CASE REPORT

Acquired hemochromatosis: a case report in a Filipino patient and literature review

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Hemochromatosis is a hereditary or acquired chronic iron overload syndrome that presents with organ damage to the liver, pancreas, heart, joints and skin due to pathologic iron deposition. Hereditary hemochromatosis is a common genetic disorder with human hemochromatosis protein (HFE) mutations found in European ethnic groups but has low-prevalence in the Asian population. Secondary or acquired hemochromatosis may result from ineffective erythropoiesis, liver disease and parenteral iron overload. A 51-year-old Filipino woman presented with generalized hyperpigmentation associated with severe anemia and hepatomegaly. Laboratory investigation revealed a markedly elevated serum ferritin (>2,000 □g/L, 10x the normal) and hepatic aminotransferases (6x elevated). Magnetic resonance imaging (MRI) T2-weighted images revealed hypotense signal of the liver with the magnetic susceptibility measurement (MSM) of iron at 12.297 mg/g indicating severe iron overload. Dermatopathology findings revealed hyperpigmented epidermis with hemosiderin found in the basal keratinocytes as well as around cutaneous adnexal structures. Special stain with Perls' Prussian blue revealed iron granules that are seen as blue pigments in the epidermis and dermis. Treatment with the oral iron chelator deferiprone (DFP) showed improvement. However, the patient developed hospital-acquired sepsis, deteriorated, and eventually died.

Keywords: Hemochromatosis, Hereditary Hemochromatosis, Secondary Hemochromatosis, Iron overload disease, HFE gene, Iron.

INTRODUCTION

Hemochromatosis, a chronic iron overload disorder, was originally described by Trousseau in 1865 but coined by von Recklinghausen in 1889, who determined that iron deposition caused pigmentary changes.[1,2] This disease can be either hereditary or acquired. Hereditary hemochromatosis is an autosomal-recessive systemic iron overload disease with 85-90% of patients homozygous to C282Y mutation in the human hemochromatosis protein (*HFE)* gene, or heterozygous to C282Y mutation and H63D mutation.[1,3] Secondary or acquired hemochromatosis is due to ineffective erythropoiesis, parenteral iron overload and liver disease.[3]

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CASE REPORT

A 51-year-old Filipino female presented with a one-year history of diffuse, ill-defined hyperpigmented patches that were asymptomatic on the anterior truncal area. She was seen by a dermatologist and was prescribed an oral antihistamine and an unrecalled ointment that provided temporary relief of pruritus. Over the course of six months, the hyperpigmentation progressively became generalized, involving the palms and the soles associated with pruritus, fatigue, and weight loss. (Figure 1)

The patient was diagnosed with microcytic hypochromic anemia during the last 2 years prior to admission and was previously admitted in the hospital for packed red blood cell transfusion. She was lost to follow-up but was readmitted due to generalized body weakness and dizziness. Physical examination revealed generalized grayish to dark brown hyperpigmentation that included the palms and soles but spared the oral mucosa and nails. (Figure 2) She was also observed to have generalized dryness of the skin, jaundice, icteric sclerae, pale palpebral conjunctivae, but with no signs of liver cirrhosis such as spider angiomata, palmar erythema and edema of the

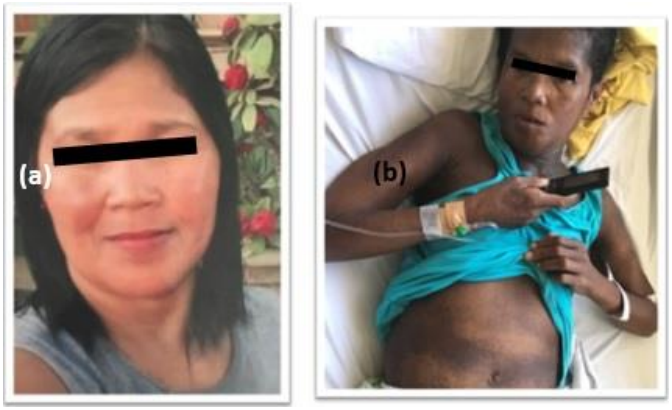

Figure 1. (a) Patient prior to appearance of symptoms. (b) Patient during admission.

lower extremities. The liver edge was palpable with a span of 14 cm with associated right upper quadrant tenderness.

