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CASE REPORT

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Stump pyometra in a spayed female dog secondary to tamoxifen

Caryn Ehrhardt[1] | Adesola Odunayo[1] | Kristina Pascutti[2] | Jose Carvajal[1] | Kathleen Ham[1] | Autumn Nourse Harris[1]

[1]Department of Small Animal Clinical Sciences, University of Florida, Gainesville, Florida, USA

[2]Upstate Vet Emergency and Specialty Care, Greenville, South Carolina, USA

Correspondence
Caryn Ehrhardt, University of Florida, College of Veterinary Medicine, Small Animal Clinical Sciences, 2015 SW 16th Avenue, Gainesville, Florida 32608, USA.
Email: c.ehrhardt@ufl.edu

Abstract

Objective: To describe a complication associated with the long-term use of tamoxifen for the treatment of sclerosing encapsulating peritonitis in a dog.

Case Summary: A 2-year-old female spayed poodle cross was evaluated for a stump pyometra. The dog was diagnosed with sclerosing encapsulating peritonitis a year prior and was treated with tamoxifen, an oestrogen receptor antagonist, for treatment of the disease. The dog developed a swollen vulva with vulvar discharge and a stump pyometra was diagnosed on ultrasound. Hormonal testing was submitted to evaluate for an ovarian remnant and the dog underwent an exploratory laparotomy, where the uterine stump was removed. No ovarian remnant tissue was identified intraoperatively, and hormonal testing (anti-Müllerian hormone, progesterone, oestradiol) and histopathology were consistent with the absence of ovarian tissue. The tamoxifen was discontinued. The dog recovered uneventfully after surgery.

New or Unique Information Provided: This report describes a complication of treatment of a rarely described clinical disease. While most cases of stump pyometra involve ovarian remnant syndrome, this case report describes a stump pyometra in a dog without remnant tissue that was undergoing treatment with tamoxifen. Tamoxifen has been reported to cause pyometra in intact female dogs. To the authors' knowledge, this is the first case report to describe a stump pyometra in a spayed female dog, secondary to the use of tamoxifen.

KEYWORDS
canine, case report, sclerosing encapsulating peritonitis, stump pyometra, tamoxifen, oestrogen

1 | INTRODUCTION

Sclerosing encapsulating peritonitis (SEP) is a rarely reported disease in dogs (Guilford & Strombeck, 1996). It is a syndrome characterised by irreversible and progressive sclerosis and thickening of the visceral and parietal peritoneum with significant adhesions (Bender & Ockner, 1983). In humans, SEP has been reported to be caused by chronic ambulatory peritoneal dialysis, blunt abdominal trauma, bacterial or fungal peritonitis, chronic infections, and exposure to asbestos (Kawanishi, 2005). Possible underlying causes in dogs include foreign body ingestion (Etchepareborde et al., 2010), fiberglass ingestion, bacterial peritonitis (Hardie et al., 1994), and leishmaniasis

(Adamama-Moraitou et al., 2004), although most canine cases appear to be idiopathic (Boothe et al., 1991).

Clinical signs in dogs are nonspecific and may include anorexia, lethargy, intermittent vomiting, diarrhoea, abdominal distension, muscle wasting, and peritoneal effusion (Adamama-Moraitou et al., 2004; Boothe et al., 1991; Hardie et al., 1994). While SEP may be suspected based on clinical signs and the presence of loculated peritoneal effusion, the diagnosis is confirmed by computed tomography (CT) findings similar to those reported in human studies, with the presence of free or loculated peritoneal fluid, encased bowel loops, and mesenteric fat stranding with extraluminal adhesions present (Berengere et al., 2022; Veiga-Parga et al., 2015). Diagnosis may also be confirmed by exploratory laparotomy and biopsy of the characteristic thickened peritoneum and fibrous adhesions.

