Hepatic Failure in Dairy Cattle Following Mastitis or Metritis

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Hepatic failure developed following mastitis or metritis in five adult cows. In all five cases, cows initially showed clinical signs compatible with endotoxemia, which resolved with appropriate therapy for the mastitis or metritis. Subsequently, signs of liver failure developed including profound anorexia, weight loss, cessation of milk production, and in one case, photosensitization. Four cows had laboratory evidence of liver disease and failure (abnormally prolonged sulfobromophthalein [BSP] clearance half-life and abnormally high serum liver enzyme activity). Hepatocellular necrosis or vacuolization was seen on histopathologic examination of liver specimens from all five cows. The hepatocellular necrosis, in some cases, was thought to be due to the direct or indirect effects of endotoxin on the liver. Three of the cows responded to symptomatic therapy. One cow failed to respond and one was not treated. (Journal of Veterinary Internal Medicine 1988; 2:80–84)

MANY of the clinical signs associated with coliform mastitis and metritis are thought to be due to the local and systemic effects of endotoxin.[1-6] These may include fever, tachycardia, mental depression, anorexia, rumen stasis, diarrhea, increased prominence of the scleral vessels, recumbancy, and local signs of inflammation such as edema and discoloration. The methods of treatment and prognosis for septic mastitis and metritis have been described.[1,2,5,6] Provided that the affected individual survives the acute stages of the infection, the long-term prognosis for return to previous performance is good.[1] Often there is a short-term loss in productivity (i.e., increased number of days open following metritis or temporarily decreased milk production from infected mammary gland), but the eventual return to normal fertility and/or milk production is expected in most cases.[5]

In this report, five cows in which hepatic failure developed following coliform mastitis or metritis are described. In each case, the initial problems (metritis or mastitis) appeared to be resolving, and the cow's failure to improve clinically was attributed to hepatic failure.

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Endotoxemia has reportedly resulted in hepatocellular damage in humans and experimental animals.[7-10] The lesions seen in these cows may have been due, in part, to endotoxemia.

Case Reports

Case 1

A 5-year-old female Holstein cow was examined 5 weeks after parturition because of weight loss and hypophagia of approximately 4 weeks duration. Parturition was uneventful, but 1 week later clinical signs consistent with coliform mastitis developed in the cow. They included fever, udder edema, a watery milk secretion, and hypophagia. Bacterial cultures of the milk were not performed. The cow was treated at the farm with intravenous oxytetracycline and local infusions to the affected gland with ticarcillin. The signs of mastitis resolved, but the appetite failed to improve and over the following 3 weeks the cow's weight decreased by approximately 125 kg.

On examination at the George D. Widener Hospital for Large Animals, the cow had normal vital signs but was dull and depressed with a poor appetite and low milk production. The mammary gland and milk secretion were normal on clinical examination, and a bacterial culture of the milk yielded no growth. Ketonuria was not present. Clinical laboratory results are summarized in Table 1. The prolonged sulfobromophthalein (BSP) clearance half-life and abnormally high serum liver enzyme concentration were evidence of hepatocellular disease with decreased hepatic function. Histologic examination of a percutaneous liver biopsy specimen showed multifocal areas

TABLE 1. Clinical Laboratory Results in Five Cows With Liver Failure

Case No.	Age (yr)	Breed	Chief Complaint	PCV (%)	TP (g/dl)	BSP (min)	AST (IU/l)	GGT (IU/l)	SDH (IU/l)	Fibrinogen (mg/dl)
1	5	Holstein	Mastitis	22	7.2	10.0	ND	34.7	110	788
2	2	Holstein	Metritis	43	5.2	15	ND	50	ND	380
		Convalescent				3.5				
3	7	Brown swiss	Mastitis	15	9.9	ND	236	ND	ND	ND
4	3	Holstein	Mastitis/metritis	35	6.9	7	284	200	ND	ND
5	6	Holstein	Metritis	35	6.8	8.2	497	560	ND	951
		Convalescent					300	264		
Normal				24–35	6–8	<5	98–278	8–28	2–6	250–450

PCV: packed cell volume; TP: plasma total Protein; BSP: sulfobromophthalein half-life; ND: not done; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; SDH: sorbitol dehydrogenase.

of hepatocellular necrosis with occasional accumulations of neutrophils, lymphocytes, and macrophages. No etiologic agent was apparent, and a bacterial culture of a liver biopsy specimen yielded no growth. The specimen did not float in formalin.

