liver, and LV function, volumes, and mass. The morphometric, functional and T2\* relaxation values are presented in [Table 2](#). The changes in LV systolic function and liver before and after treatment are illustrated in the [Supplementary material online, Images S1a–c, S2a and b, S3a–c, and S4a, b](#). Cardiac magnetic resonance findings were consistent with the diagnosis of myocardial and hepatic siderosis.

Hereditary or Type I haemochromatosis (HHC) was confirmed by a genetic test, showing the potential (>90%) homozygous genotype for the C282Y mutation of the HFE gene.

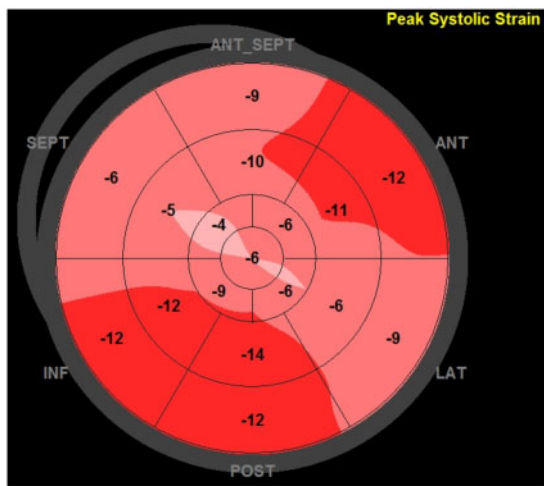
During 2 weeks of hospitalization specific therapy with deferiprone and standard HF treatment was initiated, regular phlebotomies (removing about 500 mL of blood) were also scheduled. Medical treatment at different timepoints is presented in [Table 3](#). Dietary advice included restrictions of iron intake (meaning to avoid red meat, crustaceans), as well as vitamin C and alcohol. The chelate, used for about 1 month, was discontinued due to limited availability and high cost in Lithuania. The improvement of iron metabolism markers was interpreted as a good response to regular phlebotomies, therefore, a multidisciplinary team decided to leave therapeutic phlebotomy (every 2 weeks) as a main treatment for haemochromatosis.

## Discussion

Cardiac haemochromatosis is the term used to describe the cardiac dysfunction that results from the accumulation of iron in the heart whether from primary or secondary HHC with a varying degree of cardiac involvement. The mutations leading to hereditary HHC are not rare, especially among white populations. In Lithuania, the



**Figure 1** Electrocardiogram shows atrial fibrillation with heart rate 115 b.p.m., decreased voltage in the limb leads, broadening of QRS complex, and non-specific repolarization abnormalities.



**Figure 2** Segmental representation of peak longitudinal systolic strain (bull's eye scheme) using 2D speckle tracking technique shows diffuse decrease of strain with some regional heterogeneity before treatment.

reported prevalence of C282Y mutation in the haemochromatosis (HFE) gene on chromosome 6 is 2.6% which is similar to the other Central and Eastern European countries with population of Slavic origin.<sup>1</sup> Not all patients that are homozygous for C282Y or compound heterozygous (C282Y/H63D) develop iron overload.<sup>2</sup> The factors affecting penetrance are sex, age, physiological and pathological

blood loss, blood donation, dietary intake of iron, alcohol, hepatitis C and B, obesity, and the use of dietary supplements (iron and vitamin C). Additional mechanisms associated with HFE gene mutation, such as exacerbation of coronary artery disease, direct causation of dilative cardiomyopathy, or autoimmune processes, have been discussed.<sup>2</sup>

Our case demonstrates the complexity of storage disease diagnosis. The clinical syndromes, complicating the main underlying disease, were determined first, without a recognition of particular aetiology of those. However, a combination of clinical manifestations such as chronic fatigue, lethargy, bronze skin, arthritis, cardiomyopathy, diabetes, and cirrhosis should serve as red flags and lead the scrupulous clinician to the suspicion of iron metabolism disorder (Figure 3).

