Hereditary Hemochromatosis Unmasked by Yersiniosis: Report of Three Cases

Karam Karam[1] and Elias Fiani[1]

[1]University of Balamand

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Karam Karam[1], Elias Fiani[2*]

[1] Department of Gastroenterology, University of Balamand, Beirut, Lebanon. Email: Karamek7@gmail.com

[2] Associate Professor, Department of Gastroenterology, University of Balamand, Beirut, Lebanon. Email: Elias.fiani@hotmail.com *CORRESPONDING AUTHOR

Key Clinical Message: Yersiniosis has a causal relationship with hereditary hemochromatosis (HH). Physicians should have a high index of suspicion for the diagnosis of HH when approaching a patient with yersiniosis in the setting of high ferritin levels and increased iron saturation. Yersiniosis serves as a precursor for the diagnosis of HH.

Keywords: Hereditary Hemochromatosis; *Yersinia Enterocolitica* ; *HFE* Genetic Testing; Phlebotomy; Case Series.

1-Introduction:

HH is an autosomal recessive disease with low penetrance [1]. The most common variant is the *HFE* C282Y mutation. The diagnosis of HH is established by an elevated ferritin level and a high iron saturation along with homozygosity for C282Y. Hemochromatosis is a state of iron-overload. Patients with iron overload are susceptible to infections. For instance, *Yersinia enterocolitica* is a ferrophilic organism that thrives in an environment with an excess of iron [1]. We herein present three case reports whereby HH was unveiled by a preceding *Yersinia enterocolitica* infection in the setting of elevated iron tissue deposition markers.

2-Case Description:

2.1-First Case:

A 34-year-old male patient presenting for a 3-day history of fever, abdominal pain and watery, non-bloody diarrhea. Patient is previously healthy and takes no medications regularly. He has no history of recent travel or recent blood transfusions or animal exposure. He denies any similar diarrheal illness at home. He denies any nausea or vomiting. The patient is a non-smoker, consumed no alcohol and has no significant family history. Upon detailed anamnesis, the patient mentioned a food exposure to raw-pork products. Patient was febrile with a temperature of 39.1 ^{0}C. Upon physical examination, patient had diffuse abdominal tenderness that was more localized to the right upper quadrant. The remainder of the physical exam was unremarkable.

2.2-Second Case:

A 60-year-old female presenting for a 2-day history of fever and watery, non-bloody diarrhea. She has no past medical history and takes no medications on a regular basis. She denies any history of recent travel

or blood transfusions or animal exposure. She reported no family member with similar diarrheal illness. The patient is a non-smoker, consumed no alcohol and has no significant family history. The patient had exposure to raw-pork products. She reported nausea but no vomiting. She had a temperature of 38.7 ^{0}C. Her physical examination was pertinent for diffuse abdominal tenderness. The remainder of the physical exam was unremarkable.

2.3-Third Case:

A 38-year-old male patient, previously healthy, presenting for a 3-day history of fever, non-bloody, non-bilious vomiting and watery, non-bloody diarrhea. He has no history of recent travel or blood transfusions or animal exposure. He denies any exposure to sick contact at home. He is a non-smoker, consumes no alcohol and has no significant family history He mentioned a food exposure to undercooked pork products. He has nausea and vomiting along with his diarrheal illness. His temperature was 38.9 ^{0}C. Upon physical examination, patient had diffuse abdominal tenderness. The remainder of the physical exam was unremarkable.

3-Methods:

3.1-First Case:

Biochemical workup revealed a white blood count (WBC) of 13,000/mm^3 with 80% neutrophils. C-reactive protein (CRP) was elevated with a value of 17.7 mg/dL. Liver enzymes and the remainder of the blood tests were within normal range. Stool culture using Cefsulodin-Irgasan-Novobiocin (CIN) selective agar medium produced characteristic colony morphology that grew *Yersinia enterocolitica* . He had a serum iron of 180 U g/dL with a ferritin level of 1,250 ng/mL. Total iron-binding capacity (TIBC) was 320 U g/L with a transferrin saturation (TSAT) of 57%., pointing to a state of iron-overload. The patient underwent *HFE* genetic testing and was homozygous for C282Y, indicating a diagnosis of HH. Magnetic resonance imaging (MRI) of the abdomen subsequently revealed reduced signal intensity of the liver, corroborating a diagnosis of liver hemochromatosis.

3.2-Second Case:

Blood tests revealed a WBC count of 11,500/mm^3 with 85% neutrophils. The patient had an elevated inflammatory marker with a CRP value of 9.3 mg/dL. Liver enzymes and the remainder of the blood tests were within normal range. Stool culture using CIN selective agar medium grew *Yersinia enterocolitica* . Serum iron was 108 U g/dL with a ferritin level of 1,100 ng/mL. Her TIBC was 227 U g/dL with a TSAT of 47.5%, indicating a state of iron-overload.*HFE* gene testing revealed homozygosity for C282Y, establishing a diagnosis of HH. MRI of the abdomen revealed a decreased signal on the T2 weighted sequences at the level of the liver. Findings were in favor of liver hemochromatosis.

