Secondary Hemosiderosis in a case of Alcoholic Liver Disease: Getting to the Root Cause

Abstract:

Hemosiderosis stands for the presence of demonstrable iron in tissues, mainly in parenchymal organs like liver and pancreas. Hemosiderosis in chronic liver disease often remains undiagnosed and the association between alcohol consumption and hemosiderosis may not be of common knowledge among physicians. We present the autopsy findings of a patient diagnosed with alcoholic liver disease who remained undiagnosed for secondary hemosiderosis until his demise. Pathogenesis of secondary hemosiderosis in alcoholic liver disease is discussed.

Keywords: Chronic alcoholic liver disease, secondary hemosiderosis

Introduction:

Alcoholic liver disease (ALD) is a major cause of illness and death worldwide. Prolonged and excessive consumption of alcohol is responsible for a wide spectrum liver pathology wherein steatosis, hepatitis, and fibrosis with cirrhosis are seen. [1] Hemosiderosis refers to the presence of demonstrable iron in tissues irrespective of the cause. Secondary hemosiderosis occurs when excess iron derived from exogenous sources is deposited in parenchymal organs and tissues. As per the literature, iron overload is commonly seen in end stage liver disease. [2] The hepatic iron concentrations may become markedly increased in patients of ALD. This iron overload tends to occur rapidly once cirrhosis has developed and further induces oxidative cell death in the liver. [3] It is reported to be responsible for hepatocellular carcinoma (HCC), liver failure, and death.[4,5] We present the autopsy findings of a patient of alcoholic liver disease who was diagnosed to have secondary hemosiderosis.

Case report:

A 37-year-old male, known to consume alcohol for 13 years reported to a tertiary care hospital with abdominal distension for 3 weeks and fever for 1 week. There was associated history of bilateral pedal edema, yellowish discoloration of eyes and urine, difficulty in breathing and reversal of sleep pattern. There were no bleeding manifestations, melena or hematemesis. He was admitted with a provisional diagnosis of alcohol related decompensated liver disease with grade 1 hepatic encephalopathy.

On admission, he was conscious, oriented, with pallor, icterus, bilateral pedal edema and asterixis. Abdomen was distended with fluid thrill. Laboratory evaluation revealed anemia (hemoglobin of 9.5g/dL; Reference range 13-15g/dL) , reduced platelet counts (69 x 10^3/uL; reference range 150-450 x 10^3/uL), raised serum bilirubin and transaminitis [Total bilirubin-6.8 mg/dl, AST-102 U/L, ALT-118 U/L, Sr. Cr. 1.02 mg/dl, Bl. Urea- 48 mg/dl) (Table 1). Abdominal ultrasound showed hepatomegaly with coarse echotexture, with severe ascites. He was administered 6 units of random donor platelets. A therapeutic ascitic tap with removal of 1.5 liters was performed. Fluid was transudate(proteins 1.2g/dL) with

predominantly lymphocytes Upper gastrointestinal endoscopy showed thin columns of esophageal varices. He was diagnosed as chronic ALD Child Pugh C, MELD-Na score 32.

Patient had a long course of hospitalization requiring frequent ascitic fluid drainage with multiple resolving episodes of culture positive spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy. A central venous catheter was placed and the patient was managed with broad spectrum antibiotics, fluid, electrolyte support, and diuretics. He required six units of packed red blood cells (PRBC) transfusion over a month. On the hospitalization day 48, he developed decreased urine output and bilateral pleural effusions with raised serum creatinine (1.34 mg/dl), followed by multiple spikes of fever along with hypotension and distension of abdomen with the dip in oxygen saturation. Despite fluid and inotropic support, the general condition of the patient further deteriorated with coagulopathy (INR 3.5), worsening hepatic encephalopathy breathlessness and desaturation. After two months of hospital treatment, the patient suffered cardiac

arrest and died despite all resuscitative attempts. An autopsy was conducted and tissues from various organs were sent for histopathological examination.

Autopsy findings

Ecchymoses were present over chest, both hands and legs, right forearm and cubital fossa (site of insertion of IV line). Anasarca was present with ascites, umbilical protrusion and scrotal edema. The abdominal wall was tense and shiny. The skin and sclera showed yellowish discoloration. A bed sore was noted over right gluteal region, measuring 3 cm in diameter.

