Diffuse Hepatocellular Calcification Developing in a Patient on Chronic Hemodialysis After Ischemic Hepatitis

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Abstract

Diffuse hepatic calcification is a rare condition. Previous reports have described patients with end-stage renal disease who developed diffuse hepatic calcification after ischemic hepatitis caused by shock. We herein present a similar case. A 41-year-old man on chronic hemodialysis developed ischemic hepatitis due to shock induced by ventricular tachycardia, followed by progressive hepatic failure. Necropsy of the liver revealed diffuse hepatocellular calcification. Given the similarity by which our case and previously reported cases developed this rare condition, we postulate that chronic renal failure is involved in the pathogenesis of diffuse hepatic calcification.

Key words: end-stage renal disease, hepatic calcification, ischemic hepatitis, metastatic calcification, shock

Introduction

Diffuse hepatic calcification in uremic patients is a rare condition. Given the similarity by which our case and previously reported cases developed this rare condition, the underlying mechanism by which such a process occurs remains of interest. Three reported patients suffering from end-stage renal disease developed diffuse hepatic calcification after ischemic hepatic injuries caused by episodes of shock (1-3).

Here, we present the case of a patient who developed diffuse hepatic calcification after ischemic hepatitis caused by shock.

Case Report

The patient was a 41-year-old man who had suffered from chronic renal failure due to chronic glomerulonephritis and had been on regular hemodialysis for nine years. He was admitted for acute enterocolitis in late April 1998. His symptoms gradually improved with conservative treatment, which included intravenous fluid and antibiotic therapy.

Nonetheless, on the 21st day of hospitalization he presented with dry cough and a high fever; chest radiograph revealed a pulmonary infiltrate in the left upper lobe. The patient was initially treated with cefotiam for presumptive bacterial pneumonia, but the patient’s condition and the infiltrate worsened. Considering the patient had end-stage renal disease and was accordingly immunocompromised, we initiated treatment for atypical pneumonia and pulmonary tuberculosis, administering erythromycin, trimethoprim/sulfamethoxazole, and anti-tuberculous drugs. Due to the patient’s severe condition he was not evaluated with bronchoscopy.

Unfortunately, on the 28th hospital day, due to complications with congestive heart failure, the patient’s respiratory symptoms severely deteriorated, requiring intubation. Shortly after intubation, ventricular tachycardia was documented. The patient subsequently became unconscious and his blood pressure became unmeasurable. After immediate treatment with epinephrine, lidocaine, and calcium gluconate, the patient’s vital signs stabilized. His serum potassium level at that time was 7.5 mEq/l (normal, 3.6-5.0 mEq/l), thus hyperkalemia was considered to be the cause of the ventricular tachycardia. On the next day, his serum liver enzymes were remarkably elevated; glutamic oxaloacetic transaminase (GOT) was 6465 IU/l (normal, 11-35 IU/l), glutamic pyruvic transaminase (GPT) was 735 IU/l (normal, 4-30 IU/l),...
Figure 1. Clinical course and change in the serum levels of liver enzymes and bilirubin. Markedly elevated levels of GOT and LDH were observed shortly after shock; the total bilirubin level progressively increased following subsequent decline of GOT and LDH. GOT: glutamic oxaloacetic transaminase, T-BIL: total bilirubin, LDH: lactate dehydrogenase.

Table 1. Laboratory Data

<table>
<thead>
<tr>
<th>CBC</th>
<th>T-BIL</th>
<th>GOT</th>
<th>6465 IU/l (11-35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb 8.5 g/dl</td>
<td>GPT</td>
<td>735 IU/l (4-30)</td>
<td></td>
</tr>
<tr>
<td>Hct 26.8 %</td>
<td>LDH</td>
<td>11600 IU/l (220-450)</td>
<td></td>
</tr>
<tr>
<td>PIt 7.1 × 10^9/mm^3</td>
<td>ALP</td>
<td>220 IU/l (105-275)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPK</td>
<td>679 IU/l (28-130)</td>
<td></td>
</tr>
</tbody>
</table>

