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CME CREDIT HOURS

Fever, abdominal pain, and jaundice in a 43-year-old woman

A 43-year-old Caucasian woman comes to the emergency room because of right upper abdominal pain that has lasted 2 days. The pain is dull and aching, is unrelated to food, and does not radiate. She notes that her skin tone has become more yellowish lately, and her urine is dark.

The patient says she has drunk three to four beers every day since the age of 18, and occasional drinks of vodka or gin on weekends. She abused intravenous drugs in her 20s, but quit after successful drug rehabilitation. She has no history of jaundice, hematemesis, melena, ascites, or encephalopathy. She has lost approximately 15 lb over the past 6 months, and her appetite is poor. She takes no medications, except for two to four acetaminophen tablets daily. Nothing else in her medical history is remarkable.

On physical examination, the patient appears cachexic, and her sclerae are deeply icteric. Her temperature is 39°C. Both parotid glands are enlarged, but she has no palmar erythema or spider nevi. The liver is enlarged and tender to palpation. The spleen is not palpable, the bowel sounds are normal, and there is no ascites. Cardiac auscultation discloses a loud first heart sound, with a systolic ejection murmur (grade 1/6) along the left sternal border. The lung examination is normal. The patient is drowsy with asterixis, but displays no focal neurologic deficits.

TABLE 1 summarizes the patient's relevant laboratory values.

WHAT IS THE DIAGNOSIS?

1 On the basis of the clinical picture and laboratory data, what is the most likely diagnosis?

- ☐ Acute viral hepatitis
- ☐ Acute cholecystitis
- ☐ Alcoholic hepatitis
- ☐ Acetaminophen toxicity
- ☐ Acute hepatic venous occlusion

This woman has the classic clinical triad of alcoholic hepatitis: fever, jaundice, and tender hepatomegaly.[1] However, it is imperative to exclude other causes of abdominal pain, such as biliary tract obstruction, impaired hepatic venous outflow, and intra-abdominal or systemic infection.

Alcoholic hepatitis is caused by excessive ethanol consumption, but it develops in only a minority of persons who drink heavily. Autopsy studies reveal liver disease in fewer than 20% of alcoholics. The amount of ethanol necessary to produce clinically significant disease varies markedly, but most patients with alcoholic hepatitis have consumed more than 80 g/day for at least 15 years—a daily intake of 1 cup of 80-proof whiskey, 1 liter of 12% wine, or eight 12-ounce 6% beers.[1] Women who drink are more prone to alcoholic liver disease than are men, perhaps because they have lower gastric alcohol dehydrogenase activity, leading to less gastric detoxication and a greater fraction of alcohol reaching the liver.[2]

Liver function tests in alcoholic hepatitis

Alcoholic hepatitis differs from viral hepatitis in its biochemical profile.

Aminotransferase levels. Typically, in alcoholic hepatitis, the serum level of AST (aspartate aminotransferase) is less than five times the upper limit of normal (ie, less than 200 IU/L in 95% of cases, and rarely more than 300 IU/L). The ALT (alanine aminotransferase) level is typically less than half the AST level. In contrast, acute viral hepatitis and drug-induced hepatic injury produce extremely high levels of aminotransferases (up to 10 times normal).

An AST/ALT ratio greater than 2 has been suggested as a diagnostic test for alcoholic hepatitis. However, in a Veterans Administration study,[3] only 58% of patients with alcoholic hepatitis had a ratio that exceeded 2.

In contrast, the ALT level in viral hepatitis is usually higher than the AST level.

Gamma-glutamyltransferase (GGT) levels are almost invariably elevated in alcoholic hepatitis. However, increases may reflect microsomal enzyme induction rather than liver injury, and as a result, this enzyme is less useful for diagnosis and management.

Serum bilirubin and alkaline phosphatase levels are usually elevated in alcoholic hepatitis, with values that tend to parallel one another. Biliary tract obstruction, usually extrahepatic, is easily confused with alcoholic hepatitis, given that both produce disproportionate increases in alkaline phosphatase and exquisite hepatic tenderness. Further tests, such as ultrasonography, are required to tell the difference (see below).

