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"Hemochromatosis and Xeroderma Pigmentosum: two (un)suspicious neighbors"

Filipa Oliveira Monte

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CLINICAL CASE REPORT

HEMOCHROMATOSIS AND XERODERMA PIGMENTOSUM: TWO (UN)SUSPICIOUS NEIGHBORS

Thesis Application for the Masters degree in Medicine, submitted to the Instituto de Ciências Biomédicas Abel Salazar.

Filipa Oliveira Monte

6th year Student- Masters Degree in Medicine
Student institutional identification number : 201404901
E-mail address: filipaoliveiramonte@gmail.com

Affiliation: Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto
Porto, Portugal
Rua de Jorge Viterbo Ferreira nº228, 4050-313 Porto.

Supervisor: Isabel Maria Teixeira de Carvalho Pedroto, M.D., PhD.
Affiliation: Head of the Gastroenterology Department, Centro Hospitalar Universitário do Porto (CHUP)
Porto, Portugal
Largo Prof. Abel Salazar 4099-001 Porto
Telefone: +351 222 077 500

Co-Supervisor: Mónica Sofia Gonçalves Garrido, M.D.
Affiliation: Resident, Gastroenterology Department, Centro Hospitalar Universitário do Porto (CHUP)
Porto, Portugal
Largo Prof. Abel Salazar 4099-001 Porto
Telefone: +351 222 077 500

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The present manuscript was written accordingly to the Author Guidelines imposed by *GE-Portuguese Journal of Gastroenterology , in* https://www.karger.com/Journal/Guidelines/272027 (last accessed on June 11, 2020).

This study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto. The patient authorized and signed the consent form for image recording, submission and publication of this work.

Porto, june 2020

Student's signature

Filipa Oliveira Monte

Supervisor's signature

Co-supervisor's signature

Maria Sofia Gonçalves Ganido

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The culmination of six years of effort, dedication, challenges and self-improvement is imminent and, consequently, it is vital to express my gratitude to all of those who contributed to my personal and professional development.

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Resumo

Uma mulher de 51 anos, com antecedentes pessoais de *Xeroderma pigmentosum* (XP), foi referenciada à consulta de Hepatologia por apresentar, além da hiperpigmentação cutânea, alterações nas enzimas de citólise hepática, aliadas ao aumento da ferritina sérica e de saturação da transferrina, bem como alterações ecográficas compatíveis com doença hepática crónica. A realização de um teste genético permitiu confirmar a hipótese diagnóstica de Hemocromatose Hereditária (HH).

Pela proximidade conhecida dos genes *HFE* (6p22.2) e *POLH* (6p21.1), responsáveis pela HH e pelo XP-V, respetivamente, foi realizado um teste genético que detetou um polimorfismo raro do gene *POLH*.

Reportamos o primeiro caso de uma paciente diagnosticada com XP e HH, na qual foram identificados dois genes vizinhos mutados – *POLH* e *HFE* –, possivelmente como resultado de ligação genética.

Palavras Chave: Hemocromatose Hereditária, *HFE*, *Xeroderma pigmentosum*, *POLH*, cirrose hepática.

Abstract

A 51-year-old woman, with a clinical diagnosis of *Xeroderma pigmentosum* (XP), was found to have, apart from skin hyperpigmentation, abnormalities in liver enzymes, high ferritin and transferrin saturation levels, with ultrasonographic features of chronic liver disease. Genetic testing confirmed the clinical hypothesis of Hereditary Hemochromatosis (HH). Due to the known proximity of *HFE* (6p22.2) and *POLH* (6p21.1) genes, accountable for HH and the XP-V, respectively, a genetic test was offered and a rare variant of the *POLH* gene was identified.

We report the first confirmed case, to our knowledge, of a patient diagnosed both with XP and HH, in whom two mutated neighbor genes - *POLH* and *HFE* - were identified, possibly the result of genetic linkage.

Keywords: Hereditary Hemochromatosis*, HFE, Xeroderma pigmentosum, POLH*, liver cirrhosis.

Abbreviations and Acronyms List

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMA	Anti-mitochondrial antibody
ANA	Anti-nuclear antibody
Anti- HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HCV	Anti-hepatitis C virus
Anti-LC1	Anti- liver cytosol antibody
Anti-LKM	Anti-liver-kidney microsome antibody
Anti-SLA/LP	Anti-soluble liver antigen/liver-pancreas antibody
ASMA	Anti-smooth muscle antibody
AST	Aspartate transaminase
CMV	Citomegalovirus
DNA	Deoxyribonucleic acid
FSH	Follicle-stimulating hormone
GGT	Gamma-glutamyltransferase
HBs Ag	Hepatitis B surface antigen
HH	Hereditary Hemochromatosis
Ig	Immunoglobulin
MRI	Magnetic resonance imaging
UNL	Upper Normal Limit
UVR	Ultraviolet Radiation
XP	*Xeroderma pigmentosum*
XP-V	*Xeroderma pigmentosum* variant

Contents

	Page
Acknowledgments	i.
Resumo	ii.
Abstract	iii.
Abbreviations and Acronyms List	iv.
List of Tables	vi.
List os Figures	vii.
Introduction	1,2
Case Report	3,4
Discussion/Conclusion	5-7
References	14

List of Tables

Page

Table I: Initial analytical assessment. 8-10

List of Figures

	Page
Fig. 1 - Multiple solar lentigines and xerotic appearance in the photoexposed area. Note the clear demarcation with the zone usually protected by clothes.	10
Fig. 2 – MRI documenting in axial T1-weighted (upper left) and T2-weighetd (upper right) images a decrease in the liver signal intensity. Axial T1-weighted gradient echo sequence images (lower panel) show a decreased signal intensity in the liver on the in-phase image (left) compared with the out-of-phase image (right), corroborating hepatic iron overload.	11
Fig. 3 - Fragment of liver biopsy with hematoxylin-eosin staining (100x), in which iron pigment stains brown (on the left); Fragment of liver biopsy with *Pearls* staining (100x), in which the iron pigment stains blue (on the right).	11
Fig. 4- Evolution of ferritin levels, in red, and hemoglobin, in blue, after the onset of phlebotomies, reaching ferritin target levels 68 weeks after.	12
Fig. 5 - Evolution of ALT (Alanine Transaminase), in blue, and AST (Aspartate Transaminase), in green, after the onset of phlebotomies, reaching normal range values.	12
Fig. 6- Genogram buttressing C282Y homozygosity's detection in one brother and one sister, as well as in one grandson, after genetic screening was carried out.	13

Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder of DNA repair, with an estimated incidence in the United States and Western Europe of approximately 1/1000000 live births [1], with 100% penetrance, that affects, mostly, sun-exposed skin and eyes, and less commonly, the nervous system, due to an increased sensitivity to ultraviolet radiation (UVR). Mutations in any of eight genes involved in the recognition and repair of UVR-induced DNA damage can be encountered, which ultimately leads to eight different subgroups- XPA through XPG, and XP-V. Women and men are equally affected. Compared to the general population, individuals with XP are at significantly higher risk of developing skin cancer, which also occurs at an earlier age. A clinical diagnosis can be made out of the typical skin findings that include freckling before the age of two, severe solar erythema after minimal exposure to radiation (although this feature is not usually perceived in XPC, XPE and XP-V subgroups, whose reaction to sun exposure is globally normal)[2] , xerosis, progressive atrophy and hyper/hypopigmentation; ocular findings [3] such as photophobia, xerophthalmia, conjunctival injection, ectropion, and keratitis; and, in some patients, neurodegenerative disease [4] which can manifest by sensorineural hearing loss, ataxia, areflexia, and peripheral neuropathy. Along with the clinical findings, a positive family history can corroborate the diagnosis. Genetic testing confirms and categorizes the patient into one of the eight subgroups. In these patients, it is strictly recommended regular skin and eye examination, as well as avoiding sun exposure [5] , to provide an early management of premalignant and malignant skin lesions.

Hereditary hemochromatosis (HH) is an autosomal recessive disorder, widely identified in Caucasians, in which, typically, biallelic inheritance of the p.C282Y variant in the *HFE* gene lead to inappropriately low levels of hepcidin which, by facilitating ferroportin mediated iron export, results in greater intestinal iron absorption with consequential iron overload and tissue damage over time. [6] It takes about four decades in males and five to six decades in females to reach the iron threshold (20g) from which most individuals have severe clinical manifestations. [7] Homozygosity for the p.C282Y variant (C282Y/C282Y) has an approximate prevalence of 1/150 to 1/300 in populations of north European ancestry. [8]

When hyperferritinemia is found and other frequent causes have been excluded, the transferrin saturation must be determined and, if an elevated level is confirmed in more than one determination, a genetic test with *HFE* genotyping is warranted. The diagnosis can be, therefore, made in the presence of high transferrin saturation, hyperferritinemia and homozygosity for the p.C282Y variant. Phlebotomy is the treatment of choice for reaching 50-100 µg/L ferritin targets

and preventing/reversing the complications associated with iron deposition in tissues. First-degree family members must be screened with ferritin, transferrin saturation and *HFE* genotype analysis. [9]

Case Report

A 51-year-old caucasian woman, with a history of skin hyperpigmentation since the age of 4, mainly in sun-exposed areas, was clinically diagnosed with XP at the age of 27, complicated meanwhile with three basal cell carcinomas and two keratoacanthomas, all submitted to complete surgical excision.

At the age of 49, due to upper quadrant abdominal pain, an analytical study and abdominal ultrasound were requested showing, respectively, abnormalities in liver enzymes and suggestive findings of chronic liver disease with mild splenomegaly. The patient was referred to our Hepatology consult and, in addition to the XP previously described, it was ascertained a history of menopause at the age of 40, essential arterial hypertension, osteoporosis, alcohol consumption of 12g/day and no other risk factors for liver disease, namely, drugs or sexual risk behaviors. She was unaware of family history of hereditary diseases. Her physical examination was remarkable for a good general condition, a body mass index of 22.19 kg/m^2, a waist circumference of 89 cm and marked skin hyperpigmentation (**Fig. 1**). The initial analytical assessment can be found on **Table I**, highlighting the abnormalities on liver chemistry (AST 84 U/L; ALT 75 U/L; ALP 196 U/L; GGT 286 U/L), thrombocytopenia (platelets 89 $x10^3/\mu L$), elevated transferrin saturation (90%) and ferritin levels (4806 ng/mL). An esophagogastroduodenoscopy was performed, showing no signs of portal hypertension.

Due to the substantial increase in ferritin and transferrin saturation the hypothesis of Hereditary Hemochromatosis (HH) was placed, with genotyping of the *HFE* gene revealing C282Y homozygosity, which established the definitive diagnosis of HH.

Additionally, magnetic resonance imaging was requested (**Fig. 2**), which confirmed a severe iron overload and estimated hepatic iron concentration of 300 micromoles per gram of dry weight (normal up to 36 micromoles per gram of dry weight). Liver biopsy documented complete architectural disorganization, translated by the presence of regenerative nodules confirming the diagnosis of liver cirrhosis; abundant hemosiderosis and severe steatosis (**Fig. 3**).

Dietary care was explained, focusing on cessation of alcohol consumption, and weekly therapeutic phlebotomies were started. Soon after, the patient developed large volume ascites, managed with hyposaline diet and diuretics, without recurrence. Target values of ferritin (50-100 µg/L) were reached in 68 weeks, as well as normalization of liver chemistry (**Fig.4 and Fig.5**,

respectively), corresponding to an estimated amount of 7.9g of iron removed. The patient started maintenance therapy with phlebotomies every two months thereafter. Additionally, she was administered with the hepatitis B and pneumococcal vaccines and recommended the Influenza vaccine annually. Family screening was carried out and C282Y homozygosity was detected in one brother and one sister, as well as in one grandson **(Fig. 6).**

In the last follow-up visit, at the age of 62, the patient was asymptomatic, with unremarkable laboratorial data. Liver ultrasound showed diffuse steatosis only. She was diagnosed with actinic keratosis on the right ala of the nose and on the right forearm, which was managed with cryotherapy in the Dermatology Department. Due to the known proximity of *HFE* (6p22.2) and *POLH* (6p21.1) genes, the patient was offered a genetic test to detect the latter mutation and was found to carry a rare, but potentially deleterious, homozygous variant of the *POLH* gene c.571A>C (p.(Thr191Pro)), of uncertain significance.

Discussion/Conclusion

At presentation this patient presented both laboratorial and imagological evidence of a chronic liver disease; according to the extensive analytical panel that was performed, liver transaminases levels were between 2-3 times the upper normal limit (UNL), and there was also a significant increase in GGT about 7 times the UNL and a slight increase in ALP. The deposition of iron in hepatocytes does not cause inflammation *per se* [7] and the vast majority of patients with hemochromatosis present transaminases within normal values. Given our patient history, it was not possible to exclude the role of alcohol consumption or metabolic syndrome as possible contributing causes for transaminases elevation. In fact, excess alcohol intake is a major risk factor for the development of liver disease in patients with HH, and iron overload potentiates the development of alcoholic liver disease. [10] Ferritin and transferrin saturation levels largely exceeded established cut-off values. Ferritin, being an acute-phase protein, may be increased in the context of systemic inflammatory processes, but usually at lower standard values and not accompanied by increased hepatic iron stores. [7] Portal hypertension could be accountable for the presence of splenomegaly with leuko and thrombocytopenia.