Treatment of SEP in human patients involves a combination of surgical intestinal enterolysis to remove adhesions along with administration of tamoxifen[1], a non-steroidal oestrogen receptor antagonist, either as a sole therapeutic agent or in combination with corticosteroids (Gupta & Woodrow, 2007; Moustafellos et al., 2006). Historically, most dogs have responded poorly to empirical treatment with surgery and corticosteroids, with survival times less than 5 months (Hardie et al., 1994). However, cases demonstrating improvement of dogs following treatment with tamoxifen have been reported (Etchepareborde et al., 2010; Ingrid et al., 2020). Tamoxifen has also been used in the treatment of mammary neoplasms (Morris et al., 1993), but has been demonstrated to result in estrogenic side effects in spayed dogs and pyometra in intact female dogs (Tavares et al., 2010).

This case report describes the diagnosis and treatment of a stump pyometra in a dog secondary to long-term use of tamoxifen in the absence of an identifiable ovarian remnant.

2 | CASE REPORT

A 2-year-old female spayed poodle cross, weighing 23.7 kg, was referred to the University of Florida veterinary teaching hospital emergency service for further evaluation of a cystic structure in the caudal abdomen aspirated by the referring veterinarian during an attempted cystocentesis.

During a routine ovariohysterectomy at 7 months of age, the dog was noted to have marked abdominal adhesions and free abdominal fluid. The dog had been previously healthy with no clinical signs or illness. The dog was referred to a specialty hospital for exploratory laparotomy and ovariohysterectomy. During surgery, due to the presence of marked adhesions and fibrosis, surgical biopsies of the liver, spleen, jejunum, and peritoneum were performed. Histopathology of the jejunum revealed moderate lymphoplasmacytic and eosinophilic enteritis with moderate villus blunting and dilated lacteals. There were no significant findings on the histopathology of the liver and spleen. Histopathology of the peritoneum exhibited severe, multifocal fibrosing peritonitis with marked fibrosis and granulation tissue; no saponification, foreign bodies, organisms, or tumour cells were seen. Aerobic and anaerobic cultures of the peritoneal fluid were negative for growth. A diagnosis of SEP was made based on the histopathologic results. The dog was started on a hydrolysed diet[2] for the inflammatory bowel disease by the specialty hospital and referred to the University of Florida veterinary teaching hospital's small animal internal medicine service.

Three and a half months following diagnosis, the dog was evaluated by the University of Florida small animal hospital internal medicine service for management of the SEP and inflammatory bowel disease. On physical examination, the dog had marked abdominal distension with a palpable fluid wave along with firm, irregular structures on abdominal palpation presumed to be her abdominal organs encapsulated in fibrous tissue. The dog was started on tamoxifen 0.9 mg/kg PO q24h, prednisone[3] 0.9 mg/kg PO q24h, and cyclosporine[4] 4.4 mg/kg PO q24h. At her 4-month recheck, the dog no longer had a palpable fluid wave on abdominal palpation and individual intestinal loops could be palpated. The prednisone was decreased to 0.5 mg/kg/day with no changes to the tamoxifen or cyclosporine. Subsequent rechecks revealed no return of the ascites, and the prednisone was discontinued 7 months into treatment. Four months after starting on the tamoxifen, the dog developed some vulvar swelling, but this improved without making any changes to the treatment plan. The dog continued to do well at home until the owner noticed more pronounced vulvar swelling and licking 11 months after starting on the tamoxifen, which prompted the visit to the primary veterinarian.

For a few weeks prior to presentation to the University of Florida veterinary teaching hospital's emergency department, the dog's owners had noted more pronounced vulvar swelling and licking. The owners had not noticed any urinary accidents, and the dog continued to eat and drink normally. The dog was evaluated by the referring veterinarian, where an ultrasound-guided cystocentesis was attempted for a urinalysis and culture. Purulent fluid was aspirated during the cystocentesis attempt. Further investigation with the ultrasound revealed a fluid-filled structure near the urinary bladder that was distinct from the urinary bladder and suggestive of the uterine stump. The dog was subsequently referred to the university emergency department for an abdominal ultrasound and for concerns for abdominal contamination.