The prothrombin time and albumin concentration are both used as measures of hepatic synthetic function; although these are often abnormal in alcoholic hepatitis, they provide little assistance in the initial diagnosis.

Acute hepatic venous occlusion (Budd-Chiari syndrome) is characterized by sudden onset of abdominal pain and tender hepatomegaly. It is almost invariably accompanied by ascites (95% of cases), and the liver function tests are usually surprisingly normal or only mildly deranged.

The role of ultrasonography

The diagnostic test that would yield the most information at the least cost and degree of invasiveness would be ultrasound scanning of the right upper quadrant. In experienced hands, ultrasonography can detect abnormalities of the gallbladder and biliary tract with a sensitivity approaching 95%. Liver enlargement and heterogeneity of texture suggest intrinsic liver disease. Cultures of the blood and of any ascitic fluid would supplement the diagnostic workup, as would serologic tests for hepatitis.

TABLE 1

THE PATIENT'S LABORATORY VALUES

Study	Value	
Hemoglobin	10.9	g/dL
Hematocrit	30.1	%
Mean corpuscular volume	102	fL
White blood cell count	14.9	X 10^9/L
Platelet count	97	X 10^9/L
Sodium	133	mEq/L
Potassium	3.6	mEq/L
Glucose	72	mg/dL
Blood urea nitrogen	11	mg/dL
Creatinine	0.8	mg/dL
Aspartate aminotransferase	214	U/L
Alanine aminotransferase	62	U/L
Alkaline phosphatase	225	U/L
Gamma-glutamyltransferase	674	U/L
Albumin	2.8	g/dL
Bilirubin (total)	12.0	mg/dL
Prothrombin time		
Patient	17.0	seconds
Control	12.0	seconds

PREDICTING THE OUTCOME

2 What are the most important determinants of prognosis in this patient?

- ☐ Age
- ☐ Serum aminotransferase levels
- ☐ Serum bilirubin level and prothrombin time
- ☐ Signs of portal hypertension

A combination of clinical and laboratory features predict the short-term prognosis of patients with alcoholic hepatitis.

Indices of mortality

Two indices can be used to estimate the risk of dying: the composite clinical and laboratory index devised by Orrego et al[4] (TABLE 2) and the discriminant function proposed by Maddrey et al.[5] The former is used less in clinical practice, because it uses so many variables.

The discriminant function is much simpler to calculate:

$$4.6 \times [\text{prothrombin time} - \text{control (in seconds)}] + \text{serum bilirubin (in mg/dL)}$$

More than 50% of patients with a discriminant function greater than 32 die while in the hospital. This formula has been validated prospectively as a predictor of survival and, because it is readily applicable to clinical situations, is the indicator most often used in practice.

Recent evidence[6] suggests that serum cytokine levels correlate with mortality in acute alcoholic hepatitis, and may be useful in

TABLE 2

COMPOSITE CLINICAL AND LABORATORY INDEX SCORE FOR ALCOHOLIC HEPATITIS

Sign or laboratory value	Grade	Score*
Encephalopathy	1–3	3
Collateral circulation	1–2	1
	3	3
Edema	1	1
	2–3	2
Ascites	1–3	2
Spider nevi	> 10	1
Weakness	...	1
Anorexia	...	1
Prothrombin time (seconds over control)	4–5	1
	> 5	2
Hematocrit (% of normal)	75–89.9	1
	< 75	3
Albumin level (g/dL)	2.5–2.9	2
	< 2.5	3
Bilirubin level (mg/dL)	2.1–8	2
	> 8	3
Alkaline phosphatase level (IU/dL)	> 330	2

*A total score > 10 indicates a risk of dying > 60%
From Orrego et al, reference 4

refining the prognostic accuracy of the discriminant function. Other risk factors for mortality include advanced age, encephalopathy, and low serum albumin levels. None, however, is as accurate as Maddrey's discriminant function.

