Autopsy and Case Reports
ISSN: 2236-1960
São Paulo, SP: Universidade de São Paulo, Hospital Universitário

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Autopsy and Case Reports, vol. 10, no. 3, 2020
São Paulo, SP: Universidade de São Paulo, Hospital Universitário

DOI: 10.4322/acr.2020.180

Available in: http://www.redalyc.org/articulo.oa?id=576065838012

Autopsy Case Reports

Article / Autopsy Case Report

Disseminated cryptococcosis and hemochromatosis: clues to diagnosis

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How to cite: Nichols L, Rowley L, Lall A. Disseminated cryptococcosis and hemochromatosis: clues to diagnosis. Autops Case Rep [Internet]. 2020;10(3):e2020180. https://doi.org/10.4322/acr.2020.180

ABSTRACT

Hepatic cirrhosis, diabetes mellitus and iron overload can each independently predispose to cryptococcosis. Hereditary hemochromatosis leads to all three of these predispositions. This report is the case of a patient with chronic hepatitis B virus infection and cirrhosis, who had markedly elevated serum ferritin and 99% transferrin saturation, and developed a leukemoid reaction. Autopsy revealed disseminated cryptococcosis for which the leukemoid reaction was a clue and possible hereditary hemochromatosis of which elevated ferritin and transferrin saturation can be clues. Hereditary hemochromatosis is an important diagnosis clinicians should never miss because early treatment with phlebotomy can be life-saving. Disseminated cryptococcosis can be rapidly diagnosed with serum cryptococcal antigen test and is treatable.

Keywords
Cryptococcosis; Hemochromatosis; Hepatitis; Autopsy

CASE REPORT

A 64-year-old white male retired military intelligence officer had a 6-year history of cirrhosis associated with hepatitis B virus (HBV) infection when he was admitted to a referral hospital for liver transplant evaluation. His HBV infection was thought most likely contracted in 13 years of military service in the Orient in the era of the cold war between capitalist and communist countries. The patient had no history of alcohol use, smoking or transfusions. The patient had a son, age 40, who had chronic hepatitis with negative serology for viral etiologies; the son had hyperpigmented skin and may have had elevated serum iron (according to family), but not diabetes mellitus. The patient had diabetes mellitus diagnosed 18 months ago and treated with oral hypoglycemic agents until 6 months ago when insulin therapy became necessary. He had an esophageal variceal hemorrhage 6 years ago treated with sclerotherapy and a splenocaval shunt. He had been experiencing increasing lethargy, confusion and easy bruising, starting 6 months ago. The patient developed jaundice, fatigue, poor oral intake, weakness, lethargy and mildly slurred speech, despite treatment with lactulose, spironolactone and omeprazole.

On admission, the patient was lethargic, with mildly slurred speech. His skin was markedly jaundiced. His temperature was 36.4° C, pulse 82/minute, blood pressure 110/60 mm Hg and respirations 16/minute. His chest was clear with no cardiac abnormalities noted. He had 2+ leg edema. Electrocardiogram (ECG) showed sinus rhythm and nonspecific T-wave changes. Chest radiograph showed moderate cardiomegaly and

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no pulmonary abnormalities. The patient's bilirubin was 15 mg/dL (reference range [RR]: 0.3-1.5 mg/dL), alanine aminotransferase (ALT) 119 U/L (RR: <40 U/L), aspartate aminotransferase (AST) 222 U/L (RR: <40 U/L), gamma-glutamyl-transferase (GGT) 53 U/L (RR: <30 U/L), albumin 1.8 g/dL (RR: 3.5-5 g/dL), ammonia 74 umol/L (RR: 10-47 umol/L), blood urea nitrogen (BUN) 16 mg/dL (RR: 9-20 mg/dL), creatinine 1.0 mg/dL (RR: 0.8-1.5 mg/dL), glucose 361 mg/dL (RR: 70-110 mg/dL), hemoglobin (Hgb) 11.1 g/dL (RR: 12.9-16.9 g/dL), mean corpuscular volume (MCV) 102.4 fL (RR: 80-100 fL), white blood cell (WBC) count 15,500/mm^3 (RR: 4,000-10,000/mm^3) (80% segmented neutrophils, 3% bands, 9% lymphocytes, 7% monocytes, 1% atypical lymphocytes), platelet count 102,000/mm^3 (RR: 140,000-440,000/mm^3), prothrombin time (PT) 21 seconds (RR: 10.5-13 seconds) and partial thromboplastin time (PTT) 48.4 seconds (RR: 25-33 seconds).

