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Case of *Vibrio Vulnificus* bacteremia in a patient heterozygous for HFE p.C282Y mutation and alcoholic liver cirrhosis

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Abstract

Vibrio vulnificus is a Gram-negative bacterium, a member of the *Vibrionaceae* family. *V. vulnificus* is the main cause of seafood-related deaths in the United States because it can cause severe wound infections or sepsis. This microorganism is highly dependent on iron availability. Therefore, patients with high body iron levels are more susceptible to the infection. Prompt treatment with cephalosporins as well as doxycycline is usually administered. We present a case of *V. vulnificus* bacteremia in a patient heterozygous for HFE p.C282Y mutation and underlying alcoholic liver cirrhosis.

Keywords

V. vulnificus, hemochromatosis, liver cirrhosis, ferritin, phlebotomy

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Introduction

Vibrio vulnificus is a Gram-negative bacterium that can cause wound infections, septicemia, and diarrhea. It is the leading cause of shellfish-associated deaths in the United States. Centers for Disease Control and Prevention (CDC) reports that vibriosis causes 80,000 illnesses and 100 deaths each year. *V. vulnificus* causes death of 1 in 5 people within one or two days after becoming ill.[1] Growth of *V. vulnificus is* dependent upon the availability of iron and directly related to the percentage saturation of transferrin with iron.[2] Although majority of HFE p.C282Y carriers do not have signs of iron overload, recent publications reveal the rare occasions of developing such.[3] In addition, *V. vulnificus* bacteremia was previously reported as a cause of death in a patient with cirrhosis who was a carrier of HFE p.C282Y allele rs1800562 mutation. Therefore, suggestion that carriers of the HFE p.C282Y mutation may be in the spectrum of clinical susceptibilities to *V. vulnificus* was made.[4] Here we present a case of *V. vulnificus* bacteremia in a patient heterozygous for HFE p.C282Y mutation with signs of iron overload and underlying liver cirrhosis. This case is unique because it will add to the literature suggesting a rare possibility of developing iron overload in carriers of the HFE p.C282Y mutation and their increased susceptibility to *V. vulnificus* infection.

Case

A 58-year-old male with a past medical history of liver cirrhosis secondary to alcohol consumption and diabetes presented with nausea, non-bilious non-bloody vomiting, chills, and dizziness in July of 2019 to the hospital in Michigan. He also had mild shortness of breath, blurry vision, fatigue, mild abdominal pain, and painful rash on the lower extremities accompanied by burning sensation.

The patient reported regular consumption of at least two drinks per day. He did not travel recently and had no exposure to sick people or animals. However, he ate raw oysters from Chesapeake Bay at a local restaurant a few days before presentation.

On admission, the patient had temperature 101.5 °F (38.6°C), pulse of 91, and blood pressure 163/72 mmHg. His physical exam was remarkable for scleral icterus and erythematous non-blanching tender lesions on lower extremities. His laboratory tests revealed white blood cell count of

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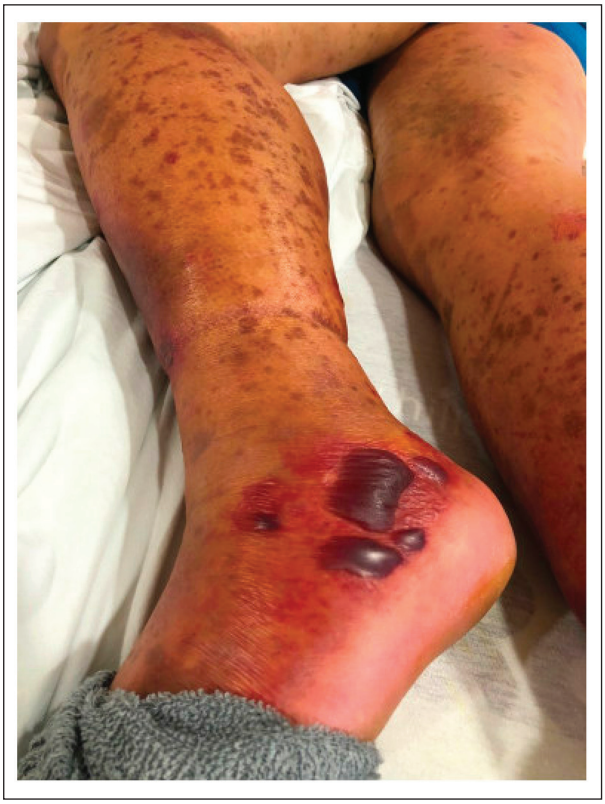

Figure 1. Hemorrhagic bullae.