On internal observation, hemorrhagic ascitic fluid of 3000 ml was drained from the abdominal cavity. Bilateral pleural effusion of 1000ml with heavy, boggy lungs was noted [right lung: 891 g ;RR 400-550g; left lung 716 g; RR 350-500g). Lower lobes of both lungs exuded pink frothy fluid. The liver weighed 1180 g (RR 1100-1500g); the capsule appeared

irregular, bumpy, with external surface showing cirrhotic nodules (Figure 1a, 1b). The cut surface was greenish grey in appearance. No necrosis or space occupying lesion were found. The spleen was enlarged, weighed 380 g (RR 140-200g), and was congested at the cut surface. The heart, pancreas and kidneys appeared unremarkable on the gross examination.

The histopathological examination of the liver showed architectural disruption with nodule formation. Microvesicular steatosis with bile duct proliferation and periportal lymphocytic infiltration with fibrosis were noted. Bile plugs and intraparenchymal pigment was seen. On Perls stain the pigment was confirmed to be hemosiderin deposits (Figure 1c, 1d). Features consistent with organizing pneumonia were noted in both lungs. The pancreas examination showed dense intracytoplasmic hemosiderin deposition in acinar cells (Figure 2a).. Left anterior descending artery showed partially occluding atherosclerotic plaque. No evidence of infarction or myocarditis were seen. Both kidneys showed enlarged glomeruli with hypercellularity. Mesangial matrix appeared increased. There was presence of hemosiderin pigment casts

(Perls Prussian Blue positive) and RBC casts in the tubules along with acute tubular necrosis (Figure 2b, 2c). The patient died of multiorgan failure.

A histopathological diagnosis of secondary hemosiderosis was made due to presence of extensive hemosiderin deposits in the liver, pancreas, heart and kidney on microscopy.

Discussion

Iron overload can be categorized into primary (hereditary) hemochromatosis and secondary hemosiderosis. The main forms of tissue iron are ferritin, hemosiderin, and heme of which the stainable iron is mainly hemosiderin. It mainly affects parenchymal organs like liver and pancreas followed by heart, joints and endocrine organs. The total body iron content is tightly controlled by the intestinal absorption by regulatory proteins mainly hepcidin, human hemochromatosis protein (HFE), hemojuvelin, transferrin receptor and ferroportin. Hepcidin plays an important role in iron metabolism.

Secondary hemochromatosis or hemosiderosis results from parenteral iron overload following repeated transfusions, long term hemodialysis, and repeated iron dextran injections. However, secondary hemosiderosis may be associated with chronic liver disease . The primary question, in this case, is whether iron played a role in the pathophysiology of the liver disease, or whether liver disease itself caused iron overload?

Liver injury may result in decreased production of hepcidin from the hepatocytes increasing iron absorption by the gut due to inhibition of the negative feedback of hepcidin. This may explain how iron stores may increase in a patient with chronic ALD. Another reason for increased iron stores could be scavenging of dead hepatocytes by Kupffer cells, that may become iron overloaded and precipitate more damage**.** This results in a vicious cycle of iron overload in the liver injury. Did repeated blood transfusions play a role in this case? Our patient received six units of PRBC transfusion, which is unlikely to result in secondary hemosiderosis per se but may have contributed for more iron overload. Therefore, in the pathophysiology of liver disease, excess iron in the liver can occur secondary to more advanced liver disease.[6] The

other causes for secondary hemochromatosis in this case include ineffective erythropoiesis with hyperplastic erythroid marrow and elevated iron with anemia of chronic disease**.**

Many authors have demonstrated that chronic ALD is associated with significant increase in hepatic iron concentration playing a role in the pathogenesis of ALD. [6- 9] Other studies suggest that iron overload does not develop in all cases of ALD, implicating the role of hereditary hemochromatosis, where alcohol is known to increase the severity of liver damage and the risk of cirrhosis. [10] Genetic tests for HFE gene comprising of C282Y, H63D and S65C mutations were tested on postmortem samples and found negative . Increased iron content in liver portends to a poor prognosis and may be predictor of death in patients of ALD [5, 11]

In such patients, testing for iron stores must be routinely performed to screen for iron overload. Iron overload may be diagnosed by elevated ferritin level and/or transferrin saturation(TSAT). In the setting of chronic inflammation, ferritin values may be difficult to value, further TSAT is a ratio, hence if total iron-binding capacity is reduced, TSAT may be

falsely elevated. Since the gold standard is a liver biopsy and an invasive methodology, imaging alternative should be explored. (12)

Anemia is fairly common in patients with liver cirrhosis and iron deficiency is documented in upto 70% of decompensated cirrhotic patients secondary to frequent variceal hemorrhage. ALD patients are frequently given iron supplements, infusions and blood transfusions further aggravating an undiagnosed iron overload.