As the diagnosis can be made in the presence of p.C282Y homozygosity and increased iron stores, the patient was offered a genetic test, which confirmed the diagnosis. C282Y/C282Y has a 13.5% penetrance and is mainly associated with liver abnormalities (5% of women develop liver fibrosis and about 2% develop hepatic cirrhosis). [11], [12]

Although the diagnosis of menopause is clinical (amenorrhea over a year), determination of serum levels of FSH (>25 UI/L) and estradiol (<20 pg/ml) can be useful in confirming its diagnosis in women aged 40 to 45 years. [13] In this woman, it would have been imperative to rule out the contribution of hypogonadotropic hypogonadism as a cause of secondary amenorrhea, which may have been misinterpreted, at first, as early menopause. Osteoporosis may be a direct consequence of hypoestrogenism, which leads to increased bone resorption.

Liver biopsy was the *gold standard* for the diagnosis of HH before *HFE* genotyping became widely available. Although it is not necessary for the diagnosis of HH, it should be performed on C282Y homozygous individuals with ferritin levels >1000ng/mL, increased transaminases, especially AST, or over 40 years of age; all the above mentioned criteria were met by our patient. [9] The histological pattern favored the diagnosis of liver cirrhosis, with very severe hemosiderosis, buttressing the clinical diagnosis of hemochromatosis.

Following the HH diagnosis, phlebotomies were initiated, reaching the target values of ferritin at the end of 68 weeks and normalization of liver biochemistry (**Fig. 4 and Fig.5**, respectively), corresponding to the removal of 7.9g of total body iron stores. Since an improvement in biochemical parameters was achieved, as well as non-recurrence of ascites after ferritin targets were attained, we may assume that iron removal, along with cessation of alcohol consumption, contributed to the decrease in serum transaminases and eventually could represent a regression of liver fibrosis, which is described to occur in about 15-50% of HH patients.[14] Nevertheless, it is not known if reversal occurs in established liver cirrhosis, which is widely accepted as a poor prognosis and worse survival factor.[15]

Although this woman had not been genetically tested for XP before, the clinical findings were supportive of an XP-V subgroup, since there is no abnormal skin reaction to sun exposure. This feature might have contributed to poor adherence to prophylactic measures, which led to hyperpigmentation and early malignant skin cancers. XP-V has been found to be caused by *POLH* gene mutations, which prevent the production of any detectable DNA polymerase eta. A loss of this enzyme forestalls cells from replicating UVR-damaged DNA effectively. [16]

Due to the proximity of *POLH* and *HFE* genes, which can both be found in the short (p) arm of chromosome 6 at position 21.1 [16] and 22.2 [17] ,respectively, we suppose they could be linked, resulting in their inheritance as a unit, instead of assorting independently during meiosis. Given this, the patient was offered a genetic test, which asserted homozygosity for a rare sequence variant (c.571A>C) in the *POLH* gene. This mutation is of uncertain significance, so it does not confirm nor excludes the diagnosis of XP. However, in light of the phenotype presented by our patient, this variant is most likely accountable for the XP.

The most similar reported case was in 1932, concerning a 60-year-old cirrhotic patient who had mottled pigmentation of the extremities and face. Although interpreted as hemochromatosis at first, a specimen from a pigmented macule on the hand revealed a typical histologic pattern of *Xeroderma pigmentosum*. [18] Despite the diagnosis of hemochromatosis was ultimately not made, we believe this case could correspond to the first association of both diseases in the same patient.

This case highlights, overall, the importance of considering associated diseases when evaluating our patients. Despite rare, both diseases have effective, prognostic changing interventions, such as avoiding sun exposure and regular skin examination to prevent skin cancers, in XP, and regular phlebotomies for HH, to avoid deleterious tissue deposition of iron and prevent, among others, liver cirrhosis. Our patient presented skin hyperpigmentation, worsening over time, initially

attributed to the XP, probably resulting in a delay of the diagnosis of HH, already in a cirrhotic stage.

In conclusion, we report the first confirmed case, to our knowledge, of a patient diagnosed both with *Xeroderma pigmentosum* and Hereditary Hemochromatosis, in whom two mutated neighbor genes - *POLH* and *HFE* - were identified. We believe this was not a by chance association, but is possibly the result of genetic linkage. Since both conditions may present with overlapping clinical features, as skin hyperpigmentation, we pretend to alert clinicians to this possible association, since timely diagnosis of both XP and HH allows early guided interventions and improved patient outcomes.

Table I- Initial analytical assessment.