The results of blood testing more specifically for liver transplant evaluation returned later, showing: hepatitis B surface antigen (HBsAg) positive, anti-HBsAg antibodies negative, anti-hepatitis B core antibodies positive, HBV e antigen negative, anti-hepatitis A virus antibodies positive (IgM negative), anti-human immunodeficiency virus (HIV) antibodies negative, anti-cytomegalovirus (CMV) antibodies >120 U/L (IgM negative), antinuclear antibodies positive at a titer of 1:40 (speckled pattern), carcinoembryonic antigen (CEA) 14.8 ng/mL (RR: <5 ng/mL), zinc 0.16 mcg/mL (RR: 0.55-1.5 mcg/mL), iron 106 mcg/dL (RR: 65-165 mcg/dL), iron binding capacity 107 mcg/dL (RR: 250-420 mcg/dL) and ferritin 4392 ng/mL (RR: 10-282 ng/mL).

The patient was treated with lactulose, neomycin, spironolactone, omeprazole and insulin. On hospital day 2, his WBC count was 19,800/mm^3, glucose 338 mg/dL and ammonia 78 umol/L. Pulmonary function testing showed a forced expiratory volume in one second (FEV1) of 2.34 L (88% of predicted), forced vital capacity (FVC) of 2.69 L (71% of predicted) and diffusing capacity of 19.9 mL/min/mm Hg (92% of predicted). Urine culture yielded Enterococcus faecalis, 50,000 colonies/mL. The patient remained afebrile, but that evening, he had increased lethargy and encephalopathy. His ammonia level rose acutely to 197 umol/L. His lactulose and neomycin were increased.

On day 3, the patient's ammonia was 45 umol/L; he had brief episodes of atrial tachycardia. ECG showed sinus rhythm and nonspecific T-wave changes. Chest x-ray showed mild bilateral interstitial pulmonary edema and a left pleural effusion. Echocardiogram showed normal left ventricular size and function, but mild mitral regurgitation. Over the next 3 days, the patient was afebrile and hemodynamically stable but had increasing jaundice. On day 6, he complained of dyspnea on exertion as well as feeling tired, weak and sleepy. He was afebrile. His WBC count rose to 31,900/mm^3 (90% segmented neutrophils, 5% lymphocytes, 5% monocytes).

On day 8, the patient was lethargic and slightly confused. His ammonia was 60 umol/L, bilirubin 25.5 mg/dL, albumin 2.2 g/dL, ALT 109 U/L, BUN 26 mg/dL and creatinine 2.5 mg/dL. He was given prednisone and zinc. Over the next 3 days, the patient was afebrile and hemodynamically stable but had increasing bilirubin, BUN and creatinine. He developed fine bibasilar pulmonary crackles with moderate pulmonary edema, along with left pleural effusion and cardiomegaly on chest x-ray, which was treated with furosemide. On day 12, the patient's mental status had slowly deteriorated. His ammonia was 31 umol/L, bilirubin 37.5 mg/dL, ALT 71 U/L, GGT 55 U/L, BUN 60 mg/dL, creatinine 4.9 mg/dL and chest x-ray unchanged. Adenosine thallium cardiac scan showed fixed defects in anterior and lateral left ventricle. He was given bumetanide and metolazone. At 15:00, his blood pressure fell to 82/48 mm Hg, with heart rate 60/minute and respirations 16/minute. At 16:15, he developed sinus bradycardia (rate 50/minute). At 16:20, arterial blood showed pH 7.37, PCO2 29 mm Hg and PO2 32 mm Hg (on room air). With 100% oxygen via facemask, his PO2 improved to 63 mm Hg, with PCO2 35 mm Hg and pH 7.35. His blood pressure increased to 113/48 mm Hg at 20:00.