Supportive care consisted of force-feeding a gruel of alfalfa and water by orogastric tube daily, and intramuscular treatment with parenteral B-vitamin injections once weekly. The cow's appetite, attitude, and milk production gradually improved over a 3-week period, following which the cow was discharged. No follow-up laboratory work was performed. Clinically, the cow returned to normal and milk production returned to a level nearly equal to that before the illness.

Case 2

A 2-year-old female Holstein cow was admitted to the hospital 3 weeks after calving. The cow had a history of dystocia and retained placenta, with extensive trauma to the vagina during extraction of the live fetus. Eight days following parturition, fever, anorexia, a decrease in milk production, tenesmus, and a fetid uterine discharge developed in the cow. Following treatment at the farm for metritis with intravenous and intrauterine oxytetracycline infusions, the appetite and milk production gradually improved with resolution of the fever and uterine discharge. Five days later, the cow's appetite and milk production began to decline without evidence of metritis. The owner estimated the cow's weight loss to be 100 kg over the 7 days before admission.

On physical examination, the cow was extremely thin and dull, with a poor appetite and no milk production. There was evidence of a resolving necrotizing vaginitis that was presumed to be due to the dystocia. Palpation per rectum indicated that the uterus was not fluid filled and no discharge was expressible, but that the uterus was slightly larger than expected. Ketonuria was not present.

Selected clinical laboratory data are listed in Table 1. The neutrophilic leukocytosis was compatible with the (resolving) metritis and vaginitis. Abnormally high serum liver enzyme activities and the prolonged BSP clearance half-life confirmed the presence of hepatic disease with hepatic failure. Microscopic examination of a liver biopsy specimen showed moderately congested sinusoids with indistinct centrilobular hepatocellular vacuolization representative of hydropic change (Fig. 1). The biopsy specimen did not float in formalin. On day 4 of hospitalization, signs of photosensitization developed in the cow. The vaginitis was treated with intramuscular procaine penicillin and with vaginal douches with an antiseptic solution. Supportive therapy for the liver failure consisted of force-feeding a gruel of alfalfa meal, water, and brewers' grain, treatment with parenteral B vitamins, and preventing further exposure to sunlight. During the 2 weeks of hospitalization, there was a gradual improvement in the cow's appetite and milk production that was accompanied by a return to normal of the BSP clearance (Table 1). Two months following discharge from the hospital, the cow was reportedly normal.

Case 3

A 7-year-old female Brown Swiss cow was examined 6 weeks after parturition for poor appetite and weight loss since calving. Parturition was uneventful, but within 12 hours the cow had signs of acute coliform mastitis including fever, anorexia, rumen stasis, and a watery milk secretion. The cow was treated for 7 days with intramuscular ampicillin and intramammary kanamycin. After 1 week of treatment, the mastitis appeared to have resolved but the cow failed to regain its appetite. Over the ensuing 5 weeks, the cow's body weight decreased by approximately 100 kg and milk production ceased. On physical examination at the hospital, the cow had normal vital signs but was thin and had a poor appetite, and rumen contractions were absent. The mammary gland was normal on clinical examination, and a bacterial culture of the milk yielded no growth. Ketonuria was not present.

Selected laboratory results are presented in Table 1. The cow had anemia and hyperproteinemia, suggestive of chronic inflammatory disease. An exploratory laparotomy was performed, and abnormalities in the abdominal cavity were found to be restricted to the liver. The liver was firm, small, and had a nodular appearance. Histologic examination of a liver biopsy specimen showed severe coagulation necrosis of unknown cause, but the severity of the lesion suggested possible infarction. The serum aspartate transaminase (AST) (SGOT) activity was normal in this cow, suggesting limited ongoing hepatocellular damage. The owner chose to sell the cow and did not elect further treatment.