Cardiac magnetic resonance with measurement of T2\* relaxation time is superior to other diagnostic modalities since not only it allows not only to detect but also to quantify myocardial iron overload.<sup>3</sup> The time constant of decay for relaxation time is inversely proportional to the iron content in the tissue: the higher iron content, the shorter T2\*.<sup>4</sup> Diastolic cardiac dysfunction secondary to restrictive physiology may be seen early in the disease, while later dilated cardiomyopathy with LV systolic dysfunction may prevail. Newer modalities such as strain imaging hold promise for earlier detection of cardiac involvement.<sup>5,6</sup>

The diagnostic pathway of our patient is presented in Figure 3. The combination of magnetic resonance imaging of the heart and liver with the result of genetic testing made a liver or cardiac biopsy unnecessary in this case.<sup>7</sup> The management of iron overload with proper iron chelation therapy and therapeutic phlebotomy guided by CMR T2\* relaxometry is the key to haemochromatosis treatment, in

**Table 1** Laboratory tests results at baseline and 6 months after treatment

Parameter	Measurement units	Baseline	6 months after treatment	Normal range
Ferritin	µg/L	2742.8	185.5	20–300
Transferrin saturation	%	94.9	NA	2–3.6
Iron	µmol/L	39.1	NA	9.5–29.9
BNP	ng/L	981.2	NA	<100
Troponin I	ng/L	85	50.3	≤34.2
Serum creatinine	µmol/L	175	62	62–115
Albumin	g/L	34.6	41.9	35–52
ALP	U/L	147	200	40–150
AST	U/L	152	69	≤40
ALT	U/L	84	50	≤40
Total bilirubin	µmol/L	36	18	<21
Direct bilirubin	µmol/L	15	9.4	<5.3
Indirect bilirubin	µmol/L	21	9.0	<15.7
Serum glucose	mmol/L	7.15	9.1	4.2–6.1
HgB	g/L	148	130	128–160
Hct	L/L	0.423	0.391	0.40–0.48
CRP	mg/L	12.6	1.2	≤5

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CRP, C-reactive protein; Hct, haematocrit; HgB, haemoglobin.

**Table 2** Dynamics of cardiac structure and function assessed by TTE and CMR at baseline and 6 months after treatment

	Baseline	6 months after treatment	Normal range
Transthoracic echocardiography			
LVEF (%)	27	50	≥55
TAPSE (cm)	1.3	1.8	≥1.7
IVC <sub>exp</sub> (cm)	3	2	≤2.1
IVC <sub>ins</sub> (cm)	2.8	—	≤1.7
IVC <sub>collapse</sub> (%)	6.6	—	>50
Cardiac magnetic resonance			
LVDD (cm)	6.4	5.7	≤5.9
LVPWDD (mm)	10	8	≤10
IVSDD (mm)	11	11	≤10
LVEDVI (mL/m <sup>2</sup> )	123	81	<92
LVESVI (mL/m <sup>2</sup> )	88	39	<30
LVEF (%)	28	52	≥55
RVEDVI (mL/m <sup>2</sup> )	128	83	≤105
RVESVI (mL/m <sup>2</sup> )	95	41	<43
RVEF (%)	26	50	≥47
CI (L/min/m <sup>2</sup> )	2.5	3.2	≥2.82
LA area 4 ch (cm <sup>2</sup> )	37	29	≤29
CMR T2* relaxation time <sup>a</sup>			
Septal myocardium (ms)	8.8	10.5	≥20
Liver tissue (ms)	2.5	3.2	>6.3

