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CASE REPORT

Estrogen Receptors A and B in a Pure Uterine Lipoma in a Dog

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A B S T R A C T

A 7-year-old female Yorkshire terrier dog presented with anorexia and fever due to pyometra; ovariohysterectomy was therefore performed. Histopathological examination showed multiple cysts of variable sizes with hyperplasticity of luteal cells, and the patient was diagnosed with cystic ovarian disease. An abnormal growth and infiltration of adipocytes in the uterus, especially at the border between the endometrium and myometrium, was accidentally identified. Based on the clinical features and histopathological findings, a diagnosis of pure uterine lipoma along with ovarian cystic disease was made. Further immunohistochemical study revealed that the lipomatous tissue was positive for the protein S-100, vimentin, and desmin, as well as estrogen receptors alpha and beta, which is in contrast to humans. Our results suggest a possible role of estrogen receptor signaling in abnormal lipomatous tissue changes in the canine female genital tract. We present here the first case of pure uterine lipoma in a dog and describe its characteristics.

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INTRODUCTION

Uterine lipomatous tumors are rare, benign neoplasms and only few cases have been reported in humans. Uterine lipomas usually occur in obese, postmenopausal women from 50-70 years of age with an incidence of 0.12-0.3% (Mignogna *et al.,* 2009). However, to the best of our knowledge, pure uterine lipoma has never been reported in veterinary medicine.

Among domestic animals, typical lipoma is most common in dogs (Meuten *et al.,* 2002). Lipomas may occur anywhere in mammals, but predominantly arise subcutaneously in the trunk, gluteal region, and proximal limbs and are predominantly seen in females. However, uterine lipoma is very rare and difficult to diagnose because most female dogs are neutered at an early age to prevent diseases such as malignant mammary gland tumors or pyometra. Moreover, most hysterectomy samples are often misdiagnosed as normal hyperplasia of adipocytes.

Uterine lipoma can be of pure or mixed type. The latter includes lipoleiomyoma and fibrolipoma, which contains variable amounts of fat, smooth muscle, and fibrous tissue (Reslova *et al.,* 2003; Erdem *et al.,* 2007). In general, mixed-type uterine lipoma occurs more frequently, while pure uterine lipoma is very rare. Preoperative diagnosis of pure uterine lipoma is difficult unless imaging modalities, such as magnetic resonance imaging (MRI), are used (Chu *et al.,* 2012). Moreover, the diagnosis should be histopathologically confirmed only if smooth muscle cells are confined to the periphery because of an abnormal growth of adipocytes (Salm, 1973). In this article, a case of pure uterine lipoma and coexistent cystic ovarian disease is reported and the histogenesis of pure uterine lipoma is discussed.

Case history, clinical examination and findings: A 7-year-old female Yorkshire terrier dog, weighing 2.8 kg, was referred to a local veterinary hospital because of anorexia and fever. A complete blood count showed slight leukopenia and lymphopenia, and the serum chemistry profile was within normal limits. Radiographs revealed an enlarged uterus and a trans-abdominal ultrasound scan showed a hypoechoic mass measuring 17 mm in diameter in the right ovary.

The patient underwent total abdominal ovario-hysterectomy. The right portion of the specimen was immediately fixed in 10% neutral buffered formalin to enable histopathological evaluation.

The right ovary had multi-lobulated cysts that were 2 cm in diameter, with serosal fluid oozing from the section. A large amount of fat with hemorrhage surrounded the

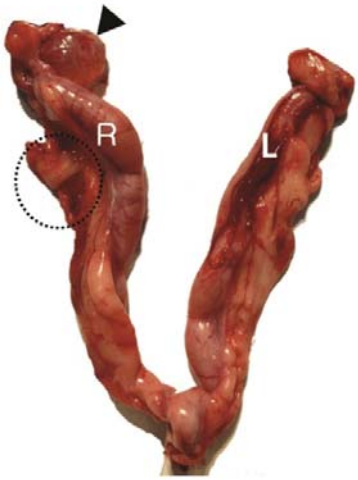

Fig. 1: Macroscopic findings of excised ovary and uterus from the patient. Arrowhead indicates a cystic ovary 2 cm in diameter. A large amount of fat with hemorrhagic lesions is seen near the infundibulum and body of the uterus (Circle).

uterus, especially near the infundibulum (Fig. 1). Dark to yellow-colored pus was detected on uterine section, and the luminal surface was narrowed, especially on the infundibulum and uterine body.

Microscopic examination of the ovary revealed multiple cysts and clusters of luteal cells that had highly eosinophilic vacuolated cytoplasm. These histopathological findings showed that the hormonal effects were prominent and resulted in multiple ovarian cysts with hyperplastic luteal cells.

Inflammatory cells, such as lymphocytes and neutrophils, infiltrated the endometrial region near the luminal surