Estrogen-induced myelotoxicity in dogs: A review
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Abstract — Exogenous estrogens used for therapeutic purposes or endogenous estrogen sources such as functional Sertoli cell or ovarian granulosa cell tumors may cause bone marrow toxicity in dogs. The condition is characterized by hematologic abnormalities including thrombocytopenia, anemia, and leukocytosis or leukopenia. Despite intensive therapy with blood or platelet-rich transfusions, broad-spectrum antibiotics, steroids, and bone marrow stimulants, prognosis is unfavorable. Due to the risk of stimulating the development of uterine diseases and the potential for inducing aplastic anemia, estrogen use in dogs is best avoided where possible. This paper describes the causes of estrogen-induced myelotoxicity, the clinical presentation of the patients, the diagnosis, and the treatment options in the dog.

Résumé — Myélotoxicité induite par les œstrogènes chez les chiens : étude. Les œstrogènes exogènes utilisés à des fins thérapeutiques ou des sources d’œstrogènes endogènes, telles que des tumeurs des cellules de Sertoli fonctionnelles ou de la granulosa, peuvent causer la toxicité de la moelle osseuse chez les chiens. L’affection se caractérise par des anomalies hématologiques incluant la thrombocytopenie, l’anémie et la leucopénie. Malgré une thérapie intensive avec des transfusions de sang ou riches en plaquettes, des antibiotiques à large spectre, des stéroïdes et des stimulants de la moelle osseuse, le pronostic est défavorable. En raison du risque de stimulation du développement de maladies utérines et du potentiel d’induction de l’anémie aplastique, il est préférable d’éviter l’utilisation des œstrogènes chez les chiens dans la mesure du possible. Cet article décrit les causes de myélotoxicité induite par les œstrogènes, la présentation clinique des patients, le diagnostic et les options de traitement pour le chien.

(Traduit par Isabelle Vallières)


Introduction

For many decades, estrogens or synthetic estrogenic compounds have been used in female dogs for the treatment of mismating (1), hormonal urinary incontinence (2), estrus induction (3), or pseudopregnancy (4), and in male dogs for the management of prostatic hypertrophy, perianal adenoma, or testicular neoplasms (5). Development of estrogen-induced myelotoxicity (EIM) and pyometra following the use of estrogens for the management of diseases (6–11) and for experimental purposes have been reported previously (12–16). Furthermore, similar spontaneous myelopoietic damage to bone marrow has been demonstrated in male dogs with testicular tumors of interstitial cell (17) and sertoli cell (18), and in females with ovarian granulosa cell tumor (19).

Clinical signs of EIM include complete loss of appetite, depression, pale mucous membranes, petechial hemorrhages, uni- or bi-lateral epistaxis, vulvar edema, and vaginal bleeding (6–19,20). Typical hematologic changes are nonregenerative anemia, thrombocytopenia, and leukocytosis followed by a leukopenia. Diagnosis of EIM is based on a history of estrogen administration, physical examination, clinical signs, and hematologic findings. Treatment options vary with the cause of the myelotoxicity and include removal of potential estrogen sources, frequent whole blood transfusions or platelet-rich plasma infusions, antibiotics, androgens, corticosteroids and bone marrow stimulants. In untreated dogs, prognosis is always considered to be unfavorable despite early diagnosis. In this paper, etiology, pathophysiology, clinical presentation, diagnosis, and treatment options for estrogen-induced myelotoxicity in the bitch are reviewed.

Estrogens

Estrogens are steroid compounds, synthesized primarily by the ovaries, and to a lesser extent by the testicles, adrenal cortex, and placenta. Other sites of estrogen production include liver, muscle, fat, and hair follicles (5). The immediate precursors to the estrogens are androstenedione or testosterone, and estradiol.
17-β and estrone are the main endogenous estrogens in most species (21). Estrogens are necessary for many physiological actions in the body including: normal growth and development of female gonads; development of secondary sexual characteristics including duct growth of the mammary glands, changes in body conformation and hair growth; production of clinical signs of estrus; normal contractility of the uterus; promotion of bactericidal activity of the uterus during estrus by increasing the rate of migration of leukocytes into the uterine lumen; sensitization of the uterine muscle to oxytocin; relaxation of the pelvic structures, softening of the pubic symphysis and enlargement of the general perineal area during parturition; regulation of skeletal growth and maintenance of the skeleton; vasostimulation and health of the skin; and increasing the coagulability of the blood.

Natural estrogens such as estradiol, estrone, and estriol are produced from natural sources such as the urine of pregnant mares and women, the adrenals and testes of stallions, and the human placenta and amniotic fluid (21). Synthetic estrogens exerting the same effect as natural estrogens including diethylstilbestrol (DES), ethinyl estradiol, and esters of estradiol such as benzoate, cypionate, propionate, valerate, enanthate, and undecynate are produced from coal-tar derivatives and other steroids (21). Clinical use of estrogens in humans and dogs is given in Table 1.

