CASE REPORT

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Fatal Acetaminophen Poisoning with Evidence of Subendocardial Necrosis of the Heart

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ABSTRACT: The authors describe a case of fatal acetaminophen overdose which occurred in a 16-year-old female. Her serum acetaminophen concentration 11.5 h postingestion was 154 mg/L. Antidotal therapy was unsuccessful, and after 9 days she died. Autopsy findings included centrilobular zonal liver necrosis, acute proximal renal tubular necrosis, and diffuse alveolar pulmonary damage. Her heart was transplanted into a young woman with congenital heart disease. The recipient expired 14 days after the transplant as a result of sepsis complicating bowel ischemia. The transplanted heart showed extensive subendocardial myocyte necrosis related to acetaminophen toxicity and not rejection.

KEYWORDS: pathology and biology, acetaminophen, poisoning, subendocardial necrosis, acetaminophen poisoning

Toxicity associated with acetaminophen overdose has been well described, although death as a consequence is relatively rare because of the effectiveness of antidotal therapy with *N*-acetylcysteine [*1,2*]. The authors report a case of fatal acetaminophen overdose which shows not only typical hepatic damage and renal change, but also subendocardial necrosis in a heart removed for transplantation.

Case History

A 16-year-old white female was admitted to a local hospital 11.5 h after ingestion of 15 g of acetaminophen (30 Extra-Strength 500-mg Tylenol tablets) in a suicide gesture. Her serum acetaminophen concentration as determined by fluorescent polarization immunoassay (TDx, Abbott Laboratories, Chicago, IL) was 154 mg/L. Immediate therapy with *N*-acetylcysteine was initiated; however, the patient experienced nausea and vom-

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iting which did not subside until 20 h after toxin ingestion. She was transferred to the authors' institution 24.5 h after the overdose for surveillance and a possible liver transplant. Physical examination revealed a well-developed, well-nourished, small white female in no apparent distress, who was alert and oriented; she complained of mild right upper quadrant tenderness. Her laboratory values on admission were significant for mild coagulopathy [prothrombin time (PT) 21 s/12 s control, partial prothrombin time (PTT) 31 s/26 s control] and metabolic acidosis (pH 7.35, pCO_2 30 mm Hg, HCO_3 17 mEq/L). Her serum acetaminophen concentration as determined by high-pressure liquid chromatography was 65 mg/L [3] (Fig. 1). Treatment was continued with *N*-acetylcysteine, 70 mg/kg every 4 h for a total of 17 doses. Her liver enzymes were normal on admission; however, by the fourth hospital day, her alanine aminotransferase (ALT) level peaked at 9700 units (U)/L and aspartate aminotransferase (AST) at 8000 U/L (Fig. 2), and she required intubation for lethargy and confusion. At this point, an urgent search for a donor liver was initiated without success. Acute renal failure developed on her sixth hospital day [blood urea nitrogen (BUN) 17 mg/dL, creatinine 5.0 mg/dL). By her seventh hospital day, the patient's encephalopathy progressed to coma status; computerize tomography (CT) of the head showed cerebral edema. The following day, her respiratory status was complicated by development of adult respiratory distress syndrome. Emergency hemodialysis because of dangerously elevated renal indices (BUN 42, creatinine 9.8) was instituted the day of her death. During this procedure, the patient deteriorated to the

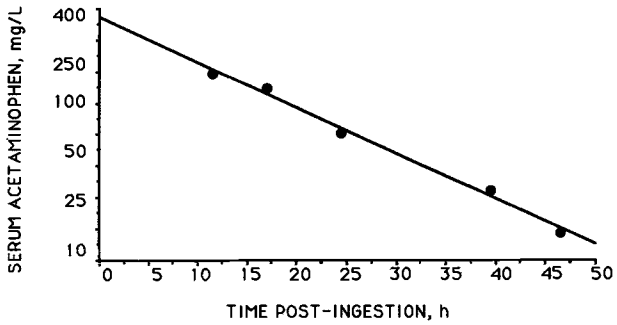

FIG. 1—*Log serum acetaminophen concentrations versus time postingestion. Regression analysis yielded* y *(log acetaminophen, mg/L)* = $-0.029 \times$ *hours* + *2.545,* $r^2 = 0.992$.

