Pancytopenia associated with bone marrow aplasia in a holstein heifer

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A 14-day-old, Holstein heifer was presented to the University of Montreal Veterinary Teaching Hospital because of bloody diarrhea. A mild diarrhea had been noticed 5 d before admission and treatment with oral sulfamethazine (Sulfa S Bolus, SmithKline Beecham, Mississauga, Ontario; 10 g once, followed by 5 g, q12h, for 2 d) had been instituted at the farm. Two days prior to presentation, diarrhea became more severe and blood was present in the feces. A combination of trimethoprim and sulfadoxine (Borgal, Hoechst Canada, Regina, Saskatchewan; 2.7 mg/kg body weight (BW) based on trimethoprim) was administered IM once, the day before presentation. All cattle in the herd older than 6 mo of age were vaccinated twice yearly against bovine viral diarrhea virus (BVDV), infectious bovine rhinotracheitis virus, parainfluenza 3 virus, bovine respiratory syncytial virus, and *Leptospira* spp. (Triangle 9, Ayerst Laboratories, Saint-Laurent, Quebec).

On initial physical examination, problems identified were lethargy, tachycardia (200 beats/min), tachypnea (70 breaths/min), dehydration (estimated to 7%), pallor of the mucous membranes, and profuse hemorrhagic diarrhea. The rectal temperature was normal (38.9°C). Tachycardia, tachypnea, and pale mucous membranes were initially attributed to profuse blood loss in the diarrhea. Because a prolonged bleeding time was noted when the indwelling catheter was inserted, hemorrhagic diathesis was also suspected.

Treatment with 7% hypertonic saline (10 mL/kg BW, IV) was instituted, until blood had been collected from a selected blood donor. During the administration of the hypertonic saline, heart sounds and spontaneous ventilation ceased. Cardiopulmonary resuscitation was immediately instituted and the animal recovered.

Ancillary tests performed on admission included packed cell volume (PCV), white blood cell count (WBC), biochemical profile analysis, and venous blood gas analysis. Severe anemia (PCV = 0.10 L/L, reference range: 0.24–0.46 L/L), leucopenia (WBC = 1.27 × 10^9/L, reference range: 4 × 10^9/L to 12 × 10^9/L) due to severe neutropenia (0.013 × 10^9/L, reference range: 0.6 × 10^9/L to 4.0 × 10^9/L), and thrombocytopenia (platelet count = 13 × 10^9/L, reference range: 100 × 10^9/L to 800 × 10^9/L) were noted. Rare neutrophils showed severe signs of toxicity. Total solids were 37 g/L (reference range: 60–80 g/L), and fibrinogen concentration was 7 g/L (reference range: <5 g/L). Endotoxemia and bone marrow failure were considered possible causes of the leucopenia. Although anemia and thrombocytopenia could have been attributed initially to impaired bone marrow production, blood loss and platelet consumption were considered the main causes. Differential diagnoses considered for bone marrow failure included bone marrow necrosis, myelofibrosis, myelodysplasia, myelophthisis, and bone marrow aplasia. Venous blood gas analysis revealed a severe mixed metabolic and respiratory acidosis (pH = 7.05, reference range: 7.35 – 7.50; PCO_2 = 43.4 mmHg, reference range: 35 – 43 mmHg; HCO_3 = 11.3 mmol/L, reference range: 20 – 28 mmol/L).

After a normal cardiopulmonary condition had been restored, oxygen therapy was administered via a nasopharyngeal tube (5 L/min). Whole blood transfusion (50 mL/kg BW, repeated twice at 12 h interval), sodium bicarbonate (6 mmol/kg BW) and Ringer's lactate (2.8 mL/kg BW/h) were administered IV. Antimicrobial therapy consisting of sodium penicillin (Penicillin G Sodium, Ayerst, Saint-Laurent, Quebec; 22 000 IU/kg BW, IV, q4h), trimethoprim-sulfa (Borgal, Hoechst Canada, Regina, Saskatchewan; 5 mg/kg BW, based on trimethoprim, IV, q12h) and metronidazole (Apometronidazole, Apotex, Weston, Ontario; 25 mg/kg BW, PO, q12h) was initiated. For economical and practical reasons, sodium penicillin was replaced, on day 2, with sodium ampicillin (Ampicillin Sodium, Novopharm, Scarborough, Ontario; 20 mg/kg BW, IV, q8h).