In small animal practice, immediate treatment of unwanted matings is the most common reason for the administration of estrogens, which prevent conception by closure of the tubal-uterine junction or their effect on the oviduct and uterus (22). Today, the use of estrogens for mismating is no longer recommended because 1) uterine disturbances including pyometra may develop; 2) most mismated dogs are reported to be nonpregnant at the time of examination; 3) availability of progesterone-receptor blockers such as aglepristone that enable clinicians to terminate pregnancies during any stage of gestation with less side effects; 4) safe and efficacious doses of estrogens do not exist; and 5) fatal myelotoxicity due to the administration of estrogens has been reported. However, a study by Tsutsui (23) demonstrated that a single treatment of estradiol benzoate at 0.2 mg/kg on day 5 post-ovulation effectively prevented pregnancy without causing any side effects. Tsutsui et al (23) indicated that side effects would be more common in animals treated with repeated administration of estradiol benzoate.

Pathophysiology of estrogen-induced myelotoxicity

Early studies in the 1940’s clearly demonstrated the myelotoxic effects of exogenous estrogens in dogs (12,13). After the use of estrogens, neutrophil production increases in the bone marrow, resulting in an increase in white blood cells in the peripheral blood and a left shift. Leukocytosis is followed by leukopenia, but persists until day 21 (12,13,24). According to Chiu (25), the effects of estrogens on the hematopoietic system occurs in 3 stages. Stage 1 (days 0–13) is associated with a brief increase in platelet numbers followed by a severe thrombocytopenia. Stage 2 (days 13–20) is characterized by bone marrow granulocyte hyperplasia with neutrophilia. Stage 3 (days 21–45) may be associated with marrow recovery or marrow aplasia depending on the dose used. The mechanism of EIM is not fully understood, but studies have confirmed estrogen-induced production of a myelopoiesis-inhibitory factor by thymic stromal cells of dogs in vitro (26) and in vivo (27).

Exogenous estrogens administered at excessive or repeated doses or at recommended dosages to dogs with idiosyncratic sensitivity and estrogen-producing ovarian or testicular neoplasms induce toxicity (10,17–19). However, most of the reported cases had an over-dosage of estrogens. In the reported cases, myelotoxicity was associated with administration of estradiol cypionate, estradiol benzoate or diethylstilbestrol in excess of or at the recommended doses (6–11). The response of the bone marrow to estrogens varies from one dog to another, because some dogs may have fatal bone marrow suppression, whereas others have only mild to moderate damage after the administration of the same dose (13). This individual sensitivity does not depend on breed, nutrition, route of administration, or the reason for use of the drug but it is highly correlated with age, type of estrogen used, total dose, and physical condition of the animal (6,13). A summary of the previously reported cases is given in Table 2.

### Clinical signs

Due to the individual sensitivity to estrogens, clinical signs may vary from completely normal to collapse. The affected animals may show complete loss of appetite, exercise intolerance, vulvar edema, vaginal bleeding, pallor, dyspnea, hematuria, melena, fever, unii- or bi-lateral epistaxis, and petechiation of the skin or mucous membranes (6–11,15,16,28). Less common clinical signs include edema around the mouth and perineal area, alopecia, mammary hypertrophy, head tilt, bilateral nystagmus, signs of feminization in males and estrus behavior and coitus with failure to conceive in females. Furthermore, development of type III vaginal prolapse has been recently reported in a young, 40-kg, cross-breed dog which had a 24-h history of estradiol benzoate administration at a dose of 0.3 mg/kg for estrus induction (29). Clinical signs including vulvar discharge, abdominal distention, vomiting, polyuria, and polydipsia may be observed, if pyometra is also induced by estrogen administration (30).

### Diagnosis

Diagnosis is based on the history of estrogen administration, clinical symptoms, physical examination findings, laboratory analysis, and bone marrow cytology (6). A complete blood (cell)
count after estrogen administration demonstrating nonregenerative anemia, thrombocytopenia and leukocytosis (until week 3) may aid in confirming the diagnosis. Although the history of estrogen administration, clinical signs, and laboratory findings are sufficient to establish the diagnosis, abdominal radiography or ultrasonography should be performed for locating and staging estrogen-producing tumors and for diagnosis of pyometra, if the physical condition of the affected animal allows. Examination of bone marrow aspirate may be performed to support the diagnosis and to evaluate the prognosis. Necrotic lesions and an inflammatory response have been demonstrated in the bone marrow of dogs receiving high doses of estrogens (13). In an advanced stage, bone marrow biopsy may reveal hypopcellularity with depletion of all hematopoietic cell lines. Differential diagnosis of EIM includes other conditions that cause pancytopenia such as toxins, drugs, infection, neoplasia, immune-mediated diseases, myelodysplasia, bone marrow necrosis, osteosclerosis, and myelofibrosis (31).