3.3-Third Case:

Biochemical workup revealed neutrophilic leukocytosis with a WBC count of 10,500/mm^3 and 87% neutrophils. CRP was elevated with a value of 10.3 mg/dL. Liver enzymes and the remainder of the blood tests were within normal range. Stool culture using selective CIN agar grew *Yersinia enterocolitica* . Serum iron was 96 U g/dL with a ferritin level of 1,420 ng/mL. TIBC was 196 U g/dL with a TSAT of 49%, favoring a state of iron-overload. *HFE* gene testing revealed homozygosity for C282Y, corroborating a diagnosis of HH. MRI of the abdomen revealed marked signal loss of the liver, favoring a diagnosis of liver hemochromatosis.

4-Conclusion and Results:

Owing to ongoing fever, neutrophilia and elevated CRP, treatment with antibiotics was indicated. Patients were prescribed ciprofloxacin 500 mg orally twice daily for the treatment of non-severe Yersinia enterocolitis for a total of 5 days.

All three patients had clinical and biochemical improvement following treatment with antibiotics and their symptoms had completely abated thereafter. No side effects were reported during the course of antibiotics.

All three patients were candidates for therapeutic phlebotomy as they were not anemic with a target serum ferritin between 50 and 100 ng/mL. They were also educated about hemochromatosis.

Phlebotomy was subsequently initiated for the management of HH with periodic monitoring of hemoglobin (Hb) and ferritin levels.

Patients were counseled regarding risk reduction whereby they were advised to avoid excess alcohol, raw-seafood and contact of open wounds with seawater. They were also counseled about the appropriateness of*HFE* testing in their first-degree relatives.

Patients were subsequently scheduled for ultrasound of the abdomen every 6 months to perform surveillance for HCC because hepatic iron overload is present in all three patients. Table 1 summarizes the three case reports in terms of patients' characteristics, biochemical and genetic workup and treatment regimens, respectively.

5-Discussion:

HH is characterized by an increased intestinal iron absorption which leads to a total-body iron overload.

HH is an autosomal recessive disorder with low penetrance. The C282Y is a common variant in the *HFE* gene represented by a guanine to adenine change at nucleotide 845, which results in the substitution of cysteine for tyrosine at amino acid 282. Homozygosity for C282Y represents more than 90% of HH cases [1].

Hemochromatosis is the state of an iron overload and is the result of pathogenic mutations in genes regulating hepcidin. This process leads to hyperabsorption of iron and subsequent accumulation of iron in tissues [1]. *HFE* C282Y causes a decreased level of hepcidin by interfering with its physiological upregulation. Decreased levels of hepcidin mediate an increase in intestinal iron absorption (heme and non-heme iron). Over years to decades, the amount of absorbed iron reaches many grams.

In HH, iron absorption ranges between 2-4 mg/day as opposed to 1-2 mg/day in unaffected individuals. Symptoms ensue when iron reaches levels of 20 grams and above. Symptoms of HH include generalized fatigue (in the absence of anemia) and pain.

The diagnosis of HH requires a combination of genetic information along with markers of tissue iron deposition. Three main components establish the diagnosis of HH: a ferritin level greater than 300 ng/mL (in males and post-menopausal females) and greater than 200 ng/mL (for pre-menopausal women), a TSAT greater than 45% and homozygosity for C282Y.

Homozygosity for *HFE* C282Y is not always associated with iron overload, which has been coined as C282Y/C282Y genotype without iron-overload [1].

Iron can deposit in the liver, heart, pancreas and pituitary gland.

Hepatic iron overload results in hepatomegaly, elevated hepatic transaminases and hepatic fibrosis that can eventually develop into liver cirrhosis.

Cardiac iron overload causes dilated cardiomyopathy, sick sinus syndrome and arrhythmias that can lead to sudden cardiac death.

Iron can deposit in endocrine organs. For instance, pancreatic iron overload leads to diabetes mellitus (DM) type II. Likewise, iron deposition in the pituitary gland can cause hypopituitarism resulting in secondary hypogonadism and secondary hypothyroidism. Secondary hypogonadism results in decreased libido and impotence in males [2].

Iron overload in the central nervous systems results in generalized cognitive impairment [3].

HH-associated arthropathy results in arthritis and arthralgias whereby the joints of the hands are commonly affected [4].

Iron deposition in the skin causes skin hyperpigmentation termed as "bronze skin".

HH can also engender porphyria cutanea tarda (PCT) and osteoporosis.

Iron overload increases the risk of cancer. For example, hepatic iron overload can cause hepatocellular carcinoma (HCC) [5].

There is a causality between iron overload and susceptibility to infections [6]. For instance, patients with iron overload are at increased risk for *Yersinia enterocolitica* and *Vibrio vulnificus* infections. *Yersinia enterocolitica* is a gram-negative organism found in wildlife and domestic livestock. Transmission to humans is foodborne. The virulence of *Yersinia enterocolitica* is heightened in the presence of excess iron. This is why *Yersinia enterocolitica* is a siderophilic bacterium [6].