On physical examination by the emergency department, the dog was quiet, alert, and responsive. The dog's vital parameters, including heart rate and respiratory rate, were within normal limits, with a body temperature of 38.8°C (101.9°F). The abdomen was soft and non-painful on palpation with no fluid wave noted. The vulva was moderately enlarged with moderate amounts of purulent discharge noted. A brief point-of-care ultrasound revealed a fluid-filled structure in the caudal abdomen near the urinary bladder and small, loculated pockets of fluid in the cranial abdomen. A CBC revealed a leukocyte count of 14,500/μl (reference interval: 5000–16,760/μl) characterised by a mature neutrophilia of 12,190/μl (reference interval: 2950–11,640/μl). No left

[1] Tamoxifen, Mayne Pharma, Greenville, NC.

[2] Hydrolyzed Protein Diet, Royal Canin, Saint Charles, MO.
[3] Prednisone, Westward Pharmaceuticals, Eatonton, NJ.
[4] Cyclosporine, Elanco, Greenfield, IN.

shift was noted. A venous blood gas did not reveal any abnormalities. Cytology of the fluid aspirated from the abdominal structure that had been collected by the referring veterinarian revealed too numerous to count rods and cocci with neutrophilic inflammation. Aerobic and anaerobic culture and sensitivity of the fluid were submitted to the microbiology lab. Cytology of the vulvar discharge was consistent with that of the aspirated abdominal fluid, with marked rods and cocci and white blood cells. An abdominal ultrasound performed by a board-certified radiologist revealed a moderately enlarged uterine stump with central echogenic fluid collections consistent with a uterine stump pyometra. The ultrasound also revealed cranial abdominal peritoneal fluid loculations compatible with the historically diagnosed SEP. No obvious ovarian remnant tissue was identified on ultrasound.

The dog was hospitalised overnight on intravenous lactated Ringer's solution[5] (40 ml/kg/day), ampicillin/sulbactam[6] 30 mg/kg IV q8h, maropitant[7] 1 mg/kg IV q24h, cyclosporine 4.4 mg/kg PO q24h, and tamoxifen 0.9 mg/kg PO q24h. The next day, prior to exploratory laparotomy, a CT study of the abdomen with intravenous contrast revealed a moderately to severely distended uterine stump along with two fluid-filled structures in the abdomen consistent with the previously diagnosed SEP (Figure 1). No ovarian remnant tissue was identified. An estradiol level, progesterone level, and anti-Mullerian hormone (AMH) level were also submitted prior to surgery.

Following the CT, the dog underwent an exploratory laparotomy. During surgery, adhesions were noted throughout the entire abdomen (Figure 2). No obvious ovarian remnant tissue was identified and the tissue around the location of the ovarian pedicles was resected and submitted for histopathology. The adrenal glands could not be visualised due to adhesions. The uterine stump was isolated from the surrounding fibrous adhesions with careful identification and dissection away from the distal ureters; the uterine stump was double ligated and removed caudal to the cervix. The entire uterine stump was submitted for histopathology with a sample submitted for aerobic and anaerobic culture and sensitivity. The abdomen was lavaged with warm sterile saline and closed routinely. The dog had no anaesthetic complications and recovered uneventfully. The dog was discharged the day following surgery on amoxicillin/clavulanic acid,[8] gabapentin,[9] and trazodone.[10] The tamoxifen was discontinued at the time of discharge.

The dog's progesterone level on an in-house analyser was 0.374 ng/ml (reference interval: 0.0–0.4 ng/ml). The hormone panel revealed an oestradiol level of 32.4 pg/ml (reference interval: 30.8–69.0 female spayed; 31.5–65.4 female intact anoestrus) and a progesterone level <0.20 ng/ml (reference interval: <0.20–0.49 female spayed; <0.20–2.16 female intact anoestrus). The AMH level was 0.18 ng/ml (reference interval: 0.16–0.19 ng/ml). The aerobic culture of the uterine fluid revealed moderate to heavy growth of *Actinomyces* sp., and anaerobic culture yielded heavy growth of mixed anaerobes. An individual species identification was not performed on the mixed anaerobes, and sensitivity of the *Actinomyces* sp. was not provided by the microbiology lab. Histopathology of the submitted uterine stump was consistent with pyometra (Figure 3) without evidence of ovarian tissues identified in the left and right lateral ovarian scar tissues.