Conclusion

Hemosiderosis in the index case supports the relation between alcohol and secondary hemosiderosis. Further larger studies need to be undertaken from the Indian subcontinent about the presence of hereditary causes and association of hemosiderosis in ALD. Like in this case, hemosiderosis in chronic liver disease often remains undiagnosed. Understanding the pathophysiology and mechanisms of iron overload inchronic ALD mechanisms may help design

strategies for the treatment and prevention. The aim of this report was to sensitize clinicians for early recognition of iron overload in patients of ALD in the presence of anemia so that appropriate interventions may be instituted at the right time.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

References

1. Osna NA, Donohue TM Jr, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res. 2017;38(2):147-161.

2. Kowdley KV. Iron Overload in Patients With Chronic Liver Disease. Gastroenterol Hepatol (N Y). 2016;12(11):695-698.

3. Dostalikova-Cimburova M, Kratka K, Balusikova K, Chmelikova J, Hejda V, Hnanicek J, et al. Duodenal expression of iron transport molecules in patients with hereditary hemochromatosis or iron deficiency. J Cell Mol Med. 2012 Aug;16(8):1816-26

4. Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology. 2004 Nov;127(5 Suppl 1):S79-86.

5. Liver iron is predictive of death in alcoholic cirrhosis: a multivariate study of 229 consecutive patients with alcoholic and/or hepatitis C virus cirrhosis: a prospective follow up study Gut 2000;46:277-282.

6. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Jul;54(1):328-43.

7. Milic S, Mikolasevic I, Orlic L, Devcic E, Starcevic-Cizmarevic N, Stimac D, Kapovic M, Ristic S. The Role of Iron and Iron Overload in Chronic Liver Disease. Med Sci Monit. 2016;22:2144-51.

8. Gramenzi A, Caputo F, Biselli M, Kuria F, Loggi E, Andreone P, Bernardi M. Review article: alcoholic liver disease--pathophysiological aspects and risk factors. Aliment Pharmacol Ther. 2006 Oct 15;24(8):1151-61.

9. Fierro-Fine A, Guerin L, Hicsasmaz H, Brown KE. Clinical Factors Associated with Hepatocellular Iron Deposition in End-stage Liver Disease. J Clin Transl Hepatol. 2020 Sep 28;8(3):231-239.

10. Abu Rajab M, Guerin L, Lee P, Brown KE. Iron overload secondary to cirrhosis: a mimic of hereditary haemochromatosis? Histopathology. 2014;65:561–69.

11. Ganne-Carrié N, Christidis C, Chastang C, Ziol M, Chapel F, Imbert-Bismut F, Trinchet JC, Guettier C, Beaugrand M. Liver iron is predictive of death in alcoholic cirrhosis: a multivariate study of 229 consecutive patients with alcoholic and/or hepatitis C virus cirrhosis: a prospective follow up study. Gut. 2000 Feb;46(2):277-82.

12. Hernando D, Levin YS, Sirlin CB, Reeder SB. Quantification of liver iron with MRI: state of the art and remaining challenges. J Magn Reson Imaging. 2014 Nov;40(5):1003-21.

