Ischemic Hepatitis Induced by Severe Anemia

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Ischemic hepatitis is caused by reduced oxygen delivery to the liver due to hypotension or hypoxemia [1,2]. However, there are no documented cases of ischemic hepatitis in which the low oxygen delivery is secondary to severe anemia. We describe the first case of ischemic hepatitis associated with severe anemia.

Patient Description

An 82 year old man was admitted to the hospital because of extreme weakness and general deterioration. Two weeks prior to admission he began to feel a generalized weakness that continued to worsen. On the day of his admission he was unable to stand or walk. He denied nausea, vomiting, abdominal pain, bloody stool, and alcohol or drug consumption. His medical history included an adenocarcinoma and subsequent prostatectomy 16 years earlier. An abdominal and pelvic computed tomography scan, bone scan and prostate-specific antigen performed 6 months earlier were unremarkable. On physical examination the patient was alert and oriented. He was very pale. His temperature was 36.7°C, blood pressure 145/75, pulse 92 beats per minute and regular. A 2/6 systolic murmur was heard at the left sternal border. Lung examination was normal. There was mild, diffuse abdominal tenderness, especially in the right upper quadrant. No organomegaly, abdominal mass or rebound tenderness were found. Bowel sounds were normal. Rectal examination and other physical parameters were unremarkable. Initial laboratory studies revealed 26.2 x10^9/L leukocytes with 84% neutrophils and 8% stabs. Hemoglobin was 3.2 g/dl with mean corpuscular volume 57.2 FL and iron 9 µg/dl. Electrolyte panel was normal. Aspartate aminotransferase was 468 U/L and alanine aminotransferase 864 U/L. Serum bilirubin was normal. Urinalysis revealed multiple leukocytes, with no erythrocytes. Normal sinus rhythm with ST depression on leads V3-5 was seen on electrocardiogram. A chest roentgenogram was normal. Arterial blood gases on room air were: PO_2 64 mmHg, PCO_2 33 mmHg, HCO_3^- 24 mmol/L, pH 7.46. Serologic tests for hepatitis A, B and C, Epstein-Barr virus and cytomegalovirus were negative.

The patient was treated with fluids, four units of packed cells, iron supplements as well as antibiotics for a suspected urinary tract infection. His hemoglobin rose to 9.9 mg/dl. Upper gastrointestinal endoscopy demonstrated esophagitis and a gastric ulcer. Treatment with an H2 blocker was initiated. Table 1 shows daily hemoglobin and liver enzyme values. The abnormal ECG returned to normal without enzymatic evidence of myocardial damage, and after 13 days of hospitalization the patient was discharged in a good clinical condition.

Comment

Ischemic hepatitis, not a rare disorder, occurs in up to 0.5% of patients admitted to medical intensive care units [3]. The two main etiologies of ischemic hepatitis are hypotension, which generally stems from a cardiac origin: congestive heart failure [1,2] or tachyarrythmia causing decrease in cardiac output, and hypoxemia (partial arterial oxygen pressure – P_aO_2 <60 mmHg or oxygen saturation <85%) [3], which follows acute respiratory failure.

The patient described here was diagnosed with ischemic hepatitis according to the Gibson and Dudley criteria: rapid and marked elevation of liver enzyme levels (greater than eight times the upper normal values); and subsequent resolution to near normal within 7 to 10 days, with exclusion of other possible causes such as viral infection or hepatotoxic agents [1]. Other typical laboratory findings are elevated lactate dehydrogenase and early peaking of AST and ALT levels (first to third hospitalization days). Our patient was admitted with severe anemia (hemoglobin 3.2 g/dl) and elevated liver enzymes (more than 13 times the normal values and peaking on the third day). LDH levels were

ECG = electrocardiogram

AST = aspartate aminotransferase
ALT = alanine aminotransferase
LDH = lactate dehydrogenase

Table 1. Time course of hemoglobin and liver enzymes

Hospitalization day	Hb	ALP	AST	ALT	GGT	LDH	BUN	Cr	PT	Alb
First	**3.2**		**468**				49	1.4	70%	
Second	**8.5**								INR=1.2	
Third	**7.7**	58	**519**	**864**	11	568	27	1.3		
Seventh	**9.1**	57		**220**	8					
Ninth	**9.6**	59	**35**	**135**			18	1.4		3
Thirteenth	**10.5**	67	**21**	**50**	16	200				3.3

ALP = alkaline phosphatase, GGT = gamma-glutamyl transferase, LDH = lactate dehydrogenase, BUN = blood urea nitrogen, PT = parathormone, Alb = albumin.

twice the normal value. Both the high liver enzyme levels and the ECG changes returned to normal after a blood transfusion [Table 1]. The patient was normotensive with a partial arterial oxygen pressure above 60 mmHg during his hospitalization. Serologic tests for hepatitis viruses A, B, C, Epstein-Barr virus, and cytomegalovirus were negative and the patient did not receive any medications prior to admission, ruling out other causes of acute hepatitis. Since the known etiologies of ischemic hepatitis were not evident in this case, no mechanism could explain this complication. It was thus hypothesized that the extreme anemia could have been the only factor directly responsible for the ischemic hepatitis, but no such etiology has ever been reported.