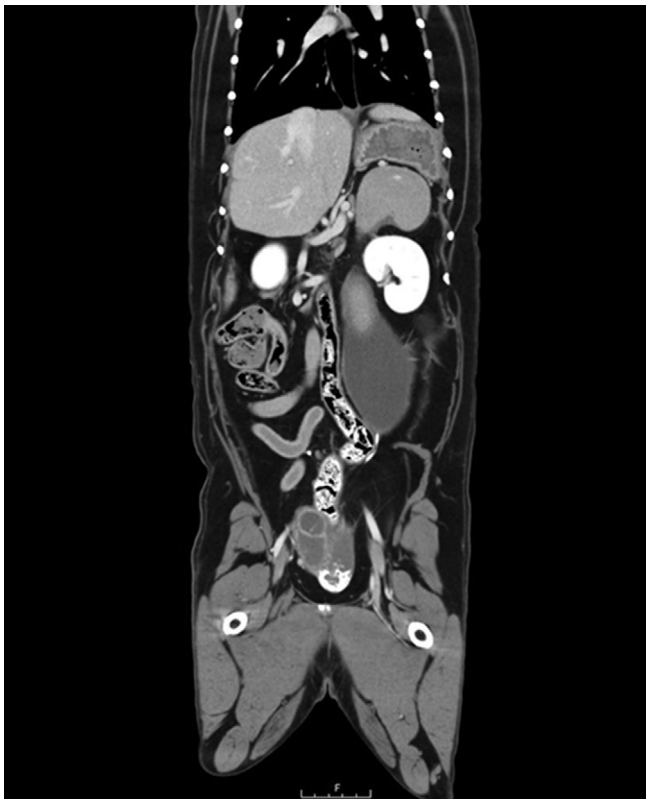

FIGURE 1 Computed tomography findings revealed a moderately to severely distended uterine stump, a well-defined, smoothly marginated 2.2 cm cystic-like structure within the cranial aspect of the uterine stump, mildly enlarged jejunal lymph nodes (0.8 cm) and right medial iliac lymph node (1 cm), and moderately thickened vulvar tissues. Extending from the ventral hepatic margins was an ill-defined, smoothly marginated, triangular shaped, peripherally soft tissue-attenuating, centrally fluid-attenuating structure measuring 12.5 × 5.1 × 2 cm and a similar structure emerging from the mid-body of the spleen connecting to the cranial aspect of the urinary bladder measuring 18.1 × 8.9 × 7.3 cm, both of which are consistent with the patient's previous diagnosis of sclerosing encapsulating peritonitis (SEP).

3 | DISCUSSION

This case report describes the diagnosis of a stump pyometra in a female spayed dog secondary to the use of tamoxifen. The dog described in this case report was treated successfully for SEP using a novel protocol including an additional immunosuppressive medication and developed a complication secondary to treatment.

SEP is a rarely described disease in dogs and is characterised by excessive, progressive, and irreversible thickening, fibrosis, and

[5] Lactated Ringer's Solution, Dechra, Northwich, UK.
[6] Ampicillin Sulbactam, Pfizer, New York, NY.
[7] Maropitant, Zoetis LLC, Kalamazoo, MI.
[8] Amoxicillin/Clavulanic Acid, Zoetis LLC, Kalamazoo, MI.
[9] Gabapentin, Ascend Labs LLC, Parsippany, NJ.
[10] Trazodone, Teva Pharmaceuticals, Parsippany, NJ.