The AST and ALT levels do not correlate significantly with survival.[1] The clinical features of portal hypertension are not useful as prognostic indicators.[1]

Few studies have addressed prognostic indicators in the long term. One of these used regression analysis to identify three variables that predict a high risk of progression from alcoholic hepatitis to cirrhosis: continued alcohol use, female gender, and severity of initial injury (by histopathology).[7]

■ TREATING ALCOHOLIC HEPATITIS

3 What is the mainstay of therapy in this patient?

- ☐ Abstinence from ethanol
- ☐ Interferon alfa
- ☐ Corticosteroids
- ☐ Abstinence from ethanol and corticosteroids

The treatment of alcoholic hepatitis is largely supportive. Although most patients do not require hospitalization, the patient described above has more than a 50% risk of dying in the short term, and should be hospitalized to optimize her chances of survival.

Sobriety is essential

Patients with alcoholic hepatitis must stop drinking, but few can achieve total abstinence—fewer than 20% on questioning,[3] and fewer than 10% on objective testing.[8] Referral to chemical dependence programs and various community-based resources is therefore paramount.

However, abstinence does not guarantee improvement. In a study from Emory University,[9] no patient recovered who continued to drink, and of these, the hepatitis progressed to cirrhosis within 18 months in 38%. Nevertheless, only 27% of abstainers returned to normal by the seventh month, and hepatitis progressed to cirrhosis in as many as 18%.

Diet therapy is difficult but important

Malnutrition, often a prominent feature of alcoholic hepatitis, increases the risk of dying.[3] Experi-mental evidence suggests that correction of malnutrition is essential for improvement of the liver disease.

Unfortunately, the anorexia associated with hepatitis often limits the replenishment of nutrients. In a Veterans Administration study in which hospitalized patients received a well-balanced, 2500-kcal diet, only 63% of the moderately ill patients and 53% of the severely ill patients met their estimated energy requirements.

Multiple trials have failed to demonstrate that hyperalimentation alone improves survival.[3] Supplemental nutrition should be provided via enteral or parenteral routes only in patients who cannot tolerate oral feeding. Expensive branched-chain amino acid mixtures have not been shown to confer any added benefit over standard total parenteral nutrition solutions, and are not routinely recommended.

Vitamin and mineral deficiencies are common and require empiric replacement therapy. A high-potency multivitamin preparation should be given that contains thiamine, folate, pyridoxine, zinc, magnesium,

calcium, and vitamins B12, A, and D. Unless iron loss is present, iron supplements should be given only with caution, in view of the increased iron absorption seen in cirrhosis and the high prevalence of hemosiderosis in alcoholic liver disease.

Corticosteroids

More than 20 years after corticosteroids were first studied for treating alcoholic hepatitis, their use remains controversial. However, two randomized, placebo-controlled trials[10,11] showed encouraging results: a 4-week course of 32 mg of methylprednisolone (or an equivalent) daily in patients with clinically severe alcoholic hepatitis (discriminant function greater than 32) halved the mortality rate.

Of note, the patients in these trials were carefully selected: none had serious infections, uncontrolled gastrointestinal bleeding, clinically significant diabetes mellitus, pancreatitis, hepatocellular carcinoma, or hepatitis B infection. The efficacy of corticosteroids in the presence of these comorbid conditions has not been established.

There is a paucity of published data on managing alcoholic hepatitis in patients with coexistent infections with hepatitis C virus or human immunodeficiency virus (HIV). For now, it seems reasonable to withhold steroid therapy from patients who have acquired immunodeficiency syndrome (AIDS).

Supportive therapy

Treatment should be directed at improving the chances of survival in the short term. Alcohol withdrawal symptoms, gastrointestinal bleeding, or occult sepsis should be treated promptly, as these often cause morbidity and death.

How long patients must stay in the hospital depends on the clinical response and the presence of intercurrent illness. Many patients can be transferred directly to an inpatient alcoholic rehabilitation unit. Steroid therapy may be tapered rapidly over the fourth week of therapy, as there is no evidence to suggest that longer treatment is beneficial.

Experimental treatments aim at stimulating hepatic regeneration with anabolic steroids and insulin glucagon infusions, decreasing oxidative stress with propylthiouracil and cyanidanol, and preventing fibrosis with D-penicillamine and colchicine.[12] None of these has reproducibly decreased the mortality rate, and none can be recommended for general clinical use as yet. However, several ongoing clinical trials are exploring these and other therapies, which may in time expand the therapeutic options for alcoholic hepatitis. ■

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