

Estriolium Treatment in the Bitch: A Risk for Uterine Infection?

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Contents

Purulent vaginal discharge in a bitch in which ovariohysterectomy has been performed is often caused by inflammation of the uterine stump. The inflammation is due to either cystic endometrial hyperplasia (CEH) induced primarily by progesterone from remnant ovarian tissue or exogenous progestagens, or it is due to the presence of unabsorbed suture material. This report describes a 9-year-old Irish setter with hemopurulent vaginal discharge and non-pruritic symmetrical alopecia, which had undergone ovariohysterectomy 3.5 years ago and which had been treated with estriolium daily for the past 2.5 years because of urinary incontinence. Vaginoscopy revealed hemopurulent discharge throughout the vagina and vestibule. Cytological examination of ultrasound-guided fine-needle aspiration biopsies of a large mass in the hypogastricum, which appeared to be the uterine cervical stump, revealed septic purulent inflammation. The concentration of plasma progesterone was low and the concentration of plasma 17- β oestradiol did not increase after gonadotrophin-releasing hormone administration. No remnant ovarian tissue was found by abdominal ultrasonography, laparotomy, or histological examination of mesovarian pedicles. Laparotomy revealed uterine stump empyema. Histological examination of the surgically removed mass excluded both CEH and unabsorbed suture material as the cause of the stump empyema. Instead, it is hypothesized that the long-term treatment with estriolium was a causative factor. This suggests that bitches treated with estriolium should be examined regularly.

Introduction

In intact bitches, purulent vaginal discharge independent of urination is most often due to disorders in the genital tract, such as cystic endometrial hyperplasia (CEH)-endometritis, postpartum metritis, vaginitis, or neoplasia. In bitches in which ovariohysterectomy has been performed, purulent vaginal discharge is often seen with the inflammation of post-ovariohysterectomy remnant endometrial tissue, also known as the uterine stump. The inflammation can be related to the remnant ovarian tissue or to unabsorbed suture material (Okkens et al. 1981). For the remnant ovarian tissue, the pathogenesis is believed to be similar to that of endometritis in the intact bitch, in which either endogenous progesterone or exogenous progestagens play an important role (Teunissen 1952; Dow 1958; Capel-Edwards et al. 1973). If preceded by oestrogen influence, such as occurs during the follicular phase, the effects of progestagens on the endometrium are enhanced (Dow 1958), probably due to an oestrogen-induced increase in the number of progesterone receptors (Lessey et al. 1981; Dhaliwal et al. 1997). Progestagens can cause hyperplasia and cystic transformation of the endometrial glands, known as CEH (Teunissen 1952; Dow 1957, 1958, 1959). When

CEH is accompanied by bacterial infection, which may easily develop during the follicular, ovulatory, and fertilization phase, endometritis may develop (Schaefer-Okkens 1996). Removal of the hormonal influence by ovariectomy may result in regression of the endometritis (Teunissen 1952; Dow 1958, 1959). If ovariectomy is performed when the uterus is normal, endometrial tissue remains quiescent in the absence of sex-steroid hormone influence (Okkens et al. 1997).

Urinary incontinence develops in 5.1–20% of bitches following ovariectomy or ovariohysterectomy (Arnold et al. 1989; Okkens et al. 1997; Thrusfield et al. 1998; Angioletti et al. 2004). Treatment with sympathicomimetics is successful in 75–95% of the cases (Arnold et al. 1989; White and Pomeroy 1989; Carofiglio et al. 2006), while in 65–75% of cases there is good response to treatment with oestrogens (Arnold et al. 1989; Janszen et al. 1997). Oestrogens, such as estriolium increase urethral closure and the bladder-storage function, thereby contributing to urinary continence (Nickel 1998). The side-effects of estriolium reported by the manufacturer include oestrous behaviour, swelling of the vulva and mammae, and, rarely, bloody vaginal discharge and alopecia (Mandigers and Nell 2001). Bone-marrow depletion in the bitch has been associated with the use of oestrogens, such as oestradiol benzoate, oestradiol cypionate, and diethylstilbesterol (Castrodale et al. 1941; De Schepper et al. 1977; Teske and Feldman 1984), but has not been reported for estriolium (Nickel 1998; Mandigers and Nell 2001; Hoeijmakers et al. 2003). Recently, the effect of gonadotrophin-releasing hormone (GnRH) analogues on urodynamic parameters and urinary incontinence has gained interest (Ponglowhapan et al. 2007; Reichler et al. 2006).