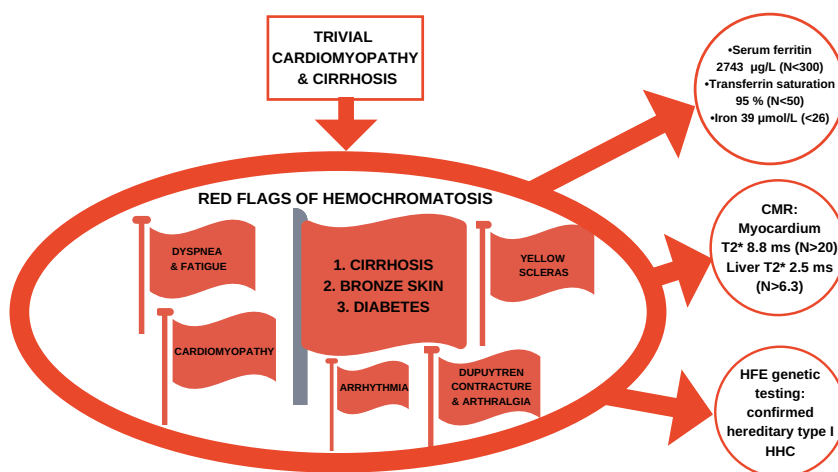
CI, cardiac index; IVC<sub>collapse</sub>, inferior vena cava at collapse; IVC<sub>exp</sub>, inferior vena cava at expiration; IVC<sub>ins</sub>, inferior vena cava at inspiration; IVSDD, intraventricular septum diastolic diameter; LA, left atrium; LVDD, left ventricular diastolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVPWDD, left ventricular posterior wall diastolic diameter; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; TAPSE, tricuspid annular plane systolic excursion.

<sup>a</sup>Standard deviation of T2 values in scan and rescan is <0.4 ms.

**Table 3** Medical treatment at different timepoints

Daily dose	First hospitalization	After 1 month	After 6 months
Medication			
Insulin	54–56 Units	38–42 Units	24–28 Units
Furosemid	120 mg	160 mg	80–120 mg
Torasemid	50 mg	50 mg	25 mg
Spirolacton	200 mg	50 mg	100 mg
Carvedilol	18.75 mg	18.75 mg	18.75 mg
Perindopril	2.5 mg	2.5 mg	2.5 mg
Rivaroxaban	—	20 mg	20 mg
Deferiprone	3000 mg	6000 mg	— <sup>a</sup>
Phlebotomy	Weekly (500 mL)	Weekly (500 mL)	Every 10–14 days (500 mL)

<sup>a</sup>Interrupted due to limited availability and high cost of deferiprone.



**Figure 3** The scheme of diagnostic workup and the red flags of haemochromatosis.

addition to other diseases-specific modalities and the conventional HF therapy.<sup>8</sup> Close family members of newly diagnosed patients should be screened for an asymptomatic disease.

The treatment decisions were influenced by the limited availability and high cost of chelates in Lithuanian market, with deferiprone accessible only. According to the recommendations,<sup>7–9</sup> phlebotomies are the treatment of choice in non-anaemic patients, with ferritin level >300 µg/L in men; with haemoglobin and haematocrit levels ranging within 120–130 g/L and 0.38–0.41, respectively, phlebotomy was considered as adequate therapy for our patient, giving a positive response.

A marked and clinically significant improvement in LVEF was observed in our case; first of all, it may be attributed to the well-known effect of anti-remodelling therapy of angiotensin-converting enzymes inhibitor, beta-blocker, and mineralocorticoid receptor antagonist,<sup>10</sup> which was newly started during index hospitalization. Second, partially effect may be associated with a reduction of iron accumulation, which similarly was reported in haemochromatosis cases

by other authors.<sup>11,12</sup> The difference between follow-up and baseline values of LVEF far exceeds the established variability of this parameter.<sup>13</sup> However, the increase of T2\* relaxation times in the heart and liver was relatively low compared with other cases reported in the literature<sup>14,15</sup>; it may be explained by the lack of chelating therapy for our patient.

## Conclusion

Hereditary or Type I haemochromatosis is an important specific cause of HF, usually manifesting in the 4–5th decade. Timely detection of this systemic disorder could prevent multiple organ damage. Physicians should remember the red flags of this disease: combination of bronze skin, diabetes, cirrhosis, arthritis, and cardiomyopathy. Biochemical indicators and T2\* relaxation time on CMR provide not only diagnostic value but also in addition help to quantify the treatment effect. Specific chelation, regular phlebotomies, and standard

HF treatment may demonstrate significant benefit even in the advanced stage.

## Lead author biography



Vaida Sudmantaitė, 5th-year medical student, is studying at the Faculty of Medicine in Vilnius University, Lithuania. Sudmantaitė is interested in cardiology since the first contact with human anatomy. She is engaged in scientific activities of cardiology and also volunteered at cardiology department.

## Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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