Complete blood count revealed anemia (Hb=53 mg/dL) while the peripheral blood smear showed hypochromic red blood cells with moderate anisocytosis. Liver function tests revealed elevated total bilirubin (3x elevated), direct bilirubin (8x elevated), alanine aminotransferase (2x elevated) and aspartate aminotransferase (6x elevated). Thyroid function tests revealed slightly elevated thyroid stimulating hormone (TSH) and a normal free T4 (FT4) count. Lactose dehydrogenase was 4x elevated. Ferritin, a test to determine the concentration of overall iron stores, was done with result of >2,000 μg/L, which was 10x elevated. Adrenocorticotropic hormone stimulation test revealed an expected rise in cortisol levels, establishing a normal adrenal glucocorticoid function.

Whole abdominal ultrasound showed an enlarged liver with suggestive parenchymal disease. Magnetic resonance imaging (MRI) T2-weighted images revealed mild hepatomegaly with diffuse hypointense signal reflective of iron deposition disease. The computed value of iron deposition through magnetic susceptibility measurement (MSM) was amounting to 12.297 mg/g, indicating severe iron overload. (Figure 3)

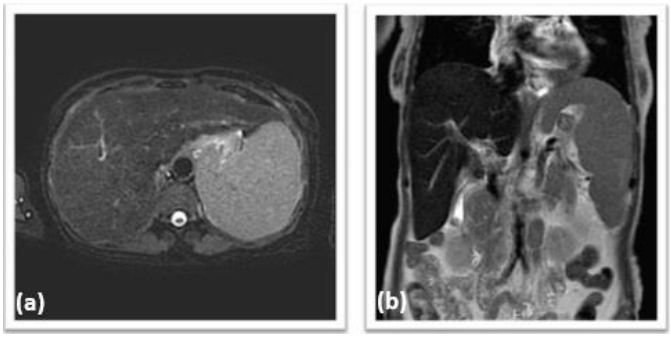

Figure 3. T2-wighted MRI of the liver (a) axial and (b) coronal views showing mild hepatomegaly with diffuse hypotense signal and magnetic susceptibility measurement of iron at 12.297 mg/g or severe iron overload

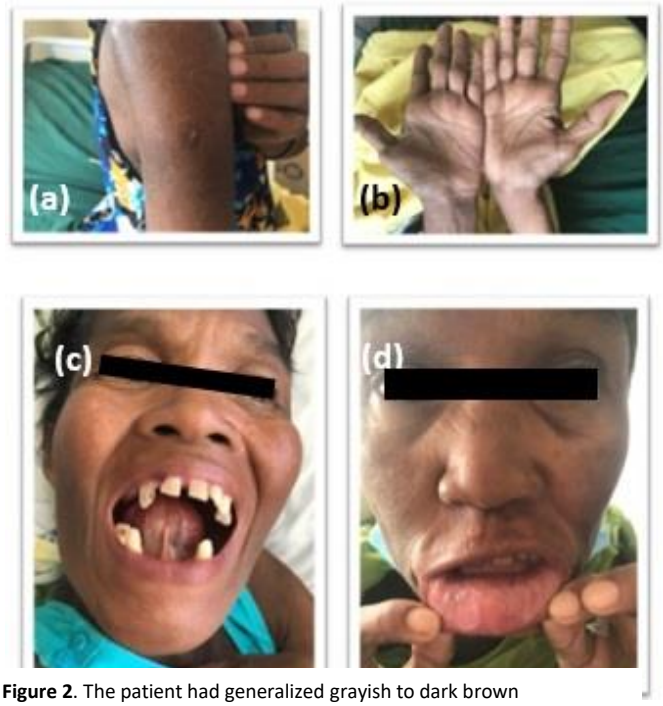

Figure 2. The patient had generalized grayish to dark brown hyperpigmentation that involved the palms and soles (a) & (b). The oral mucosa and nails were spared (c) & (d).