Leukocytes	3,13 x10^3/µL	(N 4-11)
Hemoglobin	**15,4 g/dL**	(N 12-15)
Platelets	**89 x10^3/µL**	(N 150-400)
Glucose	93 mg/dL	(N 70-105)
C-reactive protein	1,40 mg/L	(N 0-5)
Creatinine	0,56 mg/dL	(N 0,5-0,9)
Urea	24 mg/dL	(N 10-50)
Sodium	141 mmol/L	(N 135-145)
Potassium	4,04 mmol/L	(N 3,50-5,00)
Albumin	4,93 g/dL	(N 3,50-5,00)
Total Proteins	**7,53 g/dL**	(N 6-7,3)
Total Bilirubin	0,69 mg/dL	(N 0,20-1,00)
AST	**84 U/L**	(N 10-30)
ALT	**75 U/L**	(N 10-36)
ALP	**106 U/L**	(N 32-104)
GGT	**286**	(N 6 – 39)
Alfa-fetoprotein	4,5 µg/L	(N 3,5-5,0)
Total cholesterol	145 mg/dL	(N 0-200)

High density lipoprotein	42 mg/dL	(N 45-65)
Triglycerides	158 mg/dL	(N 35-135)
Serum Iron	**247 µg/dL**	(N 50-100)
Transferrin	**194 mg/dL**	(N 200-370)
Transferrin saturation	**90 %**	(N 15-45)
Ferritin	4806 ng/mL	(N 2,20-178)
IgA	244,0 mg/dL	(N 114 –457)
IgG	1090,0 mg/dL	(N 793 –1590)
IgM	293,0 mg/dL	(N 29 –226)
ANA	Negative	-
AMA	Negative	-
ASMA	Negative	-
Anti-LKM	Negative	-
Anti-LC1	0,4 U/mL	(N <18)
Anti-SLA/LP	0,1 U/mL	(N <18)
CMV IgG	70,3 AU/mL	Positive >11 Negative <9
CMV IgM	0,5 INDEX	Positive >1,2 Negative <0,8
HBs Ag	Negative	

Anti-HBs	Negative	
Anti- HBc	Negative	
Anti-HCV	Negative	
Toxoplasma IgG	0 UI/mL	Positive >30 Negative <1
Toxoplasma IgM	O,1 INDEX	Positive >1 Negative <0,8
Fasciola Hepatica	Negative	
Echinococcus IgG	3,3 INDEX	Positive >11 Negative <9

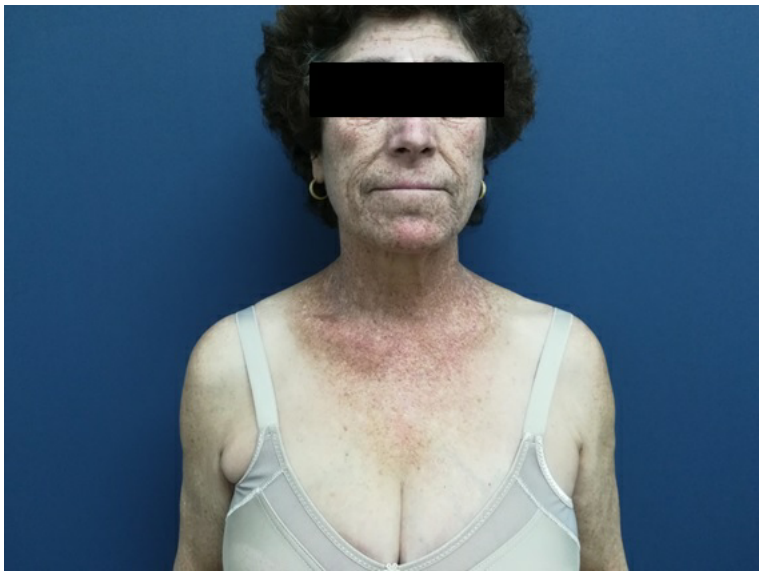

Fig. 1 - Multiple solar lentigines and xerotic appearance in the photoexposed area. Note the clear demarcation with the zone usually protected by clothes.