The liver, a highly vascular organ, receives approximately 1,100 ml of blood from the portal vein and about 350 ml from the hepatic artery into the sinusoids per minute. Liver size and blood flow decrease by up to 30% by the eighth decade (as in the above patient), thus reaching 245 ml from the hepatic artery and 770 ml from the portal vein. Liver oxygen consumption (determined by liver blood flow, hemoglobin concentration, oxygen saturation in the hepatic vessels, and liver oxygen extraction) averages 51 ml/minute [4].

Decreased liver blood flow or decreased oxygen saturation are the only proposed mechanisms of ischemic hepatitis to date, neither of which pertains to the above patient. To maintain a non-hypoxic hepatic cellular environment, the liver's oxygen extraction must equal or exceed its oxygen consumption. The oxygen consumption of the liver is calculated as the sum of oxygen delivered by the hepatic artery and portal vein, multiplied by the oxygen extraction of the liver. The oxygen delivery by hepatic artery is calculated by the following formula: hepatic artery blood flow multiplied by hemoglobin concentration multiplied by 1.34 (each gram of hemoglobin can bind a maximum of about 1.34 ml of oxygen), multiplied by arterial oxygen saturation. On admission the described patient's hemoglobin level was 3.2 g/dl, and oxygen saturation 92% (measured by arterial blood gases). Thus the calculated hepatic artery oxygen delivery is:

$$245\left[\frac{ml}{min}\right]\times 3.2\left[\frac{gr\cdot Hb}{100\,ml}\right]\times 1.34\left[\frac{ml}{gr\cdot Hb}\right]\times 0.92 = 9.6\left[\frac{ml}{min}\right]\text{ of oxygen}$$

hepatic artery blood flow	hemoglobin concentration	amount of oxygen bound to each gram HB	hepatic artery saturation

With the same formula, oxygen delivery by the portal vein is calculated: portal vein blood flow multiplied by hemoglobin concentration multiplied by 1.34 multiplied by the saturation in the portal vein. The average partial oxygen pressure in the portal vein is 49.1 mmHg [5], and according to Hill's equation is equivalent to oxygen saturation of 84%. Thus the calculated portal vein oxygen delivery is:

$$770\left[\frac{ml}{min}\right]\times 3.2\left[\frac{gr\cdot Hb}{100\,ml}\right]\times 1.34\left[\frac{ml}{gr\cdot Hb}\right]\times 0.84 \equiv 27.7\left[\frac{ml}{min}\right]\text{of oxygen}$$

portal vein blood flow	hemoglobin concentration	amount of oxygen bound to each gram of HB	portal saturation

The maximal liver oxygen consumption is calculated as: oxygen delivery by the hepatic artery plus oxygen delivery by the portal vein, multiplied by the oxygen extraction of the liver, or:

$$\left\{9.66\left[\frac{ml}{min}\right]+27.7\left[\frac{ml}{min}\right]\right\}\cdot 0.95 \equiv 35.5\left[\frac{ml}{min}\right]\text{ of oxygen}$$

oxygen delivery by hepatic artery	oxygen delivery by portal vein	consumption of oxygen by the liver

For the patient described here, the maximal possible liver oxygen consumption was 35.5 ml of oxygen per minute, 30% less than expected in the patient's age group in normal conditions (51 ml of oxygen per minute).

The maximum possible liver oxygen consumption was calculated assuming ideal blood flow to the liver as well as maximum hepatic oxygen extraction. It is thus evident that the oxygen balance, input and output do not reach the minimal levels required for normal cellular hepatic function. The ischemic tissue becomes inflamed and develops hepatitis.

In conclusion, ischemic hepatitis can manifest without severe hypoxemia or profound decrease in cardiac output providing that there is extreme anemia. To our knowledge, this is the first case reported in the English-language medical literature of ischemic hepatitis due to extreme anemia. We propose that severe anemia as an etiology should be considered when evaluating a patient with newly diagnosed ischemic hepatitis.

References

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*When humor can be made to alternate with melancholy, one has a success, but when the **same** things are funny and melancholic at the same time, it's just wonderful.*

Francois Truffaut (1932-84), French film-maker and pioneer of New Wave cinema