A 6-millimeter skin punch biopsy was revealed hyperpigmented stratum basale with granular brown pigment or hemosiderin found within the basal keratinocytes. Hemosiderophages and melanophages were seen around superficial blood vessels, eccrine glands and interstitial spaces. (Figure 4) The histopathological diagnosis was compatible with hemochromatosis. Special stain for iron or Perls' Prussian Blue was done to visualize the iron granules which were seen as blue pigments in the dermis and epidermis. (Figure 5)

The patient was transfused with a total of 3 units of packed red blood cell (RBC) during the course of her admission and was started on deferiprone, an oral iron chelator with a dosage of 500 mg/tablet given 2 tablets 3x a day. The cause of the patient's iron overload disease was suspected to be thalassemia, but hemoglobin electrophoresis showed no qualitative nor quantitative abnormality for both hemoglobin A and hemoglobin A2. Hematology referral suggested a diagnosis of thalassemia intermedia and suggested a bone marrow aspiration (BMA) biopsy but the patient acquired sepsis due to a hospital-acquired infection, deteriorated and eventually expired.

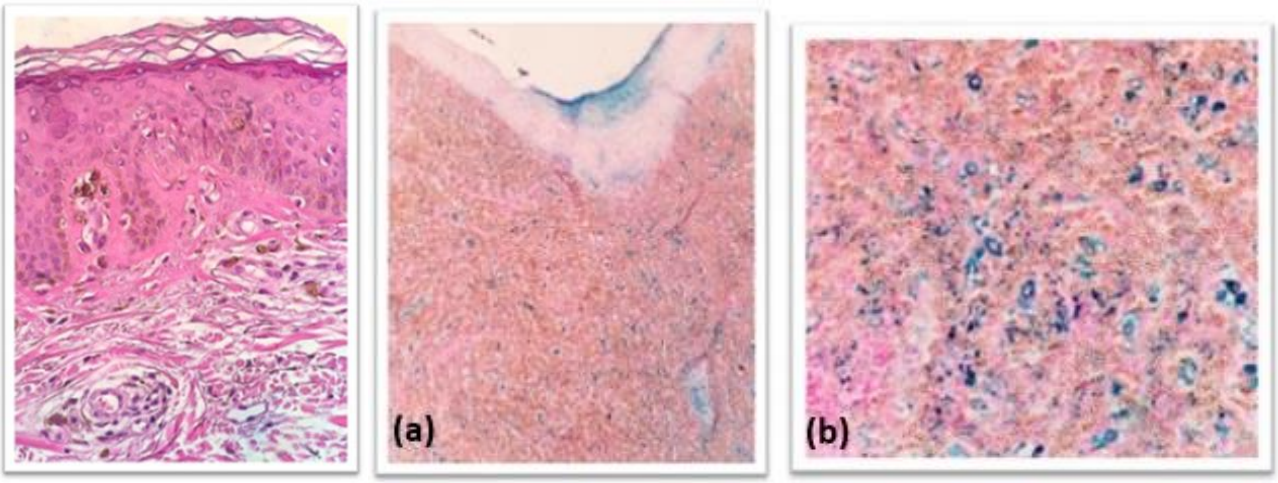

Figure 4. (left) Basal keratinocytes are hyperpigmented with presence of granular brown pigment or hemosiderin. Hemosiderophages and melanophages were seen around superficial blood vessels, eccrine glands and interstitial spaces (H & E, x400)
Figure 5. (middle & right) Perls' Prussian Blue stain, x40 (a) and (b) x200 shows bright blue pigments which indicate the presence of iron deposits in the epidermis and dermis

DISCUSSION

Hemochromatosis is a group of genetic or acquired disorders caused by continuous and excessive absorption of dietary or parenteral iron.[2] It is considered to be one of the most common, life-threatening genetic disease in North America with a prevalence of 1:250 in the US population, however it is clinically unrecognized by most physicians.[1] There are 4 cases that occur in every thousand in population with Nordic or Celtic ancestry, with the highest rate in those with Irish descent having a prevalence of 1:80.[1-3] This led researchers to hypothesize that the original hemochromatosis mutation occurred in Ireland and spread to the rest of Europe.[1] It is less common in people with African descent and even rarer in the Asian population.[1] A case review done by Yenson et al. of 80 Asian patients with hyperferritinemia in Canada (2008) showed that primary iron overload syndromes are rare in this group.[4] According to Felitti et al. (1999), the prevalence of hemochromatosis in people with Filipino origin approximates that of European descent.[1] However, the exact incidence of hemochromatosis cases in the Philippines is unknown. In a pilot study conducted by Timoteo et al. (2018) that investigated the association of single nucleotide polymorphisms (SNPs) in the hemochromatosis gene (HFE) among 109 pregnant Filipino women, only 2% of the participants carried the heterozygous genotype of HFE with signs of anemia, however a larger study population is needed.[5] There is no record of hemochromatosis diagnosis in the Philippine Dermatological Society Health Information System (PDS-HIS).[6]