On day 13 at 00:05, chest radiograph showed decreased pulmonary edema. At 01:15, he was afebrile, but his blood pressure decreased to 89/43 mm Hg and an infusion of dopamine was initiated. At 03:00, emergency hemodialysis was started. At 03:20, the patient's WBC count was 57,500/mm^3, Hgb 10.1 g/dL, platelets 94,000/mm^3, PT 20 seconds, sodium 132 mEq/L (RR: 136-145 mEq/L), potassium 3.6 mEq/L (RR: 3.5-5.1 mEq/L), chloride 97 mEq/L (RR: 95-110 mEq/L), bicarbonate 26 mEq/L (RR: 21-31 mEq/L), calcium 10.6 mg/dL (RR: 8.5-10.5 mg/dL), phosphorus 4.1 mg/dL (RR: 2.5-4.5 mg/dL), glucose 115 mg/dL, BUN 40 mg/dL, creatinine 3.7 mg/dL,

ammonia 45 umol/L, ALT 121 U/L, AST 469 U/L, GGT 62 U/L and bilirubin 42 mg/dL. At 05:15, he developed labored breathing, with arterial pH 7.36, PCO2 36 mm Hg and PO2 38 mm Hg on 100% oxygen via facemask. Manual ventilation was started. He developed bradycardia with blood pressure 70/30 mm Hg. The patient then suffered a cardiopulmonary arrest and could not be resuscitated. The patient had been afebrile, with no antibiotic therapy except oral neomycin, throughout his hospitalization.

AUTOPSY FINDINGS

Postmortem examination revealed disseminated cryptococcosis involving the lungs, heart, liver (Figures 1A, 1B and 1C), kidneys, spleen, lymph nodes, bone marrow, larynx, pancreas, aorta, prostate, bladder, esophagus, stomach, adrenals and thyroid (Figure 2). Organisms recognizable on H&E stain in solid organs by the cleared spaces from their capsules were identifiable on Grocott methenamine silver stain in large numbers in all five lobes of the lungs (Figure 3A). Mucicarmine stain confirmed that the cleared spaces around yeast forms were capsules (Figure 1D).

The autopsy also showed massive iron deposition in the liver (Figures 1A and 1C), bile duct epithelium, pancreas, heart (Figure 3B) and thyroid. Iron was also evident in kidneys and adrenals. The liver, pancreas and thyroid were brown. Prussian blue staining confirmed that brown pigment in the liver and heart was iron. Autopsy also confirmed the diagnosis of hepatic cirrhosis (Figures 1A and 1D) and revealed old granulomas in thoracic lymph nodes and right lower lobe lung. Ground-glass hepatocytes were not evident in the regenerative nodules. Quantitation of liver tissue iron showed 12,611 mcg/g (RR: 300-1,800 mcg/g). The skin was diffusely and deeply jaundiced. Postmortem culture of lung and spleen yielded Cryptococcus neoformans from both organs.