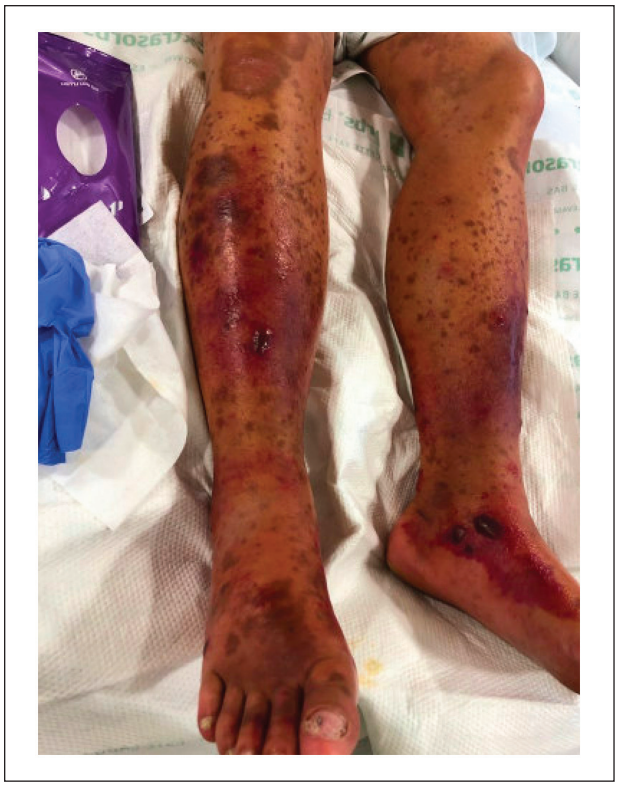

Figure 2. Erythema, edema, indurated plaques, and open bullae on the legs.

$18 \times 10^3/\mu L$, hemoglobin of 13.2 g/dL, platelet count of $59 \times 10^3/\mu L$, lactic acid of 10.1 mmol/L, D-dimer of 6235 ng/mL, C-reactive protein (CRP) of 65.9 mg/L, erythrocyte sedimentation rate (ESR) of 28 mm/h, creatine kinase of 339 U/L, and low levels of complement levels C3 and C4. His tests for human immunodeficiency virus, hepatitis, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and cryoglobulins were negative. His iron studies showed serum ferritin of 481 (reference range, 14–338) ng/mL, serum iron of 58 (reference range, 65–175) mg/dL, total iron-binding capacity of 125 (reference range, 250–425) mg/dL, and transferrin saturation of 58% (reference range, 15%–50%). Blood and urine cultures were collected.

Of note, the patient was heterozygous for HFE p.C282Y mutation and had a wild type of HFE H63D. One year prior to admission, he had a ferritin level of 1043 ng/mL.

Chest x-ray and computed tomography (CT) angiogram showed no acute process. Initially, the patient was given a fluid bolus of normal saline and was started on cefepime and vancomycin.

Two days later, the patient developed hemorrhagic bullae on his legs (Figures 1 and 2), and his blood culture sets of two sets drawn came back positive for *V. vulnificus*. Antibiotic therapy was changed to cefotaxime and doxycycline. Significant clinical improvement was achieved on the fifth day of treatment with antibiotics. The patient was discharged from the hospital with a ferritin level of 266 ng/mL.

The patient had a liver magnetic resonance imaging (MRI) outpatient which revealed significant liver cirrhosis as well as 2.3×2.1 cm liver mass. Biopsy-confirmed well-differentiated hepatocellular carcinoma and laparoscopic microwave ablation of the mass was performed. The patient has been following in a clinic and undergoing evaluation for the possible liver transplant.

Discussion

Vibrionaceae family includes pathogenic species *V. vulnificus, V. parahaemolyticus*, and *V. cholerae. V. vulnificus* is an opportunistic human pathogen which causes the highest number of seafood-related deaths in the United States.