Iron is an essential co-factor for proteins and enzymes utilized for cellular respiration, energy metabolism, DNA synthesis, cell cycle arrest and apoptosis.[7] Homeostasis of iron is maintained through daily absorption of 1 mg of dietary iron through the gut balanced with excretion through the stool (0.6 mg/day), urine (0.15-0.2 mg/day) and skin (0.2-0.25 mg/day).[8] Keratinocyte desquamation accounts for 20-25% of iron losses through the skin, and to a minor extent through sweating.[8] It has been suggested by Robert et al. (1960) that increased melanin production in chronic iron deposition is due to the progressive oxidation of the amino acid tyrosine, a feature of normal melanogenesis.[9] *Iron overload disease* refers to any disease caused by iron overload, whether it is focal (ex, primary pulmonary hemosiderosis, Hallervorden-Spatz Disease) or diffuse (ex, hemochromatosis).[1] *Hemochromatosis* refers to the tissue damage caused by the systemic iron overload disease either from HFE gene mutation or transfusion iron overload from thalassemia.[1] *Hereditary hemochromatosis* pertains to the genetically determined, systemic iron overload disease caused by excessive absorption of intestinal iron.[1] *Hemosiderosis* is a histologic terminology that refers to tissue deposition of iron, while *hemosiderin* is the aggregated form of tissue "stainable" iron and represents the product of lysosomal degradation of tissue ferritin.[1,2]

In individuals who absorb iron excessively as a result of an underlying defect other than a hereditary disorder may have secondary or acquired iron overload.[3] Bacon et al. (2011) listed the causes of secondary iron overload that included ineffective erythropoiesis, liver disease and

parenteral iron overload.[3] Ingestion or oral iron supplements do not lead to iron overload with exception to those individuals with a genetic predisposition to having ineffective erythropoiesis.[3] In the case of our patient, she presented with anemia with severe iron overload. She received blood transfusion with a total of 4 units of packed red blood cells (RBCs) in a span of 2 years prior to appearance of the lesions and was noncompliant with oral iron supplement intake. One unit of packed RBCs is approximately 350-400 mL and contains about 200 to 250 mg of iron.[10] The patient had received a total of 1 gram of iron upon transfusion and added with irregular oral iron intake, were not enough to account for the total iron in her system. The cause of her anemia was suspected to be thalassemia intermedia by the hematologist, a disorder that can cause ineffective erythropoiesis and secondary hemochromatosis.[10] However, a bone marrow aspiration biopsy was not done due to the deteriorating condition of the patient.

In a case series reported in the 1950's to the 1980's showed that majority of the patients with classical symptoms were only identified at the advanced stages of the disease.[3] In the 1990's, patients in the United States with abnormal iron studies were given routine family screening and 75% of those who were identified with hereditary hemochromatosis were asymptomatic.[3] Symptoms were noted to begin between age 30 years and age 50 years but may occur much earlier in life.[11] It was noted by Bacon et al. (2011) that more men than women have increased ferritin levels.[3] This difference between males and females may be attributed to the difference in the average body iron stores of women, which is about 8 grams compared to the men which is 20 grams.[2] The authors surmised that the difference between the sexes may be due to losses during menstruation, as well as during pregnancy and childbirth which may be seen as "protective" in hereditary hemochromatosis.[3,12]