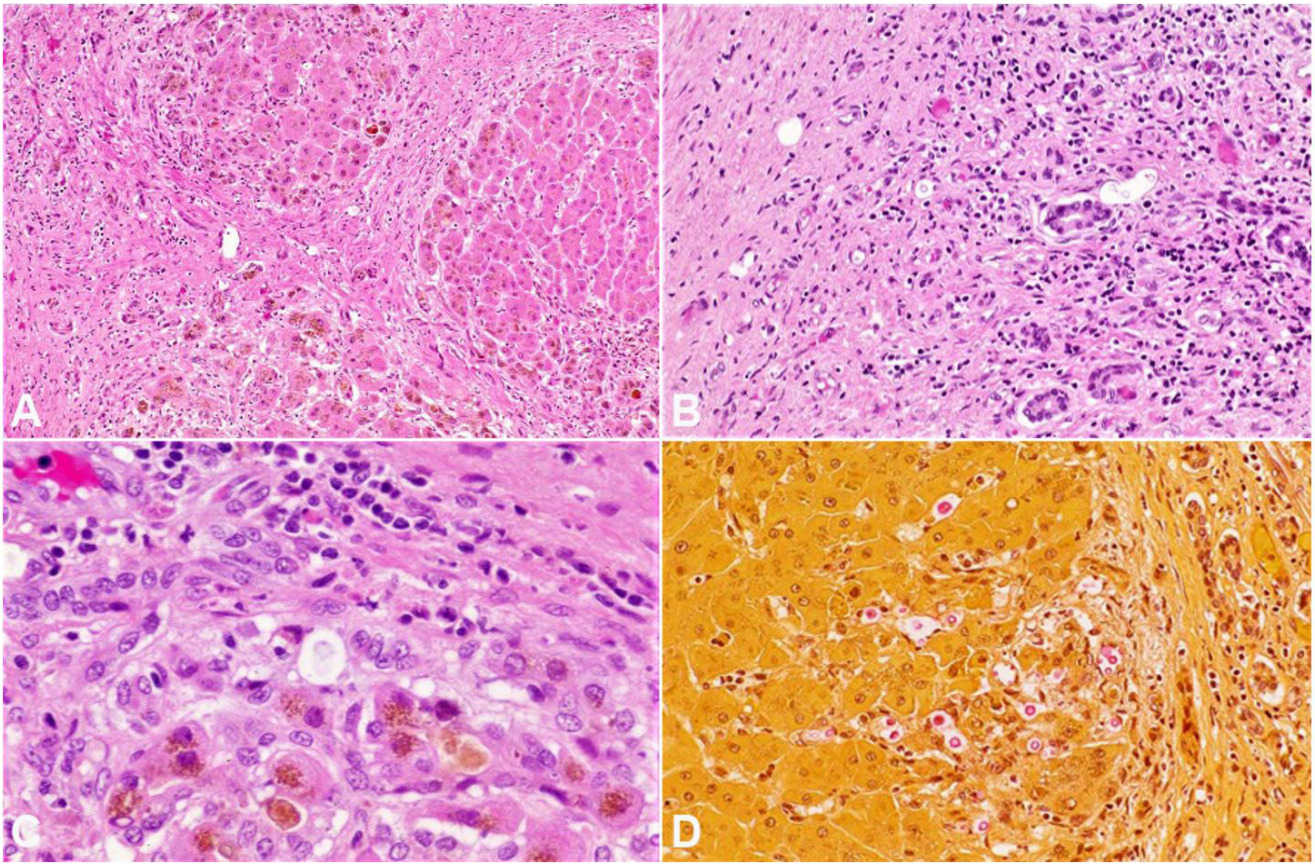

Figure 1. Photomicrographs of the liver. **A –** Hepatic cirrhosis with hepatocytic accumulation of hemosiderin and scattered round-oval spaces containing faintly staining structures (H&E, 100X); **B** – Fibrous tissue adjacent to hepatic regenerative nodule with lymphocytic infiltration, proliferating bile ductules and spaces containing faintly basophilic budding yeast forms (H&E, 200X); **C** – Edge of hepatic regenerative nodule composed of hemosiderin-laden hepatocytes, with lymphocytic infiltration of adjacent fibrous tissue and a budding Cryptococcus (H&E, 400X); **D** – Hepatic regenerative nodule infiltrated by yeast forms with positively stained capsules (Mucicarmine, 200X).