Although a fair appetite was maintained, and a temporary improvement of the animal's condition was noted on day 2, the heifer remained depressed. Rectal temperature increased gradually during hospitalization. On day 3, pneumonia was suspected, based on an increasing respiratory rate, and crackles and wheezes on auscultation. Diarrhea persisted throughout the hospitalization period, but melena ceased on day 3. Bacteriological cultures of feces were negative for *Salmonella* spp., *Clostridium* spp., and *Campylobacter* spp. Tests for BVDV antigen were negative in both feces and blood. Low antibody titer (1/20) against BVDV in serum could have been the result of passive transfer of immunity from a vaccinated dam. After 12 h, the acid-base status had improved (pH = 7.28, PCO_2 = 48.5 mmHg, HCO_3 = 21.8 mmol/L), and by day 2, the acidosis had been corrected (pH = 7.41; PCO_2 = 35.3 mmHg, HCO_3 = 21.7 mmol/L). The hematocrit was normal (PCV = 0.35 L/L) after whole blood transfusion on day 2, but the leucopenia and the thrombocytopenia had not been resolved.

Bone marrow aspiration and core biopsy were performed in the right ilium, using a PDJ 35/13 G needle (Baxter, Mississauga, Ontario), to assess the cellularity and the architecture of the bone marrow. Cytological examination of the bone marrow aspirate revealed a hypocellular sample. The cell population consisted of fusiform stromal cells, small lymphocytes, macrophages, and a large number of adipocytes. No megakaryocyte, granulocytic, or erythroid stem cells were observed. Histological examination of a bone marrow core biopsy

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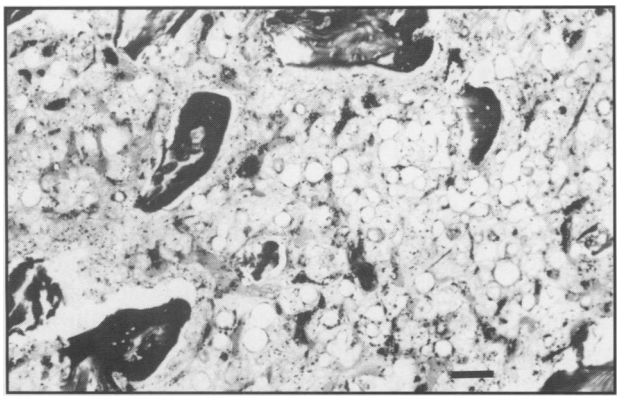

Figure 1. Photomicrograph of bone marrow from the proximal femoral diaphysis, showing severe hypocellularity. Hematoxylin-phloxin-saffron stain (Bar = 50 microns).

also revealed marked hypocellularity, consistent with bone marrow aplasia. Considering the poor prognosis associated with bone marrow aplasia and the deteriorating condition of the heifer, euthanasia was recommended.

On gross examination, numerous petechial to ecchymotic hemorrhages were observed in all serosa, cranial dura, skeletal muscles, esophageal mucosa, endocardium, and many synovial membranes. In the jejunum and ileum, there were many friable brownish masses attached to the mucosa; Peyer's patches appeared to be attenuated. The thymus was moderately atrophied. There was a fibrinohemorrhagic bronchopneumonia with fibrinous pleuritis in the cranial, middle, and accessory pulmonary lobes. In the caudal pulmonary lobes, there were multifocal hemorrhages. In the cortex of the right cerebral hemisphere, there was focal hemorrhagic malacia. The femoral and costal bone marrow was diffusely pale.

Histological examination revealed a systemic mycosis, characterized by thrombosis of many blood vessels, with hemorrhage and necrosis in the cerebral cortex, lungs, and reticulo-omasal and intestinal mucosa and submucosa. In many thrombosed vessels, there were numerous segmented and branched hyphae of varying width, compatible with zygomycetes. In the lungs, hyphae and small gram-negative bacilli were seen in alveolar and bronchiolar lumina. Hemorrhages in the epicardium, endocardium, kidneys, and spleen were not associated with vascular lesions. Examination of the femur, including the epiphyses, revealed a markedly hypocellular bone marrow in which marrow spaces were composed mainly of adipocytes (Figure 1). A few small clusters of hematopoietic precursor cells were scattered throughout the marrow; no megakaryocytes were found. Fluorescent antibody did not reveal BVDV antigen in intestine, mesenteric lymph node, spleen, kidney, lung, or thymus. Aerobic culture of the lungs yielded large numbers of *Escherichia coli*. Culture for mycotic organisms was negative, but tissues were submitted after freezing. Consequently, a final diagnosis of bone marrow aplasia was made. Pneumonia and systemic mycosis were considered to be consequences of immunodeficency associated with the pancytopenia.