Case 4

A 3-year-old female Holstein cow was examined 10 days following parturition. Calving was unassisted, but the placenta was retained for 1 week. On the fourth day postpartum, fever,

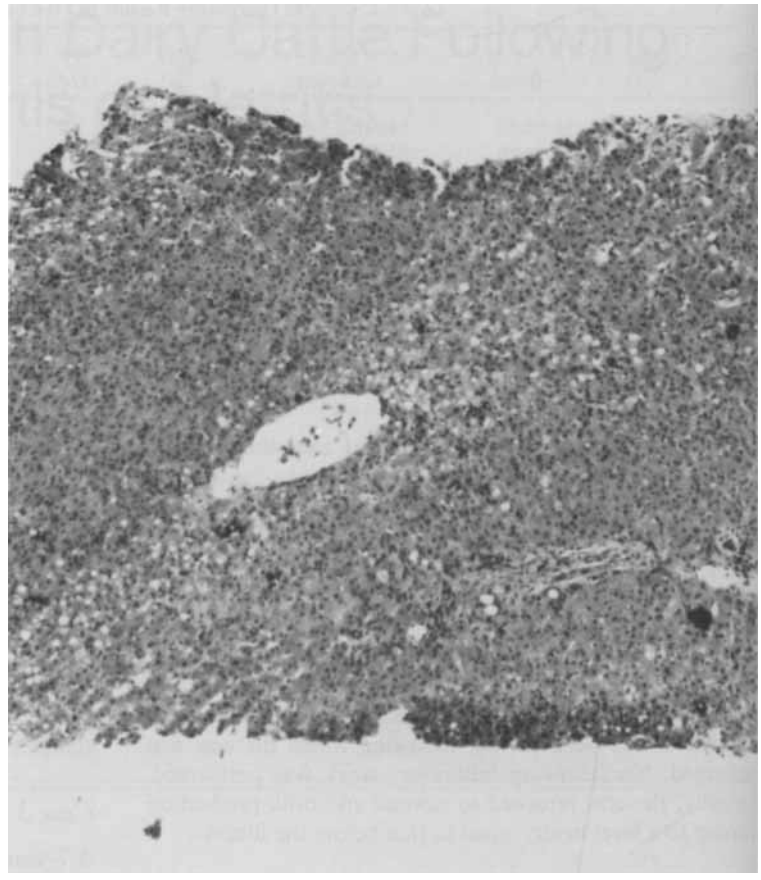

FIG. 1. Photomicrograph of liver biopsy specimen from case 2 showing a hepatic lobule in which indistinct vacuolization of centrilobular hepatocytes can be seen (H & E, ×90).

anorexia, decreased milk production, and a watery milk secretion from one quarter developed in the cow. The mastitis was treated with intramuscular ampicillin and intramammary kanamycin. The mastitis resolved partially but the fever and anorexia persisted until the cow was admitted to our clinic.

On physical examination, the cow had normal vital signs but was depressed and mildly dehydrated. The mammary gland was normal on palpation, but the secretion of the affected quarter was watery. A bacterial culture of this secretion showed a moderate growth of *Escherichia coli*. On palpation per rectum the uterus was enlarged, fluid filled, and had a red, foul-smelling discharge. Ketonuria was not present.

The cow was treated for metritis and mastitis with intravenous oxytetracycline (2.5 mg/kg twice daily). The affected quarter was infused twice daily with oxytetracycline. The uterus was drained and uterine lavage was performed with a chlorhexidine solution.

Improvement in the mastitis and metritis was not accompanied by an improvement in appetite or milk production, and further clinical laboratory test results showed evidence of liver disease (Table 1). The elevations in AST (SGOT) and gamma-glutamyl transpeptidase (GGT) activities were compatible with hepatocellular damage. The prolonged BSP clearance half-life was evidence of decreased hepatic function. The cow did not respond to continued antimicrobial and supportive therapy and was euthanatized. Postmortem examination showed that the mammary gland was normal but that the uterus was enlarged and contained necrotic placental fragments. The liver was pale, and histologic examination showed randomly distributed multifocal areas of hepatocellular necrosis and hemorrhage with mild periportal inflammatory cell accumulations.