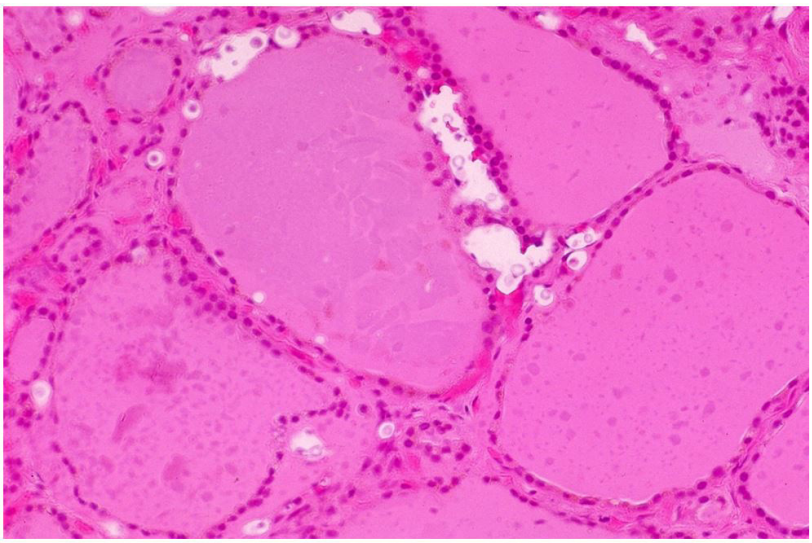

Figure 2. Thyroid follicles infiltrated by yeast forms surrounded by cleared spaces (H&E, 200X).

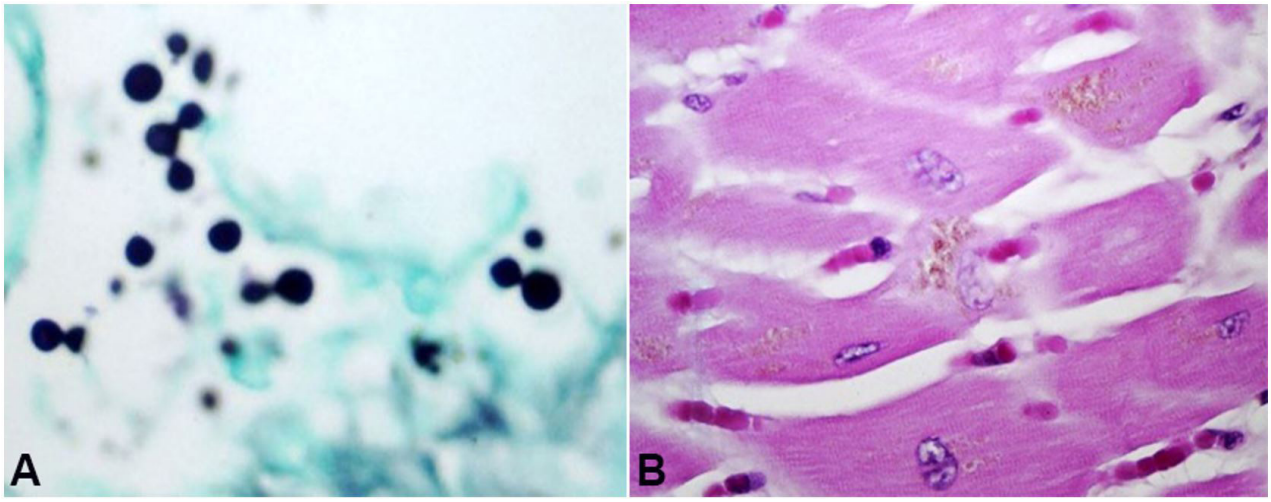

Figure 3. Photomicrographs of **A –** Lung - Pulmonary alveolus and septa infiltrated by yeast forms, many budding (GMS, 400X); **B** - Heart - Cardiac myocytes laden with hemosiderin (H&E, 400X).

DISCUSSION

This case illustrates important aspects of cryptococcosis. The immediate cause of death in the case of this report was disseminated cryptococcosis. This disseminated infection would have been easy to suspect in a patient immunosuppressed following transplantation, but this patient was only a potential candidate for transplantation undergoing initial transplant evaluation. Cryptococcosis is thought to usually result from reactivation of infection that had been latent in thoracic lymph node granulomas, similar to reactivated tuberculosis or histoplasmosis.[1] Many patients with cryptococcosis are neither on immunosuppressive medication nor have HIV infection.[2] One reason some of these patients develop cryptococcosis is diabetes, which predisposes patients to yeast infections, including cryptococcosis.[3] Another reason some of these patients develop cryptococcosis is cirrhosis. Cirrhosis predisposes to cryptococcosis by impairing host defenses, including cell-mediated immunity, phagocytic function, immunoglobulin concentration, and complement production, or indirectly as a result of associated malnutrition.[4] It is noteworthy in this regard that the patient of this report had a deficiency of zinc, a recognized cause of immunodeficiency.[5]