The classic triad of hemochromatosis included diabetes, cirrhosis and cutaneous hyperpigmentation, and was previously coined "bronze diabetes" but there is evidence to suggest that the clinical presentation is more extensive than previously described.[1,3] The broad spectrum of clinical manifestations may be the reason why it is less frequently diagnosed and what was once thought of as unrelated clinical findings may be indications of an underlying disease.[1] In a summary written by Bacon et al. (2011), they listed the most likely associated symptoms occurring with hemochromatosis.[3] This includes complaints of right upper quadrant pain, fatigue, arthralgias mainly of the second and third metacarpophalangeal joints, chondrocalcinosis, decreased libido, impotence and symptoms of heart failure or diabetes.[3] On physical examination, the findings of arthritis, congestive heart failure, enlarged liver with the presence of cirrhosis, extrahepatic manifestations of chronic liver disease, testicular atrophy, skin pigmentation and changes of porphyria cutanea tarda (PCT) should raise the suspicion of hemochromatosis.[3]

In a case series of 100 patients with idiopathic hemochromatosis done by Chevrant-Breton et al. in 1977, they found that hyperpigmentation was noted in 98% of the cases.[13] The pigmentation was described as slate-gray or metallic gray blending into brown and usually diffuse but more pronounced in areas that are exposed, flexion folds, areola of the nipple, and external genitalia.[2,13,14] About 20% of patients have hyperpigmentation of the buccal mucosa and conjunctivae but this was not present in the case of our patient.[2]

Other dermatologic manifestations include atrophy, often with scleroderma-like changes typically found in the pretibial location; ichthyosis varying from mild xerosis to generalized icthyosis vulgaris; koilonychias along with longitudinal striations and brittleness of the nails; loss of body hair including pubic hair, which may be a sign of gonadal failure.[2] The patient in this case presented with cutaneous atrophy and xerosis but did not present with koilonychias or loss of body hair. Porphyria cutanea tarda, a rare blistering disorder in areas exposed to sunlight, is associated with underlying iron overload as well as chronic hepatitis C infection.[1,15] It is recommended that all patients with porphyria cutanea tarda to be tested for hemochromatosis and those with hemochromatosis should be examined for photosensitivity and blistering disease.[1] In our patient, she neither presented with photosensitivity or any vesiculating dermatitis.

The gold standard for determining the iron overload is to quantify the iron content in hepatic tissue obtained through biopsy but is currently indicated to assess hepatic damage and determine the presence of advanced fibrosis or cirrhosis.[2,3,16] However, there are two indirect and less invasive serum markers that may indicate the presence of hemochromatosis, which are plasma transferrin and serum ferritin.[2] Plasma transferrin is normally about one third saturated or 100 to 120 μg iron per deciliter but if it reached >70% to 75% saturated then it is diagnostic of iron overload.[2] Serum ferritin directly correlates to mobilizable iron in the body and >200 μg/L in men or >150 μg/L in women is diagnostic of hemochromatosis.[2] According to Bacon et al. (2011), serum ferritin is the single most important predictor of advanced hepatic fibrosis and >1,000 μg/L had 100% sensitivity and 70% specificity in identifying cirrhosis.[3] In the case of our patient, her serum ferritin was at >2,000 μg/L, which was at least 10x elevated, thus most likely have advanced hepatic fibrosis.

Another non-invasive method to assess hepatic iron stores is through magnetic resonance imaging (MRI) as well as magnetic susceptibility measurement (MSM).[2,16] The magnetic susceptibility value of the hepatic iron deposition of the patient is 12.297 mg/g and is classified as severe iron overload. In MRI, there is a marked attenuation of the T2 signal that would appear like a "black hole" where the liver ought to be, as it was in the case of the patient.[2]

On dermatopathology, both melanin and dermal iron are increased with iron found as siderosis typically located around eccrine sweat glands, similar to the pathology seen in the patient.[2,13] Perls' Prussian blue stain evaluates the degree and distribution of iron deposition, which were seen on both the dermis and epidermis on the patient.[3]

In order to address the iron overload of hereditary hemochromatosis, the goal of treatment is to achieve iron homeostasis with weekly phlebotomy of 500 mL until normal levels are achieved.[1] On the other hand, patients with secondary hemochromatosis such as in our case, have an inherited or acquired anemia and cannot be treated with phlebotomy.[10,17] For these patients, chelators can achieve iron homeostasis without phlebotomy, as well as neutralizing harmful non-transferrin-bound iron (NTBI).[10] Only a small percentage of iron is accessible by the chelator molecule and continuous administration is needed for the treatment to be successful.[10]