Blood Chemistry

<table>
<thead>
<tr>
<th>BUN 52 mg/dl (8-20)</th>
<th>C-reactive protein 12.1 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na 136 mEq/l</td>
<td></td>
</tr>
<tr>
<td>K 7.5 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Cl 95 mEq/l</td>
<td>PTH 130 ng/ml (&lt;0.8 ng/ml)</td>
</tr>
<tr>
<td>Ca 8.8 mg/dl (8.2-10.0)</td>
<td>(before 2 months)</td>
</tr>
<tr>
<td>P 9.5 mg/dl (2.5-4.2)</td>
<td></td>
</tr>
</tbody>
</table>

Serological Test

Endocrinological Test


Figure 1. Clinical course and change in the serum levels of liver enzymes and bilirubin. Markedly elevated levels of GOT and LDH were observed shortly after shock; the total bilirubin level progressively increased following subsequent decline of GOT and LDH. GOT: glutamic oxaloacetic transaminase, T-BIL: total bilirubin, LDH: lactate dehydrogenase.

and lactate dehydrogenase (LDH) was 11600 IU/l (normal, 220-450 IU/l). Other notable laboratory data is also shown in Table 1. The patient had poor medical compliance and had poor control of his potassium and phosphate. Poorly controlled serum phosphate had caused secondary hyperparathyroidism. Indeed, he had a high parathyroid hormone (PTH) level of 130 ng/ml (normal, <0.8 ng/ml) two months before the episode of shock. Respiratory failure presumably caused by pneumonia and heart failure improved with administration of multiple antibiotics and fluid removal with hemodialysis. The pulmonary infiltrate also resolved. The etiology of his liver damage was considered to be ischemic hepatitis that developed due to shock caused by ventricular tachycardia. This was supported by the observation that marked elevation of liver enzymes appeared just after the episode of shock and rapidly declined after several days: GOT 297 IU/l, GPT 20 IU/l, and LDH 857 IU/l.

Although the liver enzyme values decreased, the serum total bilirubin level progressively increased, reaching a maximum of 14.8 mg/dl (Fig. 1). Conjugated bilirubin was predominant in this marked hyperbilirubinemia and a prolonged prothrombin time of 35.4% was observed, suggesting severe hepatic failure. Serial sonographic studies were performed, revealing that the patient’s liver became progressively hyperechoic along with the increase in serum bilirubin (Fig. 2). Nonetheless, at first, the etiology of the rapidly progressing hyperbilirubinemia and increased echogenicity of the liver remained uncertain. The patient’s condition gradually deteriorated and eventually he died on the 54th hospital day.
Figure 2. Serial sonographic studies were performed before and after the onset of ischemic hepatitis. Images demonstrate that the patient’s liver became progressively hyperechoic after ischemic hepatitis developed.

Figure 3. (A) Liver necropsy showing marked calcification in the central to mid-zonal areas of a lobule. Viable liver cells were only focally seen (H&E, original magnification ×50). (B) Intracellular calcification was observed in probable hepatocytes and some of them were completely replaced by calcium deposits. (H&E, original magnification ×400). (C) Immunohistochemistry analysis by anti-cytokeratin antibody confirmed that calcium deposits were present in hepatocytes stained brown. Necrotic hepatocytes were almost completely replaced by calcium deposits (long arrows). Hepatocytes contained granulated calcium deposits (short arrow) (original magnification ×400).

Necropsy of the liver was performed and unexpectedly histologic examination revealed calcification in necrotic hepatocytes in the central to mid-zonal areas of the lobules. Hematoxylin and eosin (H&E) stained sections suggested
calcium deposition in necrotic hepatocytes (A, B in Fig. 3) and immunochemistry analysis by anti-cytokeratin antibody confirmed that calcium deposits existed in necrotic hepatocytes (C in Fig. 3). Ischemic hepatitis is often encountered, but generally progressive hepatic failure and severe jaundice do not develop. Initially, the clinical course of ischemic hepatitis in the present case appeared to be typical in terms of steady decline in aminotransferase levels, but hepatic failure became apparent, with marked deterioration that accompanied increased hepatic echogenicity suggesting hepatic calcification. Accordingly, it was speculated that calcium deposition in a massive number of necrotic hepatocytes, not ischemic hepatitis itself, contributed most to the development of jaundice and hepatic failure.