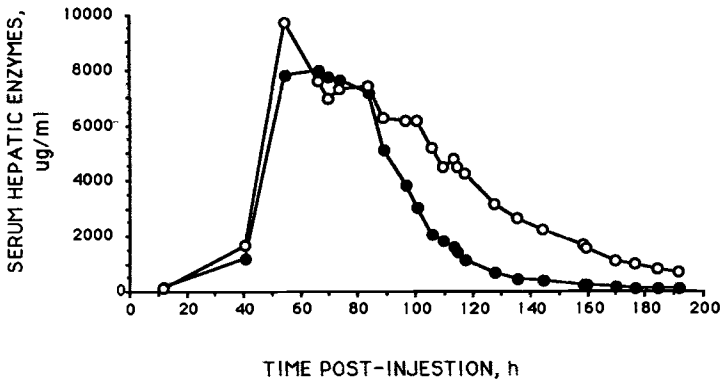

FIG. 2—*Serum hepatic enzymes versus time postingestion: (●) AST, (○) ALT.*

point of no brainstem function, which was evidenced by rostrocaudal herniation on head CT. Following these events, the patient's parents requested the Natural Death Act procedures and discontinuance of life support; they agreed to organ donation. She was pronounced dead on her ninth hospital day.

Autopsy revealed a small severely icteric white female whose heart, corneas, and long bones of the legs had been removed for donation. The liver was soft and shrunken with a wrinkled capsule. Microscopically, submassive centrilobular (Zone III) bridging necrosis consisting of collapsed reticulin was present. The remaining hepatocytes showed microvesicular fatty change (Fig. 3). The kidneys were swollen with cortical pallor. Microscopically, acute tubular necrosis was present, evidenced by proximal tubular damage, focal tubulorrhexis, cast formation, and early tubular regeneration. The lungs were firm and edematous. Histologic examination revealed prominent hyaline membranes as well as reactive pneumocytes.

The patient's heart had been donated to an 18-year-old white female with congenital cyanotic heart disease, who expired 14 days after the transplant as a result of an unresectable ischemic bowel complicated by gram-negative sepsis. The ischemic time between explantation from the donor and transplantation into the recipient was 2 h. A right ventricle endomyocardial biopsy performed 13 days after transplantation showed dys-

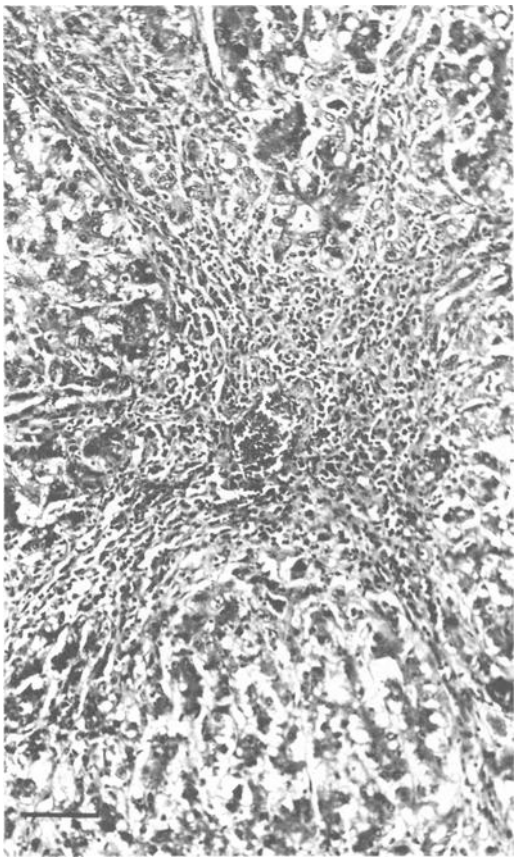

FIG. 3—*Centrilobular zonal necrosis of the liver (hematoxylin and eosin stain, the bar = 100 μm).*

trophic calcification but no evidence of rejection. Examination of the transplanted heart at autopsy revealed extensive endocardial hemorrhage involving the left interventricular septum and right ventricular free wall.

Microscopically, myocardial cells showed fatty degeneration and confluent subendocardial necrosis with striking dystrophic calcification (Fig. 4). Interstitial edema was present, with prominent reactive myocytes. There was no evidence of acute allograft rejection.

Discussion

The hepatic alterations caused by acetaminophen toxicity are well known; fortunately, death following such ingestions is now relatively infrequent, for most part, because of the widespread use of *N*-acetylcysteine [*4,5*]. The most significant prognostic factor in patients with acetaminophen overdose is the time that elapses between ingestion and initial hospital presentation [*6*]. Delay of treatment beyond 8 to 10 h after ingestion significantly increases the severity of hepatic toxicity [*2*]. In this case, the patient was admitted to the hospital 11.5 h postingestion with a serum acetaminophen concentration of 154 mg/L. Immediate administration of *N*-acetylcysteine was initiated; however, the

