A 13-year-old, 4.54-kg (10-lb) spayed female domestic medium-hair cat presented with a 1-day history of typical signs of estrus.

HISTORY

- **Behavior:** The owner reported unusual behavior that included roaming throughout the house, loud vocalization, and increased affection; however, the cat had been spayed as a kitten, with no history of this recent behavior.

- **Clinical signs:** The owner also noted that the cat had recently exhibited decreased appetite and thirst but was unable to recall changes in urine output.

- **Environment:** The cat was housed exclusively indoors and fed commercial dry cat food. There was no history of travel.

- **Medical history:** The cat was current for core vaccinations, tested negative for retroviruses as a kitten, and received only monthly parasite preventive medications.

INITIAL DIAGNOSTICS & THERAPY

**Physical Examination**
The cat had a body condition score of 4/9, with a consistent weight history over the past year. Rectal temperature, heart rate, and respiratory rate were within normal limits. Abdominal palpation and examination of external genitalia were unremarkable; no vaginal discharge was observed.

**Laboratory Analysis**
The initial laboratory database included a complete blood count, serum biochemistry, electrolytes, total thyroxine (T₄), and urinalysis and culture. The only abnormalities were:

- Mild creatinine elevation (2.2 mg/dL; reference range, 0.3–2.1 mg/dL)
- Mild hematuria.

**Imaging**
Ultrasound of the urinary bladder did not reveal masses, uroliths, or thickening or irregularity of the bladder wall.

**Therapeutic Plan**
A diagnosis of urinary tract infection was considered pending culture results, and an empirical trial of marbofloxacin (25 mg PO Q 24 H for 10 days) was initiated. The owner was instructed to report if no improvement was observed within 72 hours.

**ADDITIONAL DIAGNOSTICS**
Four days later, the cat was presented again with continued signs of estrus. According to the owner, no improvement in the cat’s behavior had been observed.

Physical examination findings were unremarkable. The urine culture exhibited no aerobic bacteria growth at 72 hours.

**Hormone Analysis**
Because increased estrogen levels trigger a negative feedback mechanism that results in reduced luteinizing hormone (LH) levels, a serum sample was submitted for LH analysis. Results were < 1 ng/mL, suggesting the presence of an endogenous or exogenous source of estrogen.

**Imaging**
**Abdominal radiography** revealed no abdominal masses. **Ultrasonographic evaluation** of the abdomen (by a board-certified veterinary radiologist) revealed no evidence of ovarian tissue. The left adrenal gland was of normal size (3.7 × 8.4 mm) and architecture; the right adrenal gland was not found.

One week following initial presentation, the cat was still exhibiting signs of estrus.

**QUESTION:** What are the differential diagnoses for this case? Considering the information provided, what differential diagnoses would you pursue?
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At this point—1-week following initial presentation—the owner disclosed that she was prescribed transdermal hormone replacement therapy (HRT) containing estradiol, progesterone, and dehydroepiandrosteron (DHEA) in emu oil. The owner described a daily routine of applying the cream to her forearms and, shortly thereafter, picking up and cradling the cat for several minutes. The owner began using the medication approximately 12 days before the cat’s initial presentation to the clinic.

Final Diagnostics
Following this disclosure, serum estradiol analysis was performed because estradiol was a component of the owner’s HRT and, most likely, the cause of the cat’s estrous-like behavior. The patient’s serum estradiol was measured at 71.06 pg/mL (reference ranges: < 15 pg/mL for a spayed cat, < 20 pg/mL for pregnant queen or queen in diestrus, and 25–50 pg/mL for queen in proestrus or estrus).

Treatment
A therapeutic trial of megestrol acetate (5 mg PO Q 24 H) was initiated because this drug has been used to terminate estrus. Megestrol is a synthetic progestin that exerts an inhibitory effect on the secretion of pituitary gonadotropins.

Two days later, the cat’s signs of estrus were resolved and therapy was discontinued.

Follow-Up
Recheck examinations performed 18, 36, and 90 days post megestrol treatment revealed serum estradiol concentrations of 32.4 pg/mL, 35.6 pg/mL, and 20.4 pg/mL, respectively.

The pharmacokinetics of estradiol in companion animals are largely unknown. Estrogens and their metabolites accumulate in adipose tissue, are excreted into urine and bile, and those in bile are reabsorbed by the gastrointestinal tract, which may explain the persistent, increased estrogen levels observed in this case.

Case Conclusion
The owner is currently using a sublingual route of HRT administration to eliminate exposure of the cat to the medication. According to the owner, all previously reported signs of estrus have resolved, and the patient has not exhibited any signs for over 12 months.

