Use of lithium for treatment of estrogen-induced bone marrow hypoplasia in a dog

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A 6-year-old 28-kg spayed Old English Sheepdog was referred for evaluation of pancytopenia. The dog had been treated intermittently for 15 months with diethylstilbestrol (18 μg/kg of body weight, PO, q 24 h) for urinary incontinence. Prior to treatment, results of CBC and urinalysis had been normal. Unknown to the referral veterinarian, the dog had been treated concurrently by another veterinarian with diethylstilbestrol (36 μg/kg, PO, q 12 h) for 3 weeks and injections of estradiol cyclopentylpropionate (0.14 mg/kg) at 11 and 10 weeks prior to referral. The dog became lethargic, and a vaginal discharge and attraction to male dogs was noticed 4 weeks after the second injection of estradiol. Complete blood count revealed anemia, neutropenia, and thrombocytopenia. Supportive treatment with amoxicillin was initiated, but CBC results obtained 1 and 2 weeks later did not indicate improvement (Fig 1).

On admission, the dog was alert but weak. Although mucous membranes were pale, capillary refill time was normal, and hemorrhage was not evident. The vulvar labia were swollen, and there was a clear vaginal discharge. Microscopic examination of a vaginal smear revealed cornified epithelial cells and a few RBC. Complete blood count revealed nonregenerative anemia (PCV, 16%) with no increase in the corrected reticulocyte count (0.6%). Thrombocytopenia (6,000 platelets/μl), leukopenia (1,800 WBC/μl), and neutropenia (650 cells/μl) were also detected. Similar results were obtained the next 2 days (Fig 1).

Marrow was aspirated from the iliac crest. The aspirate appeared hypocellular, and the spicules had small numbers of cells on the surface, which were primarily plasma cells with a few osteoclasts. Megakaryocytes were not seen, and erythroblasts and promyelocytes were rarely detected. Core biopsy revealed severe marrow hypoplasia; the marrow cavity was virtually devoid of all cellular elements except a few fibroblasts (Fig 2).

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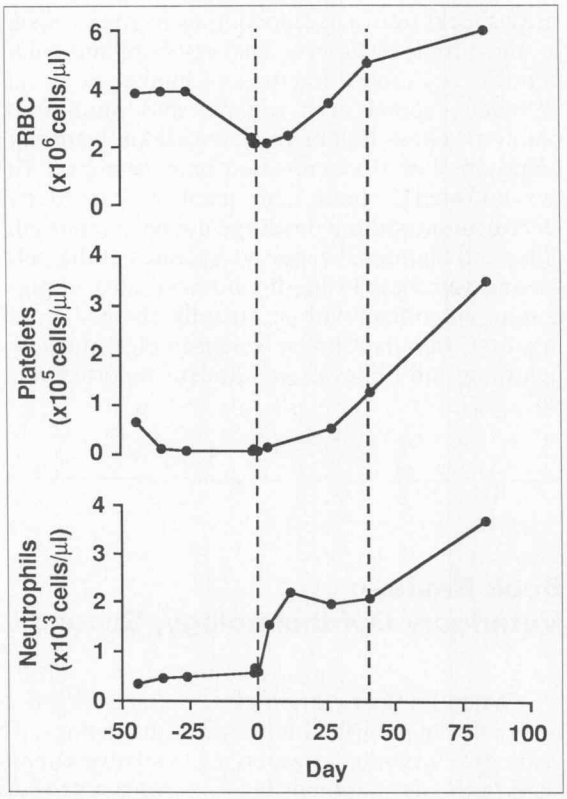

Figure 1—Platelet, RBC, and neutrophil counts from a dog with estrogen-induced marrow hypoplasia. Duration of treatment with lithium carbonate (11 mg/kg of body weight, PO, q 12 h) is marked with dotted lines.

The dog was given amoxicillin (11 mg/kg, PO, q 12 h) prophylactically once the leukopenia was detected. Treatment with lithium carbonate[a] (11 mg/kg, PO, q 12 h) was initiated when the core biopsy was performed. Except for a vitamin-mineral supplementation,[b] no other treatment was given. The dog was discharged, and the owners were instructed to continue this treatment regimen, and return for reexaminations every 5 to 7 days. Serum lithium concentration measured by flame photometry, serum creatinine concentration, and CBC (Fig

[a]Lithium carbonate capsule USP, Roxane Laboratories, Columbus, Ohio.

[b]Vi-Sorbin, Norden Laboratories Inc, Lincoln, Neb.

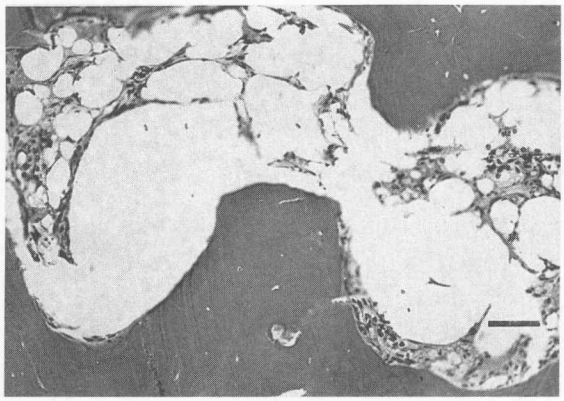

Figure 2—Photomicrograph of a section of bone marrow core biopsy specimen obtained prior to lithium treatment. Notice severe hypoplasia with an almost complete lack of cells in the marrow cavity. H&E stain; bar = 35 μm.

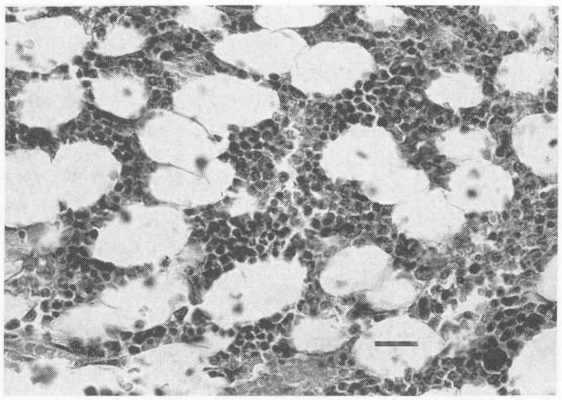

Figure 3—Photomicrograph of a section of marrow core biopsy specimen obtained after lithium treatment. Notice the normal density of erythroid and myeloid cells. H&E stain; bar = 400 μm.

1) were determined at each examination. Serum lithium concentrations, 12 hours after treatment, ranged between 0.5 and 1.3 mEq/L throughout the 6 weeks of treatment.

Neutrophil numbers doubled within 1 week of the start of lithium treatment. Amoxicillin was discontinued after 2 weeks, when the neutrophil count was >2,000 cells/μl. Numbers of platelets and RBC increased more slowly (Fig 1); however, regeneration was noticed within 2 weeks as evidenced by polychromasia, macrocytosis (MCV, 83 fl), and a corrected reticulocyte count of 5%. The vulvar swelling and vaginal discharge gradually ceased, and the dog's lethargy resolved with resolution of the anemia. After 6 weeks of lithium treatment, CBC revealed regenerative anemia (PCV, 35%), thrombocytopenia (125,000 platelets/μl), and neutropenia (2,100 cells/μl). Core biopsy of the marrow revealed normal numbers of erythroid and myeloid cells, and some megakaryocytes (Fig 3). Lithium treatment was discontinued, and CBC 1 month later confirmed full recovery.

The toxic effects of exogenous estrogens on canine marrow may be disastrous.[1-5,c] Toxicosis results when estrogen is given in excessive or repeated doses, or at recommended dosages to dogs with an idiosyncratic sensitivity. Severe marrow hypoplasia results in nonregenerative anemia, thrombocytopenia, and an initial neutrophilic leukocytosis, which may progress to a neutropenic leukopenia.[6,c] Because estradiol is a potent cause of marrow hypoplasia in dogs,[2,5,6] its use is no longer recommended[5]; however, diethylstilbestrol can also induce toxic signs.[c] This dog was given excessive amounts of estradiol, sufficient to induce signs of proestrus, when already receiving diethylstilbestrol.

Despite severe thrombocytopenia in this dog, there was no evidence of hemorrhage. Death from estrogen toxicosis frequently occurs from complications of hemorrhage and infection, and persistence of thrombocytopenia >2 weeks usually indicates a poor prognosis.[c] Dogs that survive have prolonged recovery.[3-5,7] Transfusions may be required for treatment, and other supportive measures have included treatment with anabolic steroids, androgens, and glucocorticoids,[2,7] although a close association between steroid treatment and recovery has not been confirmed.

Lithium stimulates neutrophil production,[8,9] and may also stimulate other hematopoietic cell lines.[10] In dogs, lithium stimulates granulopoiesis after cyclophosphamide-induced injury,[11] and has been used clinically to stimulate myelopoiesis in neutropenic dogs.[12] Lithium probably acts by substituting for other cations, interfering with sodium transport and cyclic 3'5', AMP-mediated hormones, and causing altered purine and pyrimidine metabolism, which thereby influences cell multiplication and differentiation in the marrow.[13] In dogs, lithium increases colony-stimulating activity required for growth of granulocyte precursors, and increases proliferation of hematopoietic stem cells.[14] Lithium may accelerate recovery of cytopenias caused by damage to stem cells of the marrow, and it is the differentiation of such stem cells that is inhibited by estrogens.[6,c]

Maddux and Shaw[15] reported a possible beneficial effect of lithium in a dog with estrogen-induced marrow hypoplasia; however, the effect was difficult to assess, because serum lithium concentrations did not reach an optimal range, and concurrent prednisolone was given. Serum lithium concentrations that have been suggested for optimal hematopoietic response in dogs are 0.5 to 1.8 mEq/L.[10] Serum concentrations are not entirely predictable on the basis of dosage,[9] and signs of lithium toxicicosis, including nephrotoxicosis, are easily induced[8]; thus, serum lithium and creatinine concentrations should be monitored. Serum creatinine concentrations did not increase, and no toxic effects were observed.

[c]Chiu T. *Studies on estrogen-induced proliferative disorders of hemopoietic tissue in dogs.* Thesis, University of Minnesota, St Paul, 1973.

Marrow cellularity may recover without treatment in 30 to 40 days after estrogen administration,[6,c] but because thrombocytopenia in the dog of this report had persisted for 10 weeks, recovery was unlikely, and a grave prognosis was given. Lithium treatment was apparently successful in inducing regeneration of the bone marrow and was discontinued after 6 weeks.

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Book Review: Diagnostic Parasitology for Veterinary Technicians

This book is a basic text for the detection and identification of internal and external parasites of companion animals, food animals, rabbits and rodents, and pet and aviary birds. The text provides general information on parasites and parasitism in chapter one and a thorough coverage of procedures for diagnosing parasitism in chapter two. The chapter on procedures has each of the procedures in a "box" format on the page with step-by-step directions for performing the test. Procedures for determining egg counts, detecting lungworm larvae, and for calibrating a micrometer are included. The quality of the photographs in chapter two is adequate, but could be improved in future editions.

The chapters on parasitism in dogs and cats contain concise information on life cycles and good-quality photographs for identification of parasites, their products, or both. The detection and identification of common equine parasites is included in chapters five and six. The differentiation of lice and ticks is a feature of the chapters on food animals. Antemortem and postmortem detection of parasitism in rabbits, mice, rats, hamsters, guinea pigs, and gerbils is described in chapter nine. The last chapter is devoted to detection of parasites of the blood, respiratory tract, and intestinal tract of birds.

This book compiles a great deal of useful information concerning diagnostic parasitology for veterinary technicians. With some improvement of photographic quality, this reasonably priced book should make an excellent text for teaching diagnostic parasitology to veterinary technicians or as a reference for graduate technicians.—[*Diagnostic Parasitology for Veterinary Technicians. Edited by Joann Colville. 266 pages; illustrated. American Veterinary Publications Inc, 5782 Thornwood Drive, Goleta, CA 93117. 1991. Price $24.50 + $4.00 shipping.*]—BOYCE C. WANAMAKER