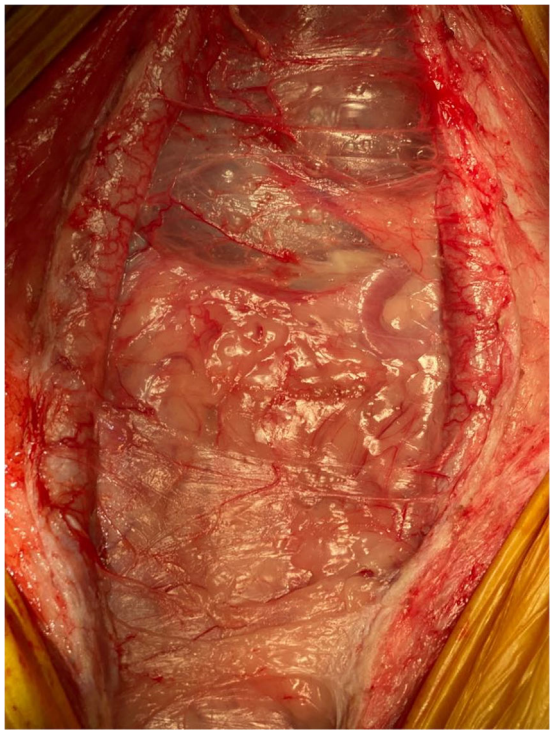

FIGURE 2 The patient's ventral midline abdominal incision during exploratory laparotomy surgery depicting marked fibrous adhesions present throughout the peritoneum

adhesions of the visceral and parietal peritoneum (Bender & Ockner, 1983). Although cases have been reported in dogs (Adamama-Moraitou et al., 2004; Berengere et al., 2022; Boothe et al., 1991; Etchepareborde et al., 2010; Hardie et al., 1994; Veiga-Parga et al., 2015) and potential underlying factors have been identified, including foreign body ingestion, leishmaniasis, fiberglass ingestion, and bacterial peritonitis, little is known about the aetiology of the disease, and it has historically carried a poor prognosis in canines. In humans, underlying causes as well as an idiopathic form have been identified, and treatment is aimed at removal of the underlying cause, corticosteroids, tamoxifen, and surgical enterolysis, if indicated; still, mortality can reach 50% within a year of diagnosis (Danford et al., 2018).

Tamoxifen is a non-steroidal anti-oestrogen drug that has been successfully used in humans and reported in dogs for the treatment of SEP, either alone or in conjunction with corticosteroids (Gupta & Woodrow, 2007; Moustafellos et al., 2006). However, its mechanism of action in the treatment of SEP is unclear, although it has been demonstrated to be an inhibitor of protein kinase C, which is essential for cell proliferation (Horgan et al., 1986). It is possible that the beneficial effects of tamoxifen in the treatment of SEP may be secondary to removal of denatured collagen and healing of the mesothelium. Metalloproteinases (MMPs) degrade and denature collagens. Tamoxifen stimulates the production of TGF-β1, which supports the synthesis of MMPs and suppresses fibroblasts (Etchepareborde et al., 2010). Therefore, it may support the removal of collagen and fibrosis and healing of the mesothelial tissues. In this particular case, the patient was treated with corticosteroids, which were successfully tapered over time, as well as tamoxifen, which was continued long-term. Additionally, the patient was treated with cyclosporine due to the eosinophilic component identified on the patient's original histopathology.

Tamoxifen competitively and selectively binds to oestrogen receptors on tumours and other target tissues, producing a complex that decreases the synthesis of DNA and inhibits the effects of oestrogen. Although it competes with oestrogen for binding site in selective tissues, it also works in oestrogen-receptor-negative breast cancers, which is suggestive of another mechanism of action (Clark et al., 1991). However, in some tissues, such as the uterus and bone, it can act as an oestrogen agonist, resulting in estrogenic side effects. Tamoxifen has also been used in the treatment of mammary neoplasms in dogs. One study evaluated the effects of tamoxifen on female dogs, both spayed and intact, over a period of 120 days (Tavares et al., 2010). In that study, vulvar enlargement and discharge were noted after about 10 days of therapy in both spayed and intact females. At about 90 days of therapy, pyometra was noted in dogs in the intact group, with increasing frequency of occurrence over time (Tavares et al., 2010). As tamoxifen exhibits oestrogen receptor-agonist activity in the uterus, intact female dogs exposed develop endometrial cell proliferation and an increase in the number of oestrogen receptors. Although there is also an increased number of progesterone receptors, the serum level of progesterone remains unaltered (Morris et al., 1993), despite reduced leucocyte recruitment to the uterus and reduction of uterine defences, predisposing to pyometra. Although the study reports that spayed females can experience a stump pyometra, none of the dogs in that study developed a stump pyometra.

There are two other case reports describing the use of tamoxifen for treating SEP in dogs. One was in a male dog (Ingrid et al., 2020) and one in a female dog (Etchepareborde et al., 2010). The female dog in the previously reported case did not develop a stump pyometra during treatment with tamoxifen; however, the dog had previously been diagnosed with ovarian remnant syndrome (ORS) and subsequent stump pyometra and underwent surgery for uterine stump and ovarian remnant excision prior to receiving tamoxifen therapy. In contrast to that case report, the uterine stump and cervix were still present in the dog in the present case report prior to starting on tamoxifen therapy, as removal of the uterine stump is not part of a routine ovariohysterectomy. Additionally, the dog in the present case report remained on tamoxifen therapy significantly longer than the dog in the previous case report (11 vs. 5 months). It is uncertain if the risk of developing a stump pyometra increases the longer the patient is on tamoxifen, but it is certainly a consideration, given that the risk of developing a pyometra in intact female dogs increased with duration of treatment in a previous study (Tavares et al., 2010).

Development of a stump pyometra in dogs occurs most commonly secondary to ORS (Pearson, 1973). ORS describes the constellation of signs, most commonly vulvar swelling, serosanguinous vaginal discharge, and pyometra, secondary to functional residual ovarian tissue after an ovariohysterectomy surgery. Because the dog's SEP allowed for decreased visualisation of the abdomen at the time of the ovariohysterectomy secondary to marked abdominal adhesions, ORS was investigated as a possible cause of the clinical signs. A case series

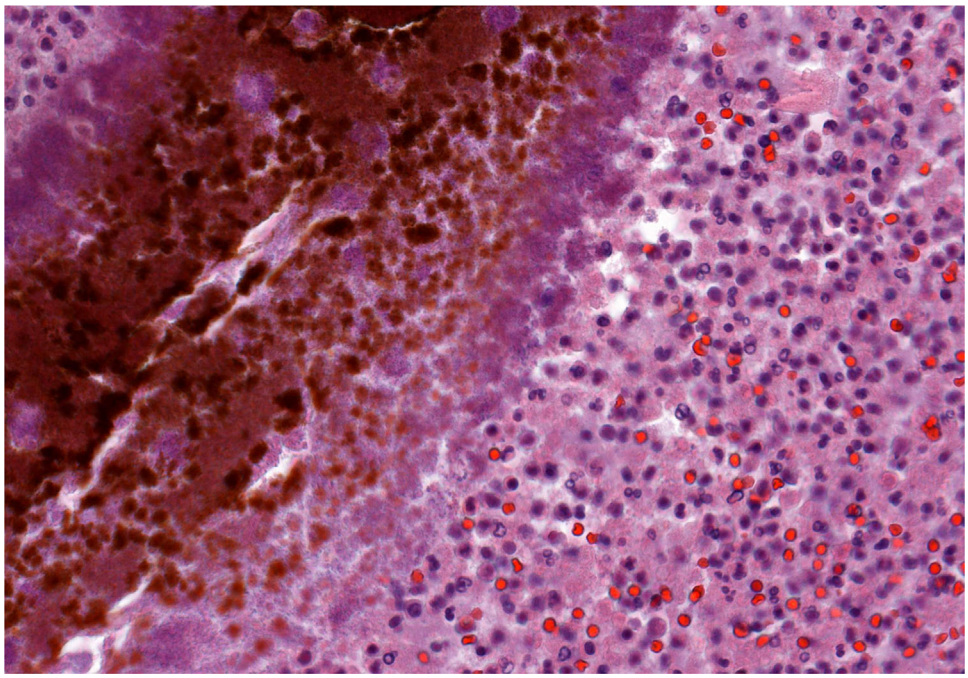

FIGURE 3 Histopathology of the uterine stump. The lumen is visualised with white blood cells, necrosis, and bacteria present.