On admission, the predominant clinical sign was severe bloody diarrhea. Hemorrhagic enteritis caused by *Clostridium perfringens* type C, *Salmonella* spp., or *Campylobacter* spp. was suspected. Necropsy revealed that the intestinal lesions were not characteristic of these infections.

Pancytopenia is defined as a deficiency of all cellular elements of the blood and is characterized by a decreased number of all stem cells associated with fat infiltration. Due to the relatively short half-life of leukocytes, leukopenia and thrombocytopenia are early manifestations of bone marrow aplasia. Pancytopenia has been reported infrequently in dogs, horses (1,2), and cattle (3–6). In cattle, pancytopenia has been attributed to bone marrow necrosis (4) and bone marrow infiltration by neoplastic lymphocytes (3). Fatal pancytopenia related to toxic protein derivatives from trichloroethylene-extracted soybean oil meal has also been documented in cattle (5,6).

Viral infections, toxins, radiation, drugs, and chemicals have been incriminated as causes of bone marrow aplasia. In the case presented here, the probable causes of bone marrow aplasia were inherited and drug induced. However, viral- or toxin-induced bone marrow aplasia could not be ruled out. In human medicine, several syndromes associated with inherited bone marrow aplasia have been described. One of them, Fanconi's anemia, is related to a chromosomal defect and can be diagnosed using a cytogenetic marker (7). To our knowledge, inherited bone marrow aplasia has never been described in cattle. Trimethoprim-sulfa has previously been incriminated as a possible cause of idiosyncratic bone marrow aplasia in dogs (8–10).

The pancytopenia exhibited by the heifer indicated that all stem cells in the bone marrow were affected. Although massive blood loss was probably the main cause of the anemia, the nonregenerative anemia suggested concurrent erythroid stem cell depression. Immune-mediated anemia has also been reported with bone marrow aplasia (2). Coombs' test could have helped to identify an immune mediated disease, but this procedure was not performed, because the heifer had received a blood transfusion at admission.

Pancytopenia often results in the death of the patient either from natural causes or through euthanasia (1,3,8,10). Recommendations for treatment include discontinuation of potentially myelotoxic drugs, with or without administration of glucocorticoids (2,7,9,11). Treatment of aplastic anemia in humans includes autogenous bone marrow transplantation, administration of androgens and glucocorticoids, and supportive care. Although they are infrequently associated with aplastic anemia in animals, mycotic infections are reported to be a major complication of bone marrow aplasia in humans (12). One should remember, when attempting treatment of this condition, that systemic mycosis and generalized bacterial infection are potential complications due to the immunodeficiency. CVJ

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COMING EVENTS

ÉVÉNEMENTS À VENIR

CVMA Conventions/ Congrès de l'ACMV

1997
Saskatoon, Saskatchewan
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1998
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SEPTEMBER/SEPTEMBRE 1996

Genetic Engineering and Animal Welfare: Preparing for the Twenty-First Century. September 5–6, 1996 in Chicago, Illinois. Topics: IACUC review of genetic engineering protocols; ethical issues; assessment of animal safety: immediate and long-term effects; transgenics and the media: the public relations aspect; agricultural animals and genetic engineering; scientists' concerns with genetically altered animals. Contact: Conferences, SAW, Golden Triangle Building One, 7833 Walker Drive, Suite 340, Greenbelt, Maryland 20770; tel.: (301) 345-3500; fax: (301) 345-3503.

The 22nd Annual International Veterinary Acupuncture Congress. September 5–8, 1996 in Spiez, Switzerland. Contact: David H. Jaggar, 268 West 3rd Street, Suite 4, P.O. Box 2074, Nederland, Colorado 80466 USA; tel.: +303-258-3767; fax: +303-258-0767; e-mail: ivasjagg@msn.com.

Third World Congress of Veterinary Dermatology. September 11–14, 1996 in Edinburgh, Scotland. The scientific programme includes: state-of-the-art addresses, supporting papers, an extensive clinical programme, and extensive workshops. Contact: Dr. Brad Baker, Baker Animal Clinic, 1627 Dundas Street East, Whitby, Ontario L1N 2K9; tel.: (905) 571-3700; fax: (905) 571-0266; or Dr. Bill Schroeder, Fenelon Animal Clinic, Box 256, Fenelon Falls, Ontario K0M 1N0; tel.: (705) 887-2731; fax: (705) 887-1510.