This report concerns the development of uterine stump empyema following long-term treatment with estriolium in a bitch in which ovariohysterectomy had been performed.

Materials and Methods

Dog

A 9-year-old neutered Irish setter was presented with purulent and bloody vaginal discharge and non-pruritic symmetrical alopecia in the flanks (Fig. 1). Following ovariohysterectomy 3.5 years before this, the dog developed urinary incontinence, probably due to sphincter incontinence, and it responded well to estriolium (Incurin®; Intervet Int., Boxmeer, The Netherlands), 1 mg/day. After 1 year of treatment with estriolium, the dog developed intermittent bloody vaginal discharge. Thirty

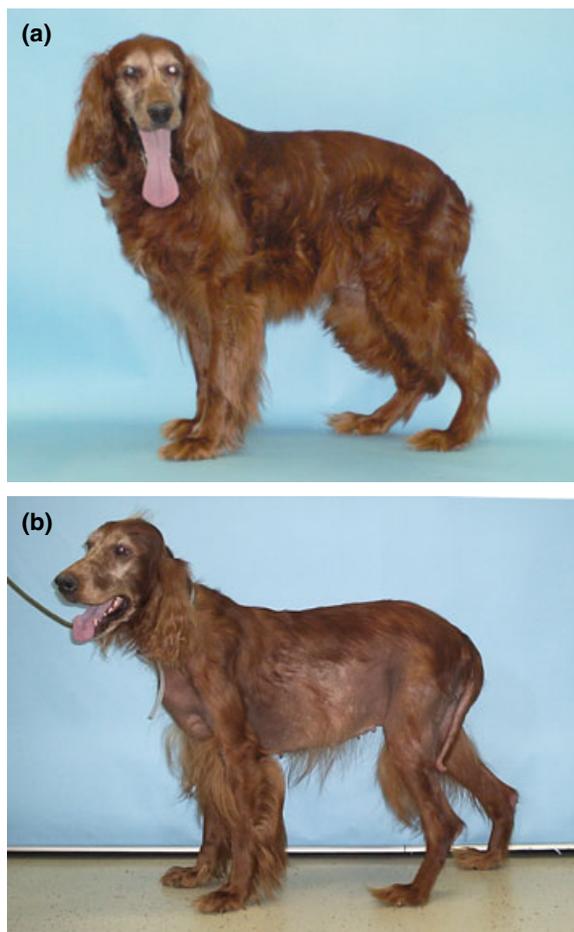


Fig. 1. The 9-year-old Irish setter, (a) with prominent alopecia of the flank, hind legs, and tail, after 2.5 years of daily treatment with estriolium for urinary incontinence, and (b) with regrowth of hair by the time of follow-up 8 months after estriolium was stopped

months after the initiation of estriolium treatment the dog was referred to this department because of hemopurulent vaginal discharge.

Diagnostic imaging

Abdominal ultrasonography was performed with the dog in dorsal recumbency, using an ultrasound unit (HDI 5000, Advanced Technology Laboratories/Philips, Eindhoven, The Netherlands), equipped with an 8.5 MHz broadband microconvex transducer.

Hormone determination

Plasma progesterone concentration was measured using a I-RIA, validated for the dog (Okkens et al. 2001). Intra- and interassay coefficients of variation were 6% and 10.8%, respectively. The sensitivity was 0.15 nmol/l.

Plasma 17- β oestradiol concentration was measured using a solid-phase RIA (Count-A-Count TKE; Diagnostic Products Corporation, Los Angeles, CA, USA) according to the manufacturer's instructions with modifications, as described previously (Dieleman and Schoenmakers 1979) and validated for the dog (Van

Haafte et al. 1994). The intra- and interassay coefficients of variation were 14% and 11.8% respectively. The sensitivity was 7 pmol/l.

GnRH stimulation test

The GnRH stimulation test was performed by intravenous administration of buserelin (Receptal®; Intervet Int., Boxmeer, The Netherlands), an equivalent of naturally occurring GnRH, in a dose of 0.4 μ g/kg body weight. Blood for determination of plasma 17- β oestradiol concentrations was collected in heparinized tubes at 40 and 0 min before and 60 and 120 min ($T = -40, 0, 60, 120$) after administration of buserelin (Rijnberk 1996; Buijtelts et al. 2006)

Histopathology

Tissue specimens from the uterine stump and the mesovarian pedicles were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections were cut at 4 μ m and stained with haematoxylin and eosin.