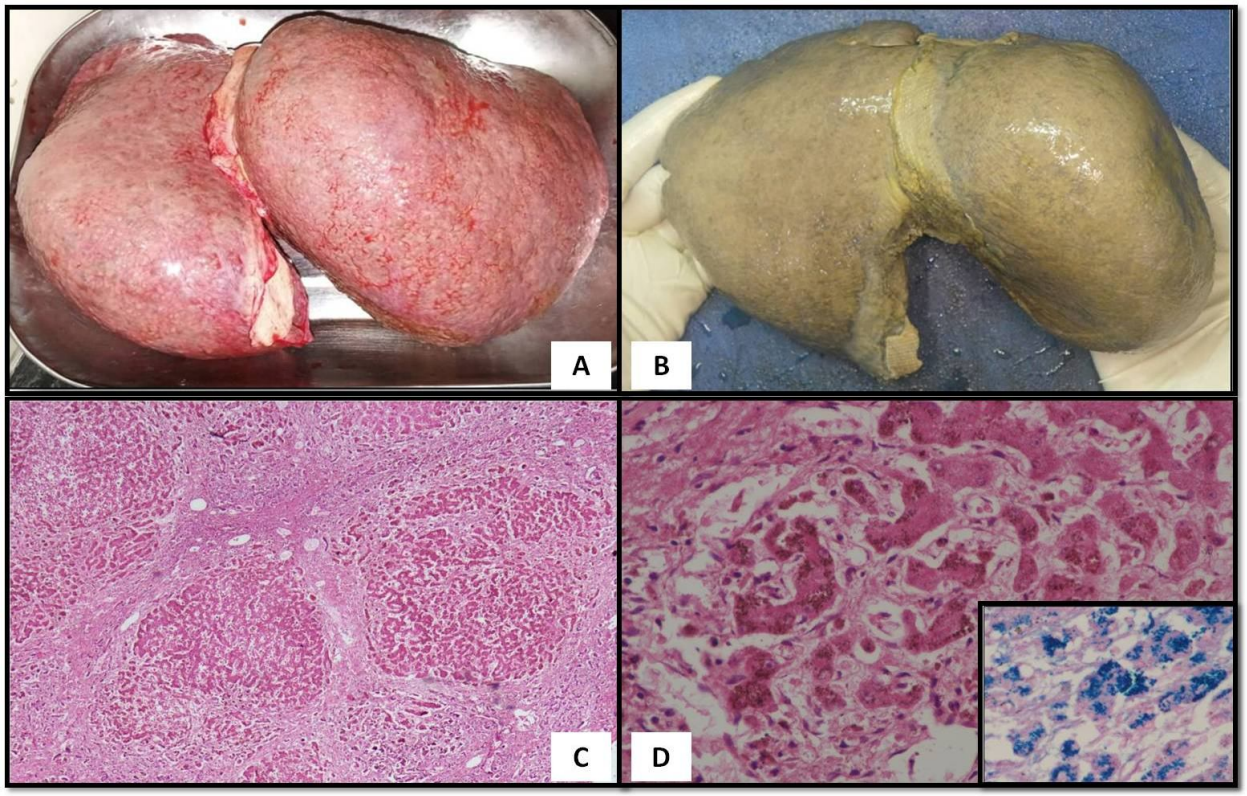

Figure Legends

Figure 1a, 1b: Liver in fresh state and fixed state showing micronodular cirrhosis

Figure 1c, 1d: Section of liver showing micronodular cirrhosis(H&E, 100x); Higher magnification showing intracytoplasmic browninsh pigment(H&E, 400x); Inset image showing granular blue intracytoplasmic staining of hemosiderin (Iron stain, 400x)