describing ORS in dogs and cats identified ultrasound as a helpful adjunct test in identifying the presence of ovarian tissue (Ball et al., 2010). However, in this case, no ovarian tissue was identified on abdominal ultrasound or CT or in the histopathology of the tissues resected from the region of the ovarian pedicles. Hormonal testing alone has not been found to be helpful in confirming ORS in dogs (Ball et al., 2010), but given the dog's long-term use of tamoxifen, as well as the anticipated likelihood of decreased visualisation of tissues in her abdomen due to marked adhesions, hormonal testing was submitted as an adjunct to help confirm the diagnosis. The results of the dog's progesterone level were not consistent with luteal activity from an ovarian remnant, and the oestradiol concentration was not consistent with follicular activity. AMH, a glycoprotein hormone produced by the Sertoli cells from the testis in men and ovarian granulosa cells in women, has been determined to be a useful diagnostic tool in the detection of an ORS in the dog (Turna Yilmaz et al., 2015). AMH concentrations in dogs with ORS are similar to those of intact female dogs; spayed females have significantly lower concentrations of AMH. The dog in this case report had an AMH level that was considered inconclusive for ORS based on the reference laboratory's reference interval for spayed female dogs; however, when paired with oestradiol level, progesterone level, and lack of ovarian tissue identified on ultrasound, CT, and histologically in the ovarian scar tissue, it is concluded that no remnant tissue is present. Tamoxifen has been demonstrated to be capable of increasing oestradiol levels in post-menopausal women (Rodatra et al., 1997). As this dog's oestradiol level was within the normal reference range, this further supports the lack of presence of ovarian tissue. Although vaginal cytology can provide supportive evidence for identifying an ovarian remnant, it unfortunately was not performed in this case.

When compared to humans, dogs diagnosed with SEP have a significantly worse outcome, with even surgical enterolysis resulting in serosal tearing (Adamama-Moraitou et al., 2004). Due to the infrequency with which the disease is diagnosed in dogs, a standardised or recommended treatment protocol is not established. While the dog in this case report did still exhibit significant abdominal adhesions during surgery for the stump pyometra, the amount of ascites present was minimal, and the dog had been doing clinically well at home, which supports the successful use of tamoxifen in this dog for the management of SEP. The suspected side effect of tamoxifen causing a stump pyometra in this dog suggests that it may be beneficial to taper and discontinue the medication sooner. One consideration is to begin a taper after the resolution of clinical signs. This consideration is especially worthwhile given the risk of causing additional adhesions with abdominal surgery for a stump pyometra. With more cases of SEP documented, it may be possible to establish some recommendations for successful management in canine patients.

4 | CONCLUSION

SEP is a rarely reported disease in dogs, with a historically poor prognosis. Although favourable outcomes have been reported in a few case reports (Brückner & Bogisch, 2022; Etchepareborde et al., 2010; Ingrid et al., 2020) with tamoxifen, an established protocol for dose and timing of treatment has not been established. Tamoxifen has been reported to cause pyometra in intact female dogs; however, this case report describes the development of a stump pyometra in a spayed female. Further investigation is needed to determine an ideal treatment protocol for the management of SEP in canine patients.

AUTHOR CONTRIBUTIONS

Caryn Ehrhardt and Adesola Odunayo conceptualised and designed the study, conducted analysis and interpretation, wrote the original draft, and performed critical revisions. Kristina Pascutti, Jose Carvajal, Kathleen Ham, and Autumn Nourse Harris conducted analysis and interpretation, wrote the original draft, and performed critical revisions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

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ORCID

Caryn Ehrhardt https://orcid.org/0000-0002-0112-3163

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