Case 5

A 6-year-old female Holstein cow was examined because of hypophagia, weight loss, and decreased milk production of 1-week duration. Two weeks before admission to the hospital, the cow aborted twin fetuses in the eighth month of gestation. The cow required assistance calving, and the placenta was retained. One week later, the cow showed signs of septic metritis including fever, dehydration, hypophagia, and agalactia. The cow was treated with intrauterine infusions of penicillin and oxytetracycline. There was improvement of the metritis but no improvement of the appetite or milk production.

On admission, the cow was afebrile but had tachycardia (92 beats/min), mild dehydration, and rumen stasis. Bilateral pneumothorax was detected and was most likely secondary to rupture of alveoli following dystocia. Palpation per rectum showed the uterus to be large and fluid filled. Results of laboratory tests (Table 1) showed an abnormally high plasma fibrinogen, consistent with inflammatory disease (metritis). Abnormally high serum activities of hepatic enzymes (GGT and AST) and a prolonged BSP half-life were compatible with liver

disease and liver failure. Ketonuria was not present. Microscopic examination of a liver biopsy specimen showed indistinct hepatocellular vacuoles consistent with hydropic change. Few hepatocytes showed evidence of fatty change and the specimen did not float in formalin.

The cow was treated with intravenous potassium penicillin (20,000 IU/kg four times daily) and gentamicin (2 mg/kg three times daily) for 5 days, and underwent uterine lavage with a chlorhexidine solution. Pneumothorax was corrected by thoracocentesis and aspiration of air. Supportive care for the liver disease consisted of a continuous intravenous infusion of 5% dextrose with multiple B vitamins for 8 days, followed by force-feeding a gruel of alfalfa meal, brewers' grain, and water by orogastric tube. The cow's condition gradually improved. Hepatic enzyme activities 8 days following admission, although above normal, were lower than on admission. The cow was discharged 20 days after admission and was doing well 1 month following discharge.

Discussion

Hepatic failure developed in each of the cows in this report during or following recovery from mastitis or metritis. The initial clinical signs reported for each of these five cases were compatible with gram negative bacterial infection and endotoxemia, although bacteriologic confirmation was obtained only in one case. Bacteriologic confirmation was not possible in two cases because the primary problem had resolved, and was not attempted in two cases. Each cow was treated with antimicrobials and supportive care. Subsequently, the clinical signs associated with the primary disease appeared to resolve or to be resolving. Common to all five cows was a period of hypophagia despite apparent resolution of the initial infection, and four of the five cows had reported weight loss. Clinical laboratory evidence for decreased hepatic function (elevated BSP half-life) was found in four of five cases. Those cows also had elevations of one or more serum liver enzyme activities. In case 2, the failure to develop a hyperfibrinogenemia in the presence of the inflammatory disease (metritis or vaginitis) may have been due to hepatic failure. All five cows had hepatic lesions confirmed by histologic examination of a liver biopsy specimen or by postmortem examination. Three of the cows had hepatocellular necrosis of varying severity, and two had hepatocellular vacuolization (hydropic change). Neither of the specimens in the latter cases floated in formalin, suggesting that there was not severe fatty infiltration (<34%).[11] Special fat stains were not performed.

The authors suggest that the hepatic failure in these five cows may have been a result of endotoxemia. The effects of endotoxin on the liver in many species have been documented. Systemic infusion of *E coli* endotoxin in experimental rats[7,8] and pigs[9] caused multifocal hepatocellular necrosis. Decreased hepatic gluconeogenesis has been demonstrated in the livers from rats in late sepsis.[12] Hepatic dysfunction and hepatocellular necrosis have been reported in human patients with endotoxemia.[13,14] Experimental intramammary or intravenous infusion of *E coli* endotoxin in cattle has been shown to cause increases in serum hepatocellular enzyme activities.[3,15] In addition, elevations of BSP clearance half-life and serum liver enzyme activities following coliform mastitis were reported in two cases.[16] While these reports did not include the results of histopathologic examinations of liver specimens, the findings of elevated serum liver enzyme activities would suggest that hepatocellular damage occurred.