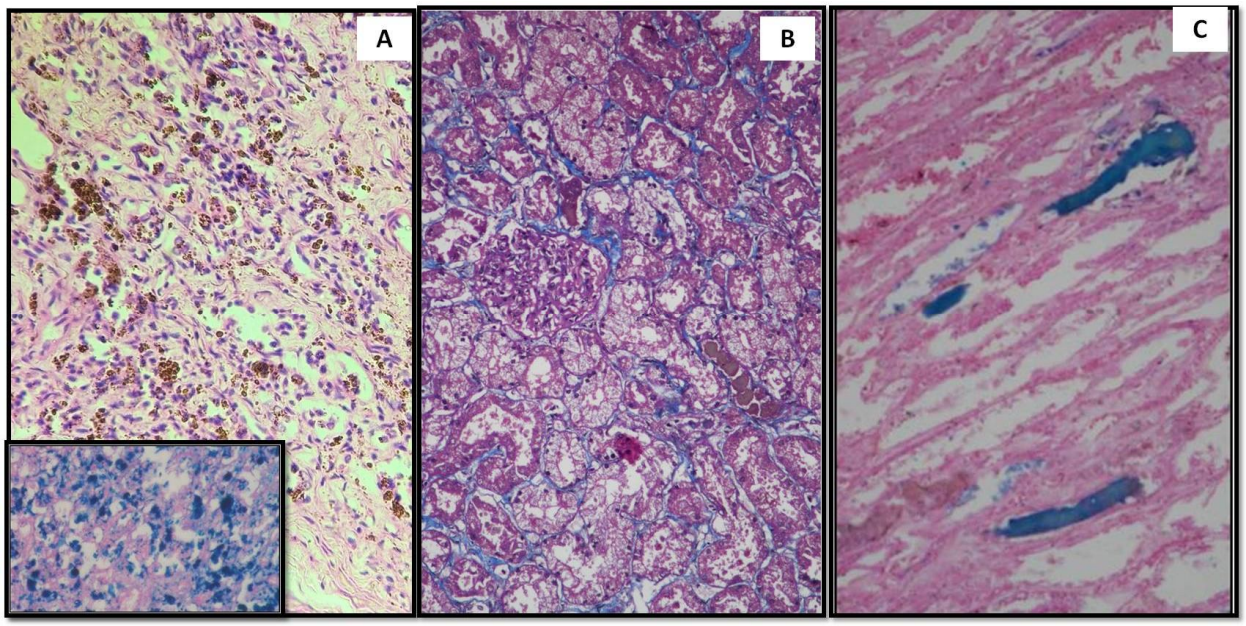

Figure 2a: Section of pancreas showing dense intracytoplasmic hemosiderin deposition in acinar cells, (H&E, 400x) Inset shows granular blue staining of hemosiderin (Iron stain, 400x)

Figure 2b, 2c: Section of kidney showing tubular necrosis with pigment casts within the tubules. (Trichrome stain, 200x) Hemosiderin deposits within the glomeruli and tubules(Iron stain, 400x)

Table 1: Day wise basic health parameters

INVESTIGATION	**Day 1**	**Day 4**	**Day 8**	**Day 15**	**Day 20**	**Day 25**	**Day 32**	**Day 40**	**Day 45**	**Day 50**	**Day 60**
Hb (gm/dl)	8.3	6.9	6.5	6.1	7.0	6.1	7.1	5.8	7.1	6.38	7.3
MCV	102.2	94.4	95.7	84	84.7	80.6	86.6	86	86.2	86.8	88.7
TLC /($x10^3$/uL)	14100	12600	9500	7400	7200	7800	7300	3100	4000	4400	6300
DLC	P79L10 M09E02	P85L08 M06E01	P79L10 M10E01	P76L13 M9E02	P74L15 M09E02	P76L12 M10E02	P70L12 M16E02	P60L26 M11E03	P58L26 M10E06	P65L18 M12E3B02	P73L12 M11E03B01
Platelet/($x10^3$/uL)	2,00,000	1,94,000	2,49,000	1,91,000	2,09,000	1,81,000	1,55,000	73000	1,14,000		1,55,000
PT	24.9	26			28.0	30.3	42.3	32.1		32.5	27.6
INR	2.22	2.36			2.58	2.85	3.25	3.30		3.36	2.54
Blood Sugar (R) mg/dl				136			163	136			103
BUN (mg/dl)		16			11	16					
Urea (mg/dl)	31		91	25		24	76	18	27	42	51
S Creat (mg/dl)	0.97	1.0	1.0	0.6	0.7	0.9	1.39	0.74	0.5	0.9	0.78
Total Bilirubin Direct Bilirubin Indirect Bilirubin (mg/dl)	11.9 8.2 3.7	10.8 8.5 2.3	10.5 8.2 2.3	9.6 5.0 4.6	11.7 7.5 4.2	10.9 8.2 2.7	12.0 8.0 4.0	9.9 4.9 5.0	9.6 5.3 4.3	10.2 5.9 4.3	12.2 5.0 7.2
Protein (g/dl)	7.1	6.8	7.4	6.7	7.3	6.5	7.4	6.0	5.9	6.1	7.0
Albumin (g/dl)	1.5	1.4	2.4	4.0	2.2	2.0	2.4	3.2	3.3	3.4	4.3
Globulin (g/dl)	5.6	5.4	5.0	2.7	5.1	4.5	5.0	2.8	2.6	2.7	3.7
AST (IU/L)	190	176	120	97	62	54	120	41	35	44	53
ALT (IU/L)	63	60	55	30	38	26	55	19	23	16	25
GGT (IU/L)	304										
Sodium (mEq/L)	127	122	126	126	127	126	128	134	131	129	139
Potassium (mEq/L)	4.6	3.9	4.2	5.6	4.6	5.0	3.7	4.4	5.4	4.1	4.8
LDH (IU/L)		223				169	167				
Peripheral smear	Macrocytic anemia. Neutrophil Leucocytosis	Macrocytic anemia. Neutrophil Leucocytosis	Normocytic normochromic anemia			Dimorphic anemia		Dimorphic anemia Thrombocytopenia		Normocytic normochromic anemia	Normocytic normochromic anemia