British Columbia Veterinary Medical Association Annual Conference. September 13–15, 1996 in Vancouver, British Columbia. Includes: Dr. Joseph Bojrab, Surgery; Dr. John Hoskins, Canine and Feline Pediatrics; Dr. Bill Bennett, Cow-Calf Herd Health; Ms. Cheryl Miller, Communication Skills for Front Office Staff. Contact: Ilona Rule, BCVMA, #155-1200 W. 73rd Avenue, Vancouver V6P 6G5; tel.: (604) 266-3441; fax: (604) 266-8447; e-mail: 74253.1252@compuserve.com.

Northern Ontario Veterinary Association Annual Conference. September 19–22, 1996 at he beautiful Killarney Mountain Lodge, in Killarney, Ontario. Seminar topics include business management for both large and small animal practitioners; feline enteric medicine; and ophthalmology. Contact: Dr. Chad Wilkinson, Lockerby Animal Hospital, RR 4, Box 25, Sudbury, Ontario P3E 4M9; tel. (705) 522-4555; fax: (705) 522-6159.

Congrès annuel de l'Ordre des médecins vétérinaires du Québec. Du 20 au 22 septembre à L'Auberge des Seigneurs, St-Hyacinthe (Québec). Contacter: Michelle Giasson, L'Ordre des médecins vétérinaires du Québec, 795, avenue du Palais, Bureau 200, St-Hyacinthe (Québec) J2S 5C6; Tél. : (514) 774-1427; Télec. : (514) 774-7635.

International Sled Dog Veterinary Medical Association. September 21–22, 1996 in Edmonton, Alberta. Topic: pediatrics, geriatrics, hypothyroidism, acupuncture, weight loss, diarrhea, dropped dog care, updates on nutrition, cardiology, pathology, and orthopedic surgery. Contact: Dr. Al Townsend, ISDVMA, P.O. Box 985, Chestertown, Maryland 21620 USA; tel.: (410) 778-1200; fax: (410) 778-1636.

British Veterinary Association Congress 1996. September 26–29, 1996 in Chester. Contact: Congress Secretary, British Veterinary Association, 7 Mansfield Street, London W1M OAT; tel.: +44 (0) 171 636 6541; fax: +44 (0) 171 436 2970.

American Holistic Veterinary Medical Association Annual Conference. September 18–October 1, 1996 in Portland, Oregon. Contact: American Holistic Veterinary Medical Association, 2214 Old Emmorton Road, Bel Air, Maryland 21015 USA; tel.: (410) 569-0795; fax: (410) 569-2346.

OCTOBER/OCTOBRE 1996

La Practique de L'an 2000/Veterinary Practice in the Year 2000. October 6, 1996 at the Sheraton Laval, Québec. Featuring guest speaker Mark Opperman (English). Contact: M^me^ Lucie Lamarche, secrétaire, Académie de médecine vétérinaire du Québec, 5929 route TransCanadienne, Bureau 120, Ville St.-Laurent (Québec) H4T 1Z6; tel.: (514) 855-0077; fax: (514) 629-8386.

28th International Congress on the History of Veterinary Medicine. October 16–20, 1996 in Vienna/Austria. Main themes: Contributions of veterinary medicine to national, social, and economic development; and national constraints in the recognition of veterinary professional rights. Contact: Secretariat, Dr. G. Forstenpointner, Institut für Anatomie, Veterinärmedizinische Universität Wien, Josef Baumanngasse 1, A-1210 VIENNA, Austria; tel.: 0043/222/ 25077-2503.

Western Canadian Association of Swine Practitioners Annual Meeting. October 18–19, 1996 at the Travelodge Hotel in Saskatoon, Saskatchewan. Contact: Dr. Chuck Rhodes, Western College of Veterinary Medicine, University of Saskatchewan, 52 Campus Drive, Saskatoon, Saskatchewan S7N 5B4; tel.: (306) 966-7068; fax: (306) 966-8747.

Canadian Pet Expo 1996. October 18–20, 1996 at Exhibition Place in Toronto, Ontario. National consumer show of pets, pet products, and services. Contact: Canadian Pet Expo, 100 Sandiford Drive, Unit 41, Stouffville, Ontario L4A 7X5; tel.: (905) 642-2422; fax: (905) 642-2660.