Results

General examination revealed non-pruritic symmetrical alopecia of the flanks and a hemopurulent vaginal discharge. Vaginoscopy revealed a hyperemic mucosa and hemopurulent exudate throughout the vagina and vestibule. There was no vaginal tumour. Laboratory examination revealed leukocytosis (21.7×10^9 cells/l, of which 17.8×10^9 cells/l were segmented neutrophils) but no biochemical abnormalities apart from increased serum total protein concentration (85 g/l, reference range 55–72 g/l) due to increased globulins [α 2-globulins 16 g/l (reference range 4–13 g/l), β 2-globulins 11 g/l (reference range 4–10 g/l), and γ -globulins 13 g/l (reference range 3–9 g/l)], consistent with an inflammatory process.

The concentration of plasma progesterone was 1.0 nmol/l. The concentration of plasma 17- β oestradiol at 40 and 0 min before and 60 and 120 min after intravenous administration of buserelin was 23.9, 28.5, 20.6 and 14.2 pmol/l, respectively.

Abdominal ultrasonography revealed a mass in the area of the uterine stump, 3.6 cm in diameter and containing several cavities (Fig. 2). No remnant ovarian tissue was observed. Cytological examination of fine-needle aspiration biopsies of the mass revealed septic, purulent inflammation.

Treatment consisted of abdominal surgery to remove the uterine stump, and mesovarian pedicles, followed by administration of amoxicillin with clavulanic acid. No remnant ovarian tissue was found during the surgery. Histological examination of the surgically removed uterine stump revealed pyogranulomatous inflammation with infiltration of macrophages, neutrophils, lymphocytes, and plasma cells in the endometrium, myometrium and parts of the perimetrium. The endometrial glands were inflamed and were lined by low cuboidal epithelium. There was no evidence of CEH (Fig. 3). The cavity of the uterine stump was filled with pus. Histological examination of the mesovarian pedicles revealed

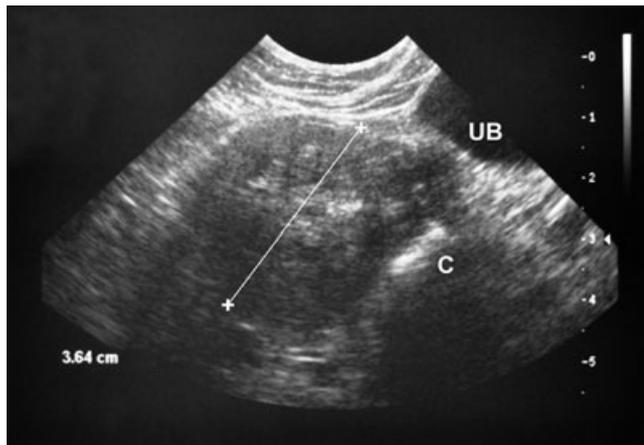


Fig. 2. Transverse ultrasonographic image of the caudal abdomen. The heterogeneous mass 3.6 cm in diameter ventral to the colon (c) and dorsal to the urinary bladder (UB) is the uterine stump. Cytological examination of fine-needle aspiration biopsies of the mass revealed septic, purulent inflammation

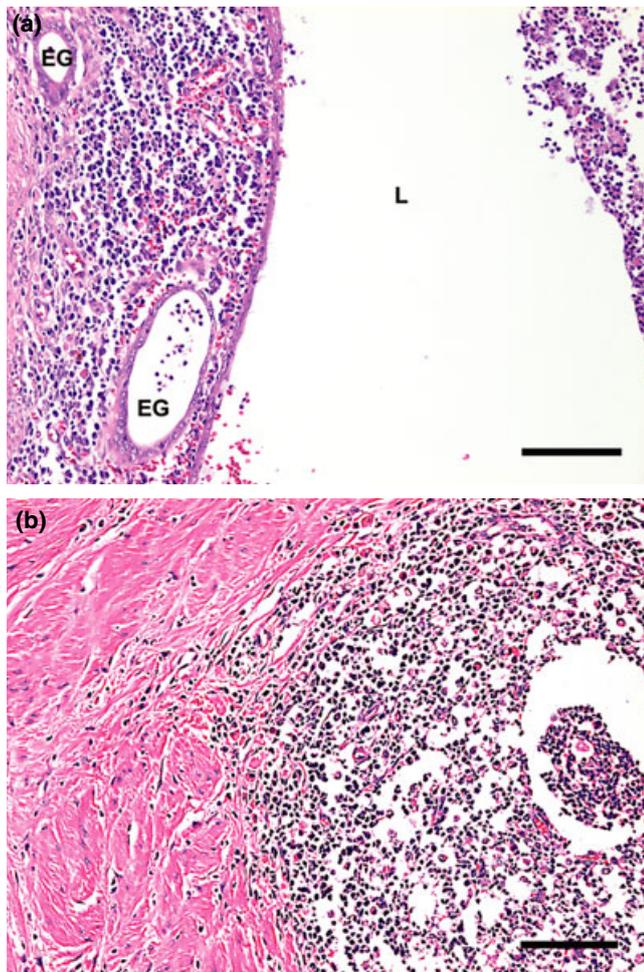


Fig. 3. The uterine stump: pyogranulomatous inflammation with macrophages, neutrophils, lymphocytes, and plasma cells in the endometrium (a), myometrium (b), and perimetrium. The endometrial glands are inflamed and lined by low cuboidal epithelium (a). There is no evidence of CEH. L, lumen, EG, endometrial gland. H & E. Bar = 100 μ m

no remnant ovarian tissue. The final diagnosis was uterine stump empyema.

Following surgery and antibiotic therapy, the hemopurulent vaginal discharge ceased and there was complete regrowth of hair by the time of the follow-up examination 8 months later (Fig. 1). The leucocyte count was normal (11.2×10^9 leucocytes/l, of which 8.7×10^9 cells/l were segmented neutrophils), and serum total protein concentration had also returned to normal (69 g/l, reference range 55–72 g/l). The concentration of plasma 17- β oestradiol was 14.5 pmol/l.

Although therapy for urinary incontinence was discontinued, urinary incontinence did not recur.

Discussion

The dog described here was presented with hemopurulent vaginal discharge and bilateral alopecia after receiving estriol daily for 2.5 years because of urinary incontinence. The most frequent cause of purulent vaginal discharge in neutered bitches is inflammation of remnant endometrial tissue after ovariohysterectomy, following CEH, associated with hormone production by remnant ovarian tissue (Okkens et al. 1981). The cervical canal is much shorter than it appears to be during laparotomy, because the horizontal extension of the cervix is covered with endometrial villi and is thus, in fact, the caudal part of the uterus (Schaefer-Okkens 1996). This is often the reason that the removal of all the endometrium during ovariohysterectomy is unsuccessful. The presence of the remnant ovarian tissue can be confirmed by the finding of a plasma progesterone level > 3 nmol/l (> 1 ng/ml) after ovariectomy or ovariohysterectomy (Okkens et al. 1981). However, the remnant ovarian tissue is not excluded by the finding that plasma progesterone does not exceed 3 nmol/l, as in this case, for a low-plasma progesterone level is also found in the bitch in anoestrus (Okkens et al. 1985; Van Haften et al. 1994; Buijtelts et al. 2006). When the ovarian tissue is present, the intravenous administration of synthetic GnRH causes an increase in level of circulating 17- β oestradiol (Buijtelts et al. 2006) and the absence of such a response in this case excluded the presence of the remnant ovarian tissue.

The mean prestimulatory plasma 17- β oestradiol concentration (26.2 pmol/l) in this dog was higher than reported by Nickel (1998) or by Buijtelts et al. (2006), in both studies, the solid-phase RIA was the same as used in this case (Buijtelts et al. 2006). The higher 17- β oestradiol concentration in this dog might be partly explained by the intra- and interassay variation of the RIA and by interindividual variation. However, the main reason is probably the cross-reaction of estriol in the RIA for 17- β oestradiol. The manufacturer (Diagnostic Products Corporation), states that this cross-reaction is 0.32%, which implies that 1000 pmol/l estriol accounts for 3.2 pmol/l of the measured 17- β oestradiol. Hoeijmakers et al. (2003) reported that daily treatment of dogs with 2-mg estriol resulted in plasma estriol concentrations of 715–3914 pmol/l. A steady level was reached after 2 days and no accumulation occurred during the 7 days of treatment (Hoeijmakers et al. 2003). Taking these results into

account, cross-reaction of estriolium cannot completely explain the increased plasma 17- β oestradiol in the dog described here. Therefore, this case might suggest that accumulation of estriolium may occur when treatment is longer than 7 days (Hoeijmakers et al. 2003). Eight months after the cessation of the estriolium treatment, the basal plasma 17- β oestradiol concentration was 14.5 pmol/l and was within normal limits as described by Nickel (1998).

Histological findings in endometritis due to hormonal influence from the remnant ovarian tissue are consistent with those in CEH-endometritis in the intact bitch (Teunissen 1952; Dow 1958). These pathological findings are characterized by hyperplastic and cystic endometrial glands lined by high cuboidal epithelial cells, reflecting the influence of progesterone, and infiltration of neutrophils, plasma cells, and lymphocytes in endometrium and myometrium (Dow 1957, 1958). Histological examination of the uterine stump of this dog revealed pyogranulomatous inflammation in the endometrium, myometrium, and perimetrium, but no hyperplastic or cystic endometrial glands. Instead, the glands were lined by low cuboidal epithelium, indicating that the influence of progesterone and/or CEH did not play a role in the pathogenesis of the uterine stump empyema.

The lack of an increase in plasma 17- β oestradiol concentrations after GnRH administration, the absence of remnant ovarian tissue confirmed by abdominal ultrasonography, laparotomy, and histological examination of mesovarian pedicles, and the histological findings in the uterine stump indicate that the uterine stump empyema in this dog was probably not related to the endogenous sex-steroid hormone influence. Consequently, a different pathogenesis had to be considered.

In 1981, Okkens et al. (1981) described a group of 54 dogs with vaginal discharge after ovariectomy or ovari-hysterectomy. A majority of these cases (47 dogs) had remnant ovarian tissue and CEH-endometritis. Seven of the dogs had neither remnant ovarian tissue, nor CEH. In these seven dogs, unabsorbed suture material in the uterine stump was found to be the cause of the inflammation (Okkens et al. 1981). In this case, however, no suture material was found in the uterine stump during surgery or by histopathological examination.

Since unabsorbed suture material or remnant ovarian tissue leading to CEH could be excluded as the cause of the uterine stump empyema in this bitch, we hypothesize that the long-term treatment with estriolium was the cause of both the stump inflammation and the symmetrical alopecia. Estriolium has several oestrogenic effects, such as the promotion of growth, vascularity, and edema of the endometrium and dilatation of the cervix (Andersen 1970; Barrau et al. 1975; Van Cruchten et al. 2004). In addition, bloody vaginal discharge has been reported as a side-effect of treatment with estriolium (Mandigers and Nell 2001). Oestrogens can also induce glandular epithelial proliferation, but long-term exposure causes endometrial gland atrophy (Dow 1959). In this case the dog was continuously subjected to the influence of estriolium for over 2.5 years. The oestrogen-induced dilatation of the cervix might have increased the risk for ascending bacterial infection (Watts et al. 1996).

In addition, the oestrogenic effects of estriolium may have increased the sensitivity of the endometrium to infection and may have optimized the genital tract for bacterial growth.

Non-pruritic, symmetrical flank alopecia is often due to an endocrine disorder. Hyperestrogenism causes bilaterally symmetric alopecia and easily epilated hair due to follicular atrophy and telogenization of the hair cycle (Scott et al. 2001). Moreover, alopecia has been reported by the manufacturer as a very rare side-effect of estriolium. In this case, regrowth of hair had occurred by 4 months after cessation of estriolium administration, suggesting that the alopecia was due to estriolium treatment. The occurrence of alopecia may demonstrate the sensitivity of the dog to estriolium. Since older dogs are more susceptible than younger dogs to the side-effects of oestrogens (Teske 1986), age may have contributed to the sensitivity of this 9-year-old Irish setter to estriolium.

Oestrogen-toxicity due to oestradiol benzoate, oestradiol cypionate, or diethylstilbesterol is known to result in bone marrow depletion (Castrodale et al. 1941; De Schepper et al. 1977; Teske and Feldman 1984; Teske 1986). In this dog, however, the leucocyte count was not decreased, although hyperestrogenism was present due to the long-term treatment with estriolium. Thus far, estriolium has not been associated with bone marrow depletion (Nickel 1998; Mandigers and Nell 2001; Hoeijmakers et al. 2003).

In conclusion, urinary incontinence occurs in a substantial percentage of bitches following ovariectomy or ovariohysterectomy. If estriolium is used for treatment, it is advisable to perform regular medical check-ups including leukocyte count, vaginoscopy, and abdominal ultrasonography, because of the possible side-effects of long-term estriolium treatment such as inflammation of the remnant uterine tissue.

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