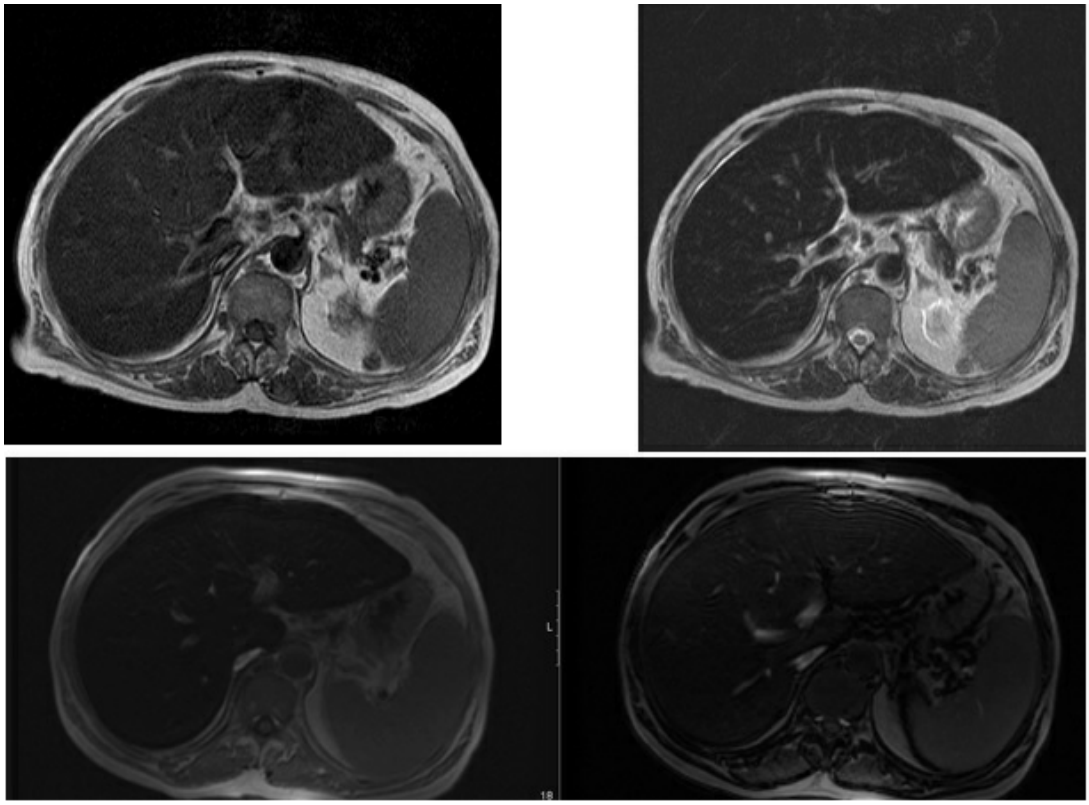

Fig. 2 – MRI documenting in axial T1-weighted (upper left) and T2-weighetd (upper right) images a decrease in the liver signal intensity. Axial T1-weighted gradient echo sequence images (lower panel) show a decreased signal intensity in the liver on the in-phase image (left) compared with the out-of-phase image (right), corroborating hepatic iron overload.

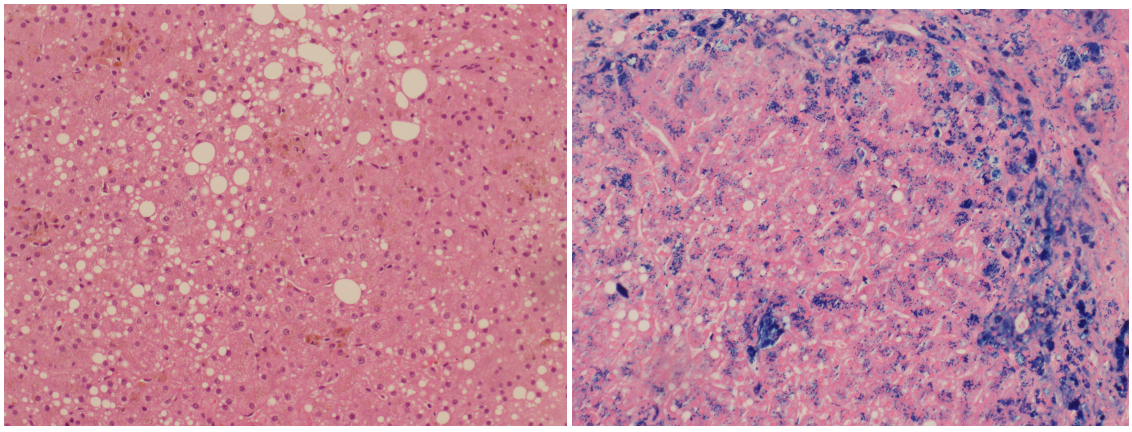

Fig. 3 - Fragment of liver biopsy with hematoxylin-eosin staining (100x), in which iron pigment stains brown (on the left); Fragment of liver biopsy with *Pearls* staining (100x), in which the iron pigment stains blue (on the right).