Perhaps the most important condition predisposing to cryptococcosis in this case was iron overload. Cryptococci compete with infected patients for iron.[6] Iron uptake by Cryptococcus neoformans uses siderophore-mediated and heme

uptake pathways; it correlates with the elaboration of virulence factors.[7] Hepatic iron overload is strongly associated with invasive fungal infections in the first year following liver transplantation.[8] In two recently reported cases of cryptococcosis surfacing one to six days following liver transplantation, retrospective testing showed cryptococcal antigen in the serum of both patients pre-transplantation.[9] Neither of these patients was transplanted for hemochromatosis, but one had diabetes and both had cirrhosis.[9]

The patient of this report had a progressive leukocytosis, starting with a WBC count of 15,500/mm3 and culminating in a leukemoid reaction with a WBC count of 57,700/cmm^3. A leukemoid reaction is an elevation of peripheral blood leukocyte count into the range usually due to leukemia, variously defined as above 30,000/mm^3, above 40,000/mm^3 or above 50,000/mm^3. Infections are among the most common causes of leukemoid reactions.[10,11] The infections associated with a leukemoid reaction are mostly bacterial.[11] A leukemoid reaction can also be a manifestation of a severe fungal infection, a clue to the diagnosis, as illustrated in this case.

Another clue to the diagnosis of disseminated cryptococcosis in this case was the co-occurrence of iron overload, diabetes mellitus and cirrhosis, all of which can independently predispose to cryptococcosis. This patient's cirrhosis was no doubt multifactorial, due to a combination of chronic hepatitis B and iron overloading. The patient had a splenocaval shunt and hemochromatosis has been reported in association with portosystemic shunts and attributed to the shunting. One report was a 40-year-old man with alcoholism, transferrin saturation of 89% and extensive iron deposition in liver, heart, pancreas, thyroid, adrenal and kidney.[12] Another report was a 52-year-old woman with hyperpigmented skin, diabetes mellitus and iron deposition in liver, heart, pancreas, adrenals and kidneys.[13] The iron overload in such cases can, however, be interpreted as a manifestation of hereditary hemochromatosis not yet manifest at the time of shunting. Shunting presumably contributed to the iron overload in the patient of our report, but a study of quantitative hepatic iron analysis showed far less liver iron in patients shunted for nonalcoholic cirrhosis than in patients with hereditary hemochromatosis.[14]

The patient of this case report was thought to have iron overload due to hereditary hemochromatosis rather than shunting on the basis of quantitative hepatic iron analysis, family history and the presence of iron overload in endocrine organs. Patients with homozygous hereditary hemochromatosis usually have an elevated ratio of hepatic iron concentration over age (hepatic iron index) greater than two, with hepatic iron concentration expressed in micromoles/gram, while those with other causes of iron overload usually have a ratio less than two.[14] This patient's hepatic iron index was 3.5. The patient's son had chronic hepatitis, with negative viral serologies, and skin hyperpigmentation thought most likely to be due to hereditary hemochromatosis. Genetic test results for this family are not, however, available.

Hereditary hemochromatosis (also called genetic hemochromatosis) is a slowly progressive disease of organ-damaging iron accumulation primarily involving liver, heart, joints and endocrine organs.[15,16] It is autosomal recessive, with low penetrance, but highly prevalent in people of northern European descent.[17,18] The comorbidity of hemochromatosis and other chronic liver-injuring diseases, hepatitis B in this case, accelerates the progression to cirrhosis and end-stage liver disease.[17,18] Obesity and alcohol have been identified as major risk factors for accelerated liver injury in patients with hemochromatosis.[16] This makes it paramount to counsel patients with hemochromatosis to avoid alcohol, to vaccinate patients with hemochromatosis against hepatitis B, and for patients with hemochromatosis and hepatitis C, to cure them of the hepatitis C with direct-acting antiviral therapy.