Most *Vibrionaceae* are found in warmer marine environments. Therefore, the incidence of diseases caused by *V. vulnificus* is the highest in summer months. The countries with the most documented cases of *V. vulnificus* are the United States, South Korea, Taiwan, Japan, and Mexico. Disease in the southern hemisphere is much less common than in the northern hemisphere which is likely related to the paucity of monsoon climates in the southern hemisphere.[5] Oysters normally filter water through their bodies to feed which results in concentration of *V. vulnificus* in their bodies. The highest concentration of *V. vulnificus* is in oysters coming from Chesapeake Bay and the United States Gulf Coast.[1]

Major comorbidities which increase the risk of developing sepsis from the initial infection include chronic liver disease, diabetes, malignancy, renal disease, and HIV.[5]

V. vulnificus has several iron-sequestration systems including a hemin uptake system. *V. vulnificus* hemin uptake system consist of HupA, an outer membrane protein, and HvtA protein receptor. Interestingly, the growth of the bacterium becomes exponential when transferrin iron saturation exceeds 70%.[6] The organism is not virulent in healthy individuals; however, the virulence can be greatly increased by injections of iron compounds.[2]

The liver is known for its major role in iron homeostasis. Thus, iron regulation is disturbed in patients with chronic liver disease. High iron levels in the body are present in patients with hereditary hemochromatosis, alcoholic liver disease, nonalcoholic fatty liver disease, or hepatitis C viral infection. Chronic liver disease decreases the synthetic functions of the liver, including the production of hepcidin, an important protein in iron metabolism. Lower levels of hepcidin result in iron overload and subsequent iron deposits in the liver as well as higher levels of non-transferrin-bound iron in the bloodstream.[7] Therefore, low level of hepcidin results in increased susceptibility to *V. vulnificus* infection.[8] Studies also reported that liver cirrhosis may result in decreased production of mannose-binding lectin, serum protein produced by the liver and involved in innate host defense mechanisms. Therefore, patients with cirrhosis are more susceptible to the infection due to relative immunocompromised state.[9]

Hereditary hemochromatosis is an autosomal recessive disorder of iron metabolism, which is caused by a reduction in the concentration of the iron regulatory hormone hepcidins or reduced hepcidin-ferroportin binding. Genetic testing for hemochromatosis commonly involves genotyping of a cysteine-to-tyrosine substitution at amino acid position 282 (C282Y) as well as histidine-to-aspartic acid substitution at amino acid position 63 (H63D) in HFE gene. Positive result of the genetic test is defined as homozygosity of the C282Y allele, or compound heterozygosity with one allele C282Y with an H63D allele.[10] Homozygosity for HFE p.C282Y accounts for approximately 90% of hemochromatosis cases. Clinical manifestations generally do not occur until the age of 40 years in males and before menopause in females. Nonspecific symptoms such as fatigue, lethargy, and apathy are common. Patients who do not undergo treatment can develop cirrhosis, hepatocellular cancer, heart failure, arrhythmias, type 2 diabetes, hypogonadism, cognitive changes, and bronze-colored skin.[11] Main treatment options are phlebotomy and chelation therapy. Therapeutic phlebotomy is usually appropriate when serum ferritin is $\geq$500 ng/mL or if there is evidence of tissue injury.[12]

One study revealed that mean serum iron concentrations and transferrin-saturation values were higher in heterozygotes for HFE p.C282Y mutation than in patients with normal genotype. However, complications due to iron overload alone in heterozygotes were found to be extremely rare.[13] Another study reported that the HFE p.C282Y mutation does not cause increased level of mean serum ferritin level.[14] In our case, the patient had abnormal iron studies due to alcoholic liver cirrhosis, ongoing *V. vulnificus* infection, and possibly genetic mutation. The patient consumed raw oysters which resulted in *V. vulnificus* bacteremia. The optimal treatment of *V. vulnificus* sepsis is early antibiotics administration. Commonly used regiments are the third-generation cephalosporin plus either tetracycline or fluoroquinolone.

Conclusion

V. vulnificus is considered the main cause of seafood-associated mortality in the United States.

Correlation between increased susceptibility to *V. vulnificus* bacteremia and liver diseases was previously established. Deficiency of mannose-binding lectin plays a role in increased frequency of bacterial infections in patients with liver diseases. Patients with liver cirrhosis heterozygous for HFE p.C282Y may be more susceptible to *V. vulnificus* bacteremia due to abnormalities of iron metabolism.

Author contributions

K.S. wrote the manuscript. M.K. reviewed and edited the manuscript. N.M. reviewed the manuscript. All authors gave written consent for publication.

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Ethical approval

The present study conforms to the ethical standards and guidelines of the journal.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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