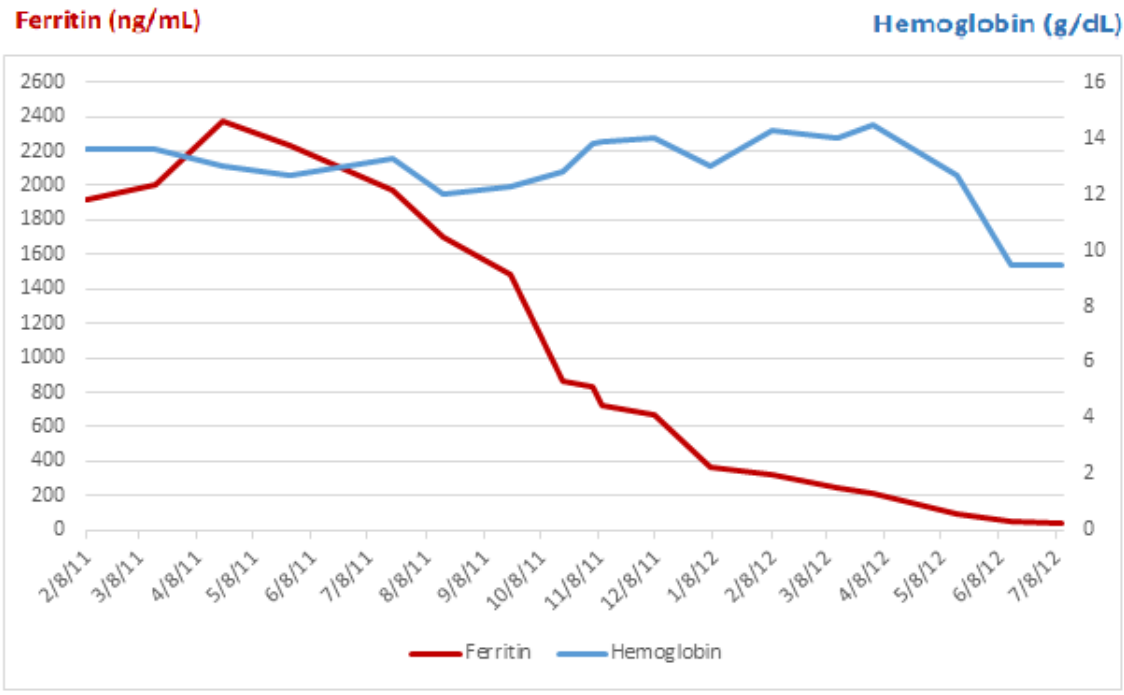

Fig. 4- Evolution of ferritin levels, in red, and hemoglobin, in blue, after the onset of phlebotomies, reaching ferritin target levels 68 weeks after.