MRI is appropriate if serum ferritin is greater than 800 to 1,000 ng/mL. A liver biopsy is not required for diagnosis and it is replaced by MRI for estimation of iron stores.

Management of HH is through iron removal and normalization of iron stores. Removing excess iron by phlebotomy is the mainstay of treatment. Therapeutic phlebotomy is effective and devoid of toxicities provided that the patient is not severely anemic.

In adults, therapeutic phlebotomy is recommended once weekly initially and can be performed more frequently in the setting of severe iron-overload. Performing phlebotomy twice weekly is possible provided that Hb level remains in the safe range (>11 g/dL).

Erythrocytapheresis and iron chelation are alternatives to phlebotomy. In erythrocytapheresis, red blood cells (RBCs) are removed in an isovolumic manner and the patient's plasma is returned in a closed circuit.

Iron chelation is represented by the usage of oral or parenteral iron-chelating agents. They are commonly used in hemoglobinopathies, such as sickle cell disease and thalassemia.

The typical schedule for phlebotomy is once weekly until target ferritin is reached in accordance with anemia status and patient's tolerance. The number of phlebotomies can be estimated and determined by Hb and ferritin levels that should be monitored periodically. Target ferritin level is 50 to 100 ng/mL. Of note, iron-deficiency should be avoided. Once target is met, patients should be monitored with maintenance phlebotomies or expectant management guided by the ferritin level.

The prognosis of HH is dictated by the severity of iron overload at diagnosis and extent of iron removal. Normal survival is defined as a ferritin level less than 1,000 ng/mL at diagnosis.

Major causes of death are cirrhosis, diabetes and HCC.

Yersinioses are zoonotic infections of domestic and wild animals. Humans are incidental hosts. Three species have been identified: *Yersinia pestis* , *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* [7].

Y. pestis causes plague, whereas *Y. enterocolitica* and *Y. pseudotuberculosis* cause yersiniosis that results in diarrheal illness.

Transmission of *Y. enterocolitica* is largely foodborne (raw/undercooked pork products) and occasionally waterborne. *Y. enterocolitica* can also be transmitted through blood transfusions of packed red blood cells [8].

Y. enterocolitica is ferrophilic and has a predilection for patients with derangements of iron metabolism, such as hemochromatosis, cirrhosis, aplastic anemia, sickle cell disease, DM, malignancy and immunosuppression.

Patients get infected by consumption of uncooked or raw pork products and untreated water.

Y. enterocolitica is a facultative, gram negative and anaerobic coccobacillus [9].

Virulent subtypes are O:3, O:5,27, O:8 and O:9.

Clinical manifestations of *Y. enterocolitica* are acute febrile enterocolitis and pseudo-appendicitis syndrome.

Yersiniosis can have gastrointestinal (GI) and extra-intestinal complications and post-infectious sequelae [10].

Acute yersiniosis has an incubation period of 4 to 6 days [11].

Clinical manifestations of yersiniosis are fever, abdominal pain, diarrhea, nausea and vomiting [12].

A localized right upper quadrant pain is a diagnostic clue for yersiniosis [12]. Yersiniosis can also cause pharyngitis, bacteremia and sepsis [13].

Patients with iron-overload states are more prone to develop bacteremia and sepsis.

GI complications of yersiniosis are perforation, toxic megacolon and paralytic ileus [14].

Extra-intestinal complications are liver abscess, endocarditis and osteomyelitis.

Post-infectious sequelae are erythema nodosum and reactive arthritis, specifically in patients with HLA-B27 tissue type [15].

Diagnosis is isolation of the pathogen by stool culture [16]. *Y. enterocolitica* requires a specific growth medium, which is the CIN agar [17].

Adequate hydration and electrolytes correction are the mainstay treatments of mild enterocolitis. There is no rationale behind using antibiotics for mild enterocolitis due to the lack of benefit [18]. The only benefit is that the usage of antibiotics decreases stool shedding of *Y. enterocolitica* [19].

When indicated, commonly used antibiotics are ciprofloxacin and levofloxacin. Alternative agents are doxycycline and trimethoprim-sulfamethoxazole [18]. The duration of treatment is 5 days.

Intravenous (IV) antibiotics are reserved for cases of bacteremia, sepsis, high fevers and grossly bloody stools [20].

Ceftriaxone 2 g IV once daily in combination with gentamicin (5 mg/Kg/day) is the mainstay of IV antibiotics treatment. The duration of treatment is at least 3 weeks. Ciprofloxacin 400 mg IV twice daily is an alternative to ceftriaxone [20].

Longer treatment duration is warranted in patients with compromised immunity and extra-intestinal infections. Patients should be switched to oral treatment once clinical improvement is achieved [13].

In conclusion, physicians should exclude the diagnosis of HH when approaching a patient with yersiniosis in the setting of hyper-ferritinemia and elevated iron saturation. A prompt diagnosis is warranted for timely management that can be conducive to better clinical outcomes and favorable prognosis.

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Dr. Karam Karam: Investigation, methodology and writing original draft.

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