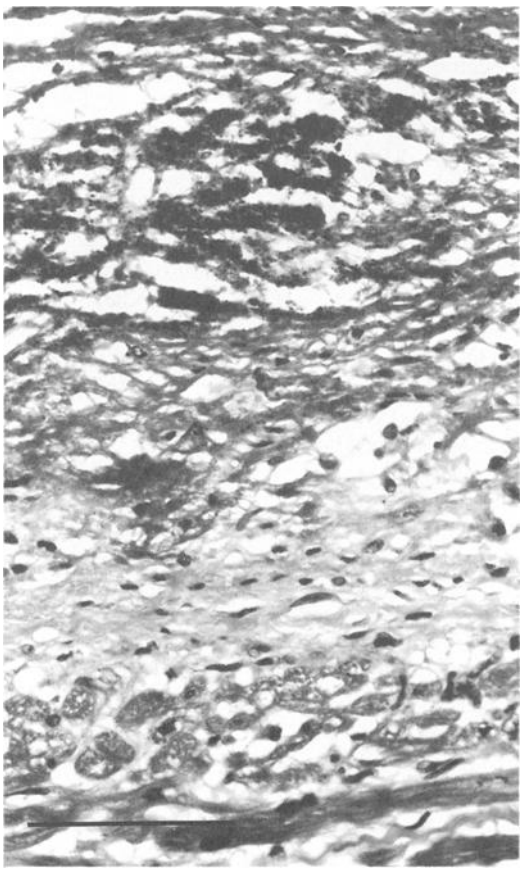

FIG. 4—*Subendocardial necrosis of the heart, with interstitial edema and dystrophic calcification (hematoxylin and eosine stain, the bar = 100 μm).*

patient's nausea and vomiting further delayed absorption of the antidote. A semilogarithmic plot of serum acetaminophen concentrations versus time determined that her serum half-life was 10.4 h (Fig. 1). The normal half-life of acetaminophen is 2 to 3 h; hepatotoxicity is observed with an increased half-life of 5 to 8 h and hepatic coma with a half-life of 10 to 12 h [7]. Using the area under the serum acetaminophen concentration versus time curve, the calculated amount of drug absorbed was 13.5 g, which was in good agreement with the dose, assuming a history of 15 g [8]. A plot of serum ALT and AST concentrations versus time (Fig. 2) demonstrates the absence of blunting of serum hepatic enzymes seen with adequate *N*-acetylcysteine therapy [2].

Intravenous acetylcysteine is felt by some to be the treatment of choice for severely poisoned individuals [9]. This form of therapy is not available in this country, but is used in the United Kingdom. This route of therapy is also most beneficial when administered within 8 h of toxin ingestion, but has been shown to be protective in decreasing the severity of damage in cases of delayed presentation [9]. The argument for the advantage of using an oral agent is the high portal vein concentrations obtained following intestinal absorption [2]. However, in a patient with nausea and vomiting, such as the one presented here, oral treatment is impractical.

Acetaminophen hepatotoxicity has been well described [2,10]. The classical finding of centrilobular zonal collapse produced by toxic metabolites covalently bound to hepatic macromolecules was present in this case. Likewise, renal failure, which has been previously reported and which necessitates dialysis, was present in the form of acute proximal tubular necrosis [10]. This damage is thought to be a direct toxic effect of the ingested poison, further complicated by hypotension, and is reduced by antidotal therapy [11]. In this rather unique situation, it was possible for us to examine this patient's donated heart. Cardiac toxicity following acetaminophen poisoning was first reported in 1968 [12]. Since then, few cases have been recognized [13,14]. In the case presented here, extensive subendocardial hemorrhage and necrosis, dystrophic calcification, myocyte fatty degeneration, and interstitial edema were seen. Similar features have been described previously in fatal acetaminophen overdose [12–14]. These changes did not resemble those characteristic of immune mediated acute graft rejection or those of reperfusion injury [15]. Recent electron microscopy studies have shown that similarly damaged cardiac myocytes contain lipid vacuoles [16]. It is undetermined whether the cardiac changes are a result of the severe metabolic derrangement of liver failure or are direct toxic effects [17]. Although the toxic myocardial damage demonstrated in this case may not have contributed to the demise of the transplant recipient, cardiac transplants from cases of acetaminophen toxicity present a transplant risk and should be considered with caution.

Summary

A case of fatal acetaminophen overdose has been presented which occurred in a 16-year-old female. Her unfortunate late initial presentation, further delayed by her inability to ingest the oral antidote, diminished her chances of potential recovery. Submassive liver necrosis, renal damage, and diffuse alveolar damage were present at autopsy. Her heart, which had been taken for donation, showed extensive subendocardial necrosis.

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