The three types of chelators commonly used are deferoxamine, deferasirox and deferiprone.[10] Deferoxamine (DFO) is the standard chelator and it is given parenterally with a very short half-life of 20 minutes.[10] The dose is 30 to 50 mg/kg and given as an infusion for 8 to 10 hours, five times a week.[10] Side effects of deferoxamine include local irritation at the injection site, with erythema, induration and tenderness.[10] Hypersensitivity reactions to deferoxamine are rare but severe reactions such as anaphylaxis have been recorded.[10] The main obstacle with this chelator is poor compliance due to continuous and prolonged parenteral infusions given at least 250 times a year, which can deter patients seeking treatment.[10]

Deferasirox (DFX) is an oral chelator that is indicated for thalassemia as well as transfusion-induced iron overload and is considered to be a breakthrough treatment of secondary hemochromatosis.[10] It is given at 20 to 30 mg/kg/day and tablets are dissolved in liquids before consuming.[10] The efficacy of this chelator resulted in reduction of hepatic iron and ferritin values similar to deferoxamine after one year of treatment.[10] Side effects of this medication include abdominal symptoms such as diarrhea, cutaneous eruptions and elevation of serum creatinine level.[10]

Deferiprone (DFP) is an oral iron chelator that is given at 75 mg/kg/day in 3 divided doses due to its short half-life (1.5 hours).[10] Aside from having the convenience of taking deferiprone orally, it has similar efficacy as deferoxamine with better prevention and reduction of cardiac iron overload.[10] This was chosen by the patient's hematologist and upon initiation of treatment, the patient showed signs of improvement with a reduction in her liver enzymes. However, the treatment was halted due to the patient's deteriorating status and ferritin status of the patient was not re-examined.[5]

Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis.[2,4,6] Diagnosis of CL (confirmed case), according to WHO 2014 is based on clinical features, and parasitological confirmation of the diagnosis (positive smear or culture).[7]

Overall, there are more than 20 species of Leishmania worldwide and the subtype of disease relates to the species of infecting Leishmania and the interplay of the genetic background and immune status of the host. [8]

Simple cutaneous lesions are most often self-healing within 1 to 2 years but in some cases, such as those caused by *L. panamensis, L. mexicana* and *L. braziliensis*, can progress to involve mucocutaneous tissue. The resolution of cutaneous lesions can often be accelerated by medical treatment.[5]

Pentavalent antimonials is the conventional treatment of choice; however, some cases of resistance have been reported. Amphotericin B is the second-choice therapy. These drugs are expensive and difficult to obtain, especially in the non-endemic area. They must be delivered parenterally, have numerous adverse effects, and many cases of drug-resistant parasites have been reported.[9] Alternative treatment for CL include miltefosine, pentamidine isethionate, antifungal agents (such as, ketoconazole, fluconazole, itraconazole), paromomycin, granulocyte macrophage colony-stimulating factor, and heat therapy or cryotherapy had shown favorable efficacy in some literatures.[2,6,8,9]

CONCLUSION

Hemochromatosis is a disorder of excessive iron storage in the body that often goes unrecognized. The clinical manifestations are widespread but are usually asymptomatic until the patient presents with severe organ damage particularly to the liver. Most physicians often fail to make the connection that the symptoms may be part of a syndrome and miss the chance to diagnose this preventable disease. Our patient was admitted for hemolytic anemia and was referred to the dermatology service due to generalized hyperpigmentation. Hemochromatosis was one of the main considerations in the dermatologic standpoint and upon further workup of liver enzymes and iron stores confirmed this diagnosis. Non-invasive diagnostic methods include serum ferritin

concentration, transferrin saturation, as well as magnetic resonance imaging and magnetic susceptibility measurement. Administering iron chelators for patients with secondary hemochromatosis associated with anemia is the treatment of choice. Oral iron chelators are convenient with better patient compliance and is considered a breakthrough treatment for secondary hemochromatosis. Screening for the single point mutation of the HFE gene for the patient and family members may be useful for those at risk of hereditary hemochromatosis. This poses a challenge in the Philippines due to lack of commercially available and affordable genetic screening methods. This is the first case report of hemochromatosis in the Philippines and hopefully more cases can be detected and screened in the future.

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