Endotoxemia-related hepatocellular necrosis may be due, in part, to decreased hepatic blood flow.[10] The hepatocellular necrosis resulting from liver hypoxia in humans with hemodynamic shock is well documented,[17-20] and it is certainly plausible that decreased hepatic blood flow could occur in cows with endotoxic shock. Decreased hepatic blood flow and extensive liver anoxia developed in rats with sepsis, and rats and miniature pigs given endotoxin.[8,10,20-22] The hepatocellular necrosis seen in the cases reported here was possibly due, in part, to decreased hepatic blood flow and liver anoxia.

Endotoxin is also thought to have a direct hepatotoxic effect.[10] The fixed macrophages of the liver (Kupffer cells) play an important role in the detoxification of endotoxin.[10,23] However, the interaction of endotoxin with the Kupffer cells can cause these macrophages to release lysosomal enzymes, prostaglandins, and collagenase that can damage hepatocytes.[10] Endotoxin that is not detoxified by the Kupffer cells may interact directly with the hepatocytes, causing lysosomal damage and decreased mitrochondrial function leading to necrosis.[10] Thus, endotoxin, either by its direct effects on the hepatocytes, through the release of mediators by the Kupffer cells, or by its effect on hepatic blood flow, may cause hepatocellular necrosis. It is reasonable to speculate that since these cows showed clinical signs compatible with endotoxemia, the ensuing hepatic disease may have been due to the direct or indirect effects of endotoxin.

This syndrome must be distinguished from hepatic lipidosis caused by fat mobilization, which also may occur in postpartum cows following anorexia due to mastitis, metritis, or other disease.[24] The anorexia, decreased milk production, and rapid weight loss seen in the cows reported on here was more pronounced than that usually seen in cows with hepatic lipidosis. Ketonuria was not present in the cows reported on here, whereas it is usually present in cows with fatty liver syndrome. None of the liver specimens of the cows presented here showed severe fatty change, as would be expected in cows with chronic fat mobilization. While the clinical laboratory findings in these two syndromes may be similar, history, absence of ketonuria, and histologic appearance of a liver biopsy specimen should enable the clinician to differentiate the two diseases.[24,25]

Other diseases such as displaced abomasum and ke-

tosis also must be considered in the postpartum anorexic cow with mastitis or metritis, but these should be readily diagnosed on the basis of physical examination or clinical laboratory findings. Mycotic rumenitis and omasitis are rare sequelae to endotoxemia, but should be considered in cows with anorexia that have been treated with antimicrobials for septic mastitis or septic metritis.

The treatment for hepatic failure associated with sepsis in cattle is nonspecific and involves providing supportive nutrition and nursing care while the liver regenerates. These include the force-feeding of alfalfa meal and dried brewers' grain (3 to 5 kg each daily) via an orogastric tube, rumen transfaunations when indicated, antimicrobial therapy if the infection persists, parenteral B vitamins, and, in some cases, administration of intravenous fluids containing glucose. The role of oxytetracycline in the pathogenesis of liver failure in four of these five cases is unknown. Although hepatic lipidosis was observed in oxytetracycline-treated cattle with experimentally induced respiratory infections,[26] lesions similar to those reported in the present study have not been reproduced.[26,27] However, the authors recommend that oxytetracycline not be given to cows with clinical evidence of liver disease.

Three of the five cows in this study survived and eventually returned to normal productivity. One cow was euthanatized after failing to respond to symptomatic therapy, and one cow was not treated. These results indicate that, in many cases, if the animal survives the initial disease (metritis or mastitis), the regenerative capacity of the liver will allow recovery from the hepatic necrosis. Thus, treatment should be attempted if economically feasible.

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