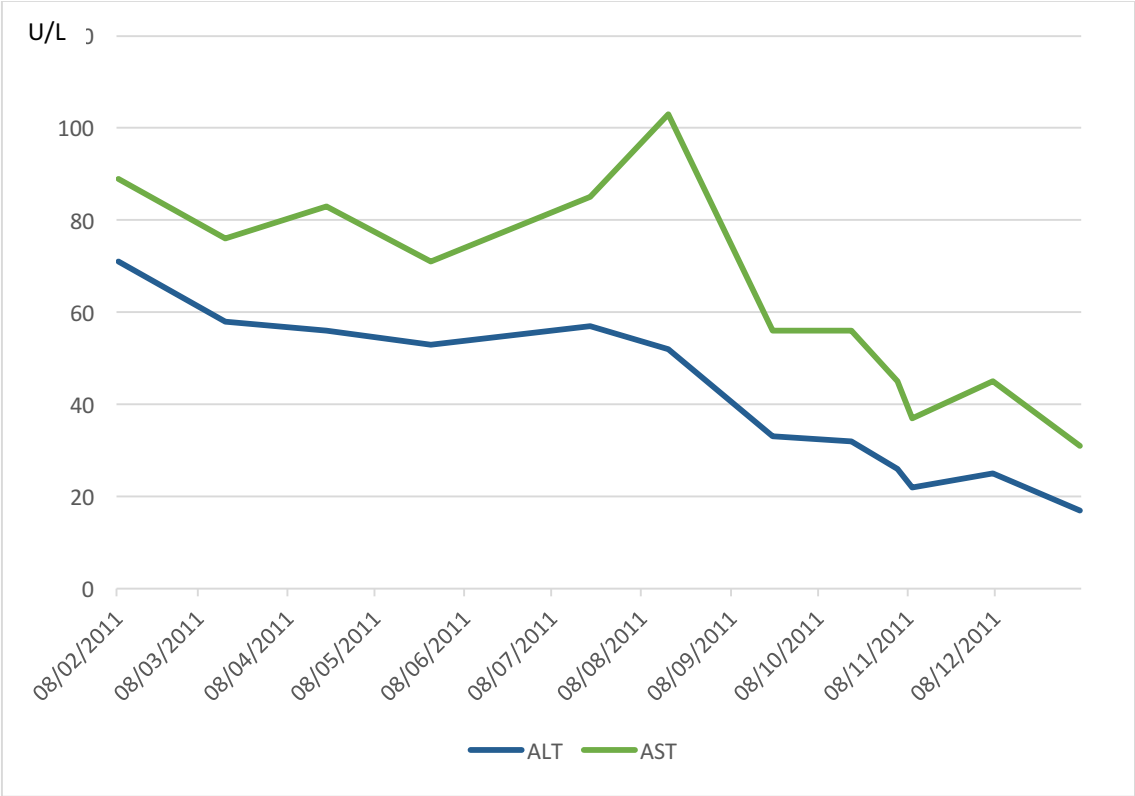

Fig. 5 - Evolution of ALT (Alanine Transaminase), in blue, and AST (Aspartate Transaminase), in green, after the onset of phlebotomies, reaching normal range values.

Symbol definitions

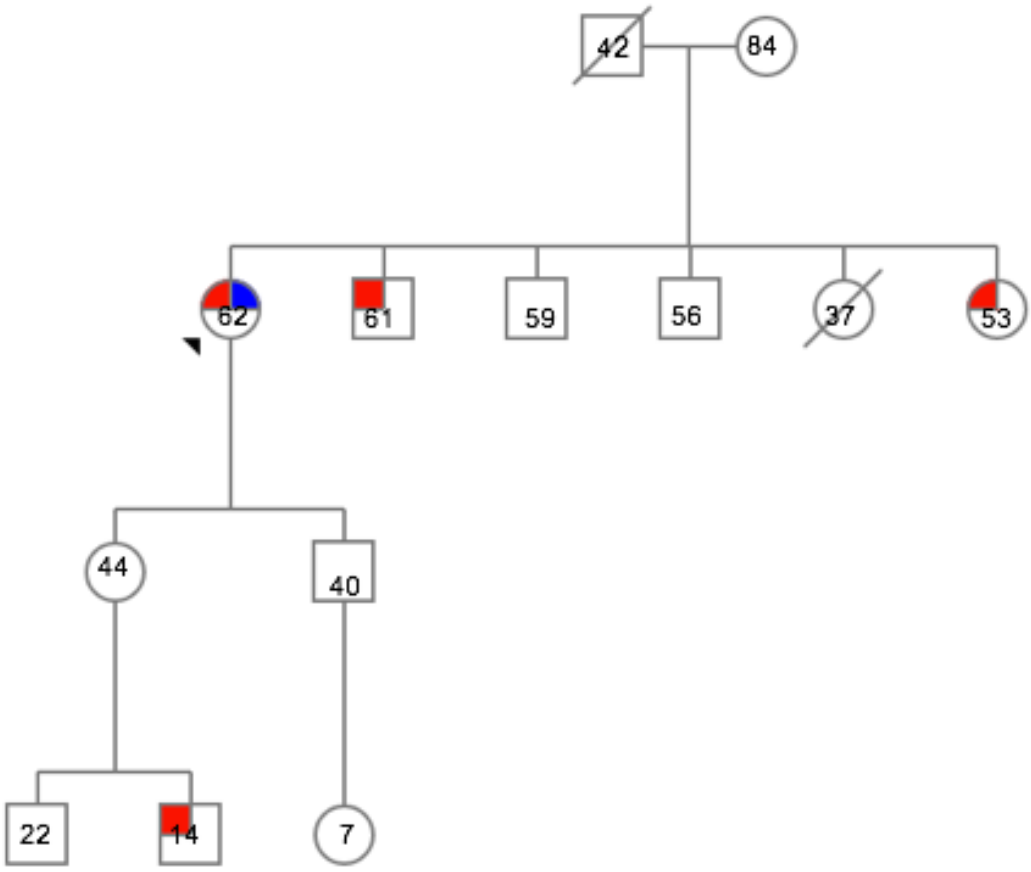

Fig. 6- Genogram buttressing C282Y homozygosity's detection in one brother and one sister, as well as in one grandson, after genetic screening was carried out.

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