Table 2. Characteristics of previously reported cases of estrogen-induced myelotoxicity in bitches

<table>
<thead>
<tr>
<th>Reference</th>
<th>Breed</th>
<th>Age (y)</th>
<th>Reproductive status</th>
<th>BW (kg)</th>
<th>Drug/Dose</th>
<th>Route, Frequency</th>
<th>Reason for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Cross-bred shepherd</td>
<td>6</td>
<td>intact</td>
<td>57</td>
<td>ECP/10 mg</td>
<td>IM, once</td>
<td>mismating</td>
</tr>
</tbody>
</table>
| 6         | St. Bernard | 4         | intact | NS  | a) ECP/10 mg  
|           |         |           |       | b) DES/90 mg | a) IM, 2 times 1 wk apart  
|           |         |           |       |       | b) 50 mg, IM once + 5 mg PO, q24h for 8 d | infertility |
| 8         | NS      | NS       | NS      | NS  | ECP/0.22 mg/kg | IM 2 times at 21 d interval | urinary incontinence |
| 8         | NS      | NS       | NS      | NS  | ECP/0.08 mg/kg | IM 2 times at 15 d interval | urinary incontinence |
| 8         | NS      | NS       | NS      | NS  | NS | IM once | mismating |
| 9         | Airdale terrier | 4         | intact | 20  | ECP/2 mg | IM 3 times at 48- to 72-hour interval | mismating |
| 10        | Old English sheepdog | 6         | spayed | 28  | a) DES/18 µg/kg  
|           |         |           |       | b) DES/36 µg/kg  
|           |         |           |       | c) ECP/0.14 mg/kg | a) PO, q24h for 15 mo  
|           |         |           |       |       | b) PO, q12h for 3 wk  
|           |         |           |       |       | c) IM 2 times at 1 wk intervals | urinary incontinence |
| 11        | Glen of Imaal terrier | 2         | intact | NS  | EB/10 µg/kg | SC 3 times at 2–3 d intervals | mismating |
| 20        | Poodle | 2         | intact | 3.6  | ECP/1 mg | IM 2 times at 1 wk intervals | mismating |

NS — not specified, ECP — estradiol cypionate, DES — diethyl stilbesterol, EB — estradiol benzoate, IM — intramuscular, SC — subcutaneous, PO — per os.

Table 3. Summary of treatment and outcomes of cases of estrogen-induced myelotoxicity in bitches

<table>
<thead>
<tr>
<th>Reference</th>
<th>Delaya</th>
<th>Hematologic findings</th>
<th>Clinical signs</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>14</td>
<td>Anemia, leukocytosis, thrombocytopenia</td>
<td>Petechial hemorrhages, lethargy, decreased appetite</td>
<td>Corticosteroids, antibiotics, whole blood transfusions</td>
<td>Died 16 d after administration of ECP (2 days after diagnosis)</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>Leukocytosis</td>
<td>Vulvar swelling, vaginal discharge</td>
<td>Antibiotics</td>
<td>Full recovery in 90 d</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>Leukopenia, thrombocytopenia</td>
<td>Cutaneous ecchymotic hemorrhages</td>
<td>No treatment</td>
<td>Euthanized</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>Leukopenia, thrombocytopenia</td>
<td>Vulvar swelling</td>
<td>Platelet-rich plasma transfusions</td>
<td>Full recovery in 70 d</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>Anemia, leukocytosis, thrombocytopenia</td>
<td>Bloody vulvar discharge</td>
<td>No treatment</td>
<td>Euthanized</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>Anemia, thrombocytopenia, leukopenia</td>
<td>Lethargy, anorexia, fever, ocular discharge, lameness, vaginal discharge</td>
<td>Fresh blood, antibiotics, vitamin-mineral supplement, anabolic steroid</td>
<td>Full recovery in 81 d</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>Anemia, leukopenia, thrombocytopenia</td>
<td>Lethargy, vaginal discharge, attraction to male dogs</td>
<td>Antibiotics, vitamin-mineral supplement, lithium carbonate</td>
<td>Full recovery in 42 d</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>Anemia, thrombocytopenia, leukocytosis</td>
<td>Collapse</td>
<td>Fluid therapy, whole blood transfusion, platelet-rich transfusion, antibiotics</td>
<td>Full recovery in 14 d</td>
</tr>
<tr>
<td>20</td>
<td>21</td>
<td>Anemia, thrombocytopenia, normal leukocyte count</td>
<td>Hematuria, uncoordination, head tilt, scleral hemorrhage</td>
<td>Corticosteroids, antibiotics, vitamin-mineral supplement, platelet-rich plasma, lithium citrate</td>
<td>Full recovery in 48 d</td>
</tr>
</tbody>
</table>

a Days between estrogen administration and presentation. ECP — Estradiol cypionate.
**References**