Once a patient has been diagnosed with hereditary hemochromatosis, it is also obviously important to test other family members for hemochromatosis. Hereditary hemochromatosis can be suspected in patients with unexplained chronic liver disease, cirrhosis, heart failure, cardiac conduction defects, early onset type 2 diabetes mellitus, male sexual dysfunction or skin hyperpigmentation.[15,16] The patient of this report had diabetes mellitus and may have had skin hyperpigmentation obscured by severe jaundice. His son had skin hyperpigmentation. The patient had fixed defects on adenosine thallium cardiac scan, but only myocardial iron deposition and no infarction at autopsy, so this can be regarded as a clue to the diagnosis of hereditary hemochromatosis. Early organ

injury due to iron overload can be suspected in patients who present with unexplained chronic fatigue, lethargy or arthritis, especially involving the second and third metacarpophalangeal joints.[15,16,19]

Testing should begin with iron studies: serum iron, transferrin, transferrin saturation and ferritin. Hereditary hemochromatosis causes abnormally high saturation of serum transferrin (iron binding capacity), over 45%.[15,16] It also causes elevated levels of serum ferritin, the circulating iron storage protein, over 300 ng/mL in men or over 200 ng/mL in women.[15,16] Either high transferrin saturation or ferritin can be indicative of iron overload, although ferritin is an acute phase reactant and also released by any hepatocytic injury, rendering it less specific than transferrin saturation. Elevated transferrin saturation often precedes elevated ferritin in patients with hereditary hemochromatosis.[15] The patient of this report had a transferrin saturation of 99% and ferritin of 4392 ng/mL, both indicative of the iron overload found at autopsy, illustrating the diagnostic value of these tests.

Hereditary hemochromatosis is a diagnosis clinicians should never miss because life-saving treatment is usually simple phlebotomy, with minimal risk of adverse effects.[15,16] It is most effective in prevention before organ damage has led to fibrosis, but even in advanced cardiac disease due to hemochromatosis, some echocardiographic parameters, including radial strain, isovolumic relaxation time and left atrial force have been shown to significantly improve with a course of therapeutic phlebotomy.[15] There is evidence suggesting that early fibrosis in the liver can be reversed by phlebotomy.[20] As exemplified in the case of this report, however, once the liver disease of hemochromatosis has progressed to end-stage, liver transplantation becomes the only major therapeutic option. Neither the disseminated cryptococcosis nor the hemochromatosis in this case were diagnosed antemortem, so the case also demonstrates the value of autopsy.

CONCLUSION

This is the report of a case of disseminated cryptococcosis in a patient with hepatic cirrhosis due to a synergistically liver-damaging combination of hepatitis B virus infection and possible hereditary hemochromatosis. The cryptococcosis and hemochromatosis were diagnosed only at autopsy. Diagnosing hereditary hemochromatosis in one patient can save multiple other family members lives because the treatment for them is usually simple phlebotomy. This case serves as a reminder that unexplained fatigue, lethargy, arthritis, chronic liver disease or heart failure should raise suspicion of the diagnosis of hereditary hemochromatosis and prompt testing for iron overload. This case also serves as a reminder that patients with diabetes, cirrhosis, iron overload, or some combination of these conditions, occasionally get disseminated fungal infections for which a leukemoid reaction can be a clue.

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Authors' contributions: Nichols L signed out the autopsy and wrote most of the manuscript. Rowley L researched the medical literature on hemochromatosis and contributed to the discussion. Lall A researched the medical literature on cryptococcosis and contributed to the discussion.

Informed consent by the next of kin was retained by the institution where the autopsy was performed, whose institutional review board waives approval of case report manuscripts.

Conflict of interest: None

Financial support: None

Submitted on: April 6th, 2020
Accepted on: May 11th, 2020

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