Discussion

Calcification in the liver is rarely seen, but it may occur secondary to granulomatous disease, infections, hydatid disease, neoplasms, among other causes (4-6). Most calcification is localized in one part of the liver; such diffuse hepatic calcification as we encountered in the present case is a rare entity. We find it of interest that there are case reports that describe uremic patients who developed diffuse hepatic calcification, as demonstrated in the present case. Accordingly, it might be postulated that chronic renal failure is involved in the pathogenesis of diffuse hepatic calcification (1-3, 7).

Pathologic calcification is classically divided into two main categories: metastatic and dystrophic calcification. Metastatic calcification occurs in normal viable tissue when serum levels of calcium and/or phosphate are elevated, i.e. a high serum calcium-phosphorus product. On the other hand, dystrophic calcification develops in injured or necrotic tissue when serum levels of calcium and phosphate are normal (5, 8-10).

Soft tissue and vascular calcification are highly prevalent in end-stage renal disease, although calcification in the liver, as seen in our case, is rare. Recently novel insight into the pathophysiology of undesirable calcification in end-stage renal disease have been gained. Disturbances of mineral metabolism such as hyperphosphatemia and hypercalcemia appear to contribute to progressive calcification, not only by passive precipitation, but by actively inducing changes in vascular smooth muscle cell behavior toward an osteoblast-like phenotype. Specific calcium-regulatory proteins may act as calcification inhibitors; dysregulation of calcification inhibitors may also represent pathophysiologically relevant factors in the context of uremic extrasosseous calcification (11).

It is often observed that hepatocytes are injured and occasionally become necrotic due to certain disorders, such as ischemic hepatitis. In such conditions, injured hepatocytes could exhibit increased plasma membrane permeability, which would cause an intracellular influx of calcium and subsequent dystrophic calcification. Nonetheless, even in such situations, dystrophic calcification in necrotic hepatocytes usually does not occur (10). It is worth noting that, in addition to hepatic necrosis, previous cases of hepatic calcification have demonstrated a high serum calcium-phosphorus product, which is often seen in end-stage renal disease (1-3, 7). Accordingly, a high serum calcium-phosphorus product appears to play a key role in the development of hepatic calcification (10). Similar to other reported cases, the serum calcium-phosphorus product in our patient was high: Ca 8.8 mg/dl×P 9.5 mg/dl=83.6.

The mechanism by which intraculcular calcification occurs in injured hepatocytes is not completely understood. It is speculated that an increase in plasma membrane permeability in injured hepatocytes could cause an intracellular influx of calcium and subsequent intracellular calcification (10), and this process is induced or accentuated by coexistent abnormalities in calcium-phosphorous metabolism, which are frequently manifested in patients with end-stage renal disease as a high serum calcium-phosphorus product (1, 7, 10, 12). Consequently, a high incidence of an elevated serum calcium-phosphorus product in uremic patients could make them susceptible to developing diffuse hepatic calcification in necrotic hepatocytes.

Patients on hemodialysis are vulnerable to ischemic hepatitis since they tend to be hemodynamically unstable during hemodialysis sessions, occasionally developing shock, as well as existing in a chronic hypervolemic state, predisposing them to passive liver congestion. Shock and passive liver congestion are well known risk factors for ischemic hepatitis (13, 14). The present patient became transiently hypotensive due to ventricular tachycardia. It was surprising that with such a short duration of shock, massive ischemic hepatic necrosis occurred. In addition to shock, the underlying passive liver congestion due to heart failure in our patient might have contributed to such massive hepatocellular necrosis (15). Such massive hepatocellular necrosis and the subsequent calcification in necrotic hepatocytes appeared to be the cause of the severe hepatic failure.

Accordingly, if a patient with chronic renal failure develops ischemic hepatitis, especially when a high serum calcium-phosphorus product exists, serial image studies such as ultrasonography or CT scanning need to be performed in order to detect early subsequent calcification of the liver, which could cause severe hepatic dysfunction, as seen in our case.

References