Differential diagnoses to consider include:
- Exposure to exogenous estrogens
- Increased production of sex hormones (due to pathology of the zona reticularis of the adrenal cortex)
- Ovarian remnant syndrome
- Presence of accessory ovaries (congenital anomaly)
- Adrenocortical carcinoma (which was recently reported to cause estrous-like behavior in a spayed female cat).

A weakness in this case’s workup was failure to visualize the right adrenal gland on ultrasound. An estrogen secreting tumor could have been missed if one was present.

When a cat’s right adrenal gland is healthy, it is difficult for even board-certified radiologists to identify; however, the presence of an adrenal tumor increases the organ’s size, which makes it easier to locate.

We believe that the presence of an adrenal tumor can be ruled out because the cat remained estrus-free for 12 months following discontinuation of the owner’s transdermal hormone use.

Hyperestrogenism and estrogen toxicity in pets due to exposure to human HRTs are a growing veterinary medical concern.

More than 100 suspected cases are reported anecdotally, with most involving canine patients. Despite the existence of this phenomenon, we are aware of but 1 single case reported in the literature. To our knowledge, no feline cases have been reported.
Human Risks
The danger of exposing children and other family members to HRTs has been acknowledged and was explained to the owner by her physician. Awareness of the issue has increased due in part to recent attention by the United States Food and Drug Administration. 6, 7 However, physicians typically do not warn patients about the potential dangers of exposing pets to these hormones.

Companion Animal Risks
Chronic exposure to high doses of endogenous estrogens is toxic to mammals. Susceptibility to estrogen toxicity in cats is greater than it is in dogs, ferrets, rats, and mice. 8

Prolonged hyperestrogenism in the cat is associated with: 9, 10
• Steroid alopecia
• Mammary tissue growth
• Hepatic pathology
• Pancreatic hypertrophy
• Pancytopenia.

As in the bitch, cats may be at risk for coagulopathies and stump pyometra secondary to pancytopenia induced by hyperestrogenism.

Diagnosis of Estrus
Diagnosis of exposure to exogenous estrogens and subsequent hyperestrogenism in the feline patient is complicated by the difficulties in detecting estrus in the species.

Dogs Versus Cats. In the bitch, estrus is diagnosed by several distinct signs, including vulvar enlargement, vaginal hemorrhage, and perivulvar alopecia. However, the feline vulvar labia do not respond to estradiol and, therefore, do not typically change appearance during estrus as in the bitch. 10

Feline Behavior. Feline behavioral signs, such as rolling, head rubbing, hindlimb treading, posturing, vocalization, and permitting mounting by male cats, are generally the only indication of estrus in queens. 11 Although these changes may be quite dramatic in some individuals, in others, they may be difficult to distinguish from normal affectionate behavior.

Vaginal Cytology. Estrus in the bitch is easily confirmed by vaginal cytology, but it is not a routine diagnostic tool used in feline medicine given the anatomic limitations of the feline vagina. 10

Diagnostics in this Case
One could take the position that vaginal cytology should be performed in cats with the history and clinical signs seen in this case. It could even be argued that it was a significant oversight. However, we chose not to perform vaginal cytology based on its cited limitations. 10 Instead, documentation of very elevated serum estradiol concentrations confirmed that the clinical signs were due to estrus.

To eliminate any doubts regarding the cause of this patient’s signs, a trial of re-exposure to the transdermal cream with documentation of identical signs would be ideal, however, impractical. Further testing for potential ovarian remnant syndrome with GnRH-induced ovulation and subsequent measurement of serum progesterone was declined by the owner due to resolution of clinical signs.

DHEA = dehydroepiandrosterone; HRT = hormone replacement therapy; LH = luteinizing hormone

References

Gary D. Norsworthy, DVM, Diplomate ABVP (Feline), is the owner of Alamo Feline Health Center in San Antonio, Texas, where he practices full time. His 40 years of private practice include 15 years specializing in feline medicine. Dr. Norsworthy also holds adjunct professorships in clinical medicine at Mississippi State University and Western University of Health Sciences. He has lectured to veterinary associations on feline topics in the United States, Canada, Brazil, and Australia and is the editor of 6 feline textbooks. Dr. Norsworthy received his DVM from Texas A&M University.

Erin O. Dresner, MS, DVM, is currently completing a small animal rotating internship at North Houston Veterinary Specialists in Spring, Texas. She received her DVM from Western University of Health Sciences College of Veterinary Medicine in 2012. Prior to her veterinary education, Dr. Dresner completed an MS focused on parasitology at Texas State University. Her clinical and research interests include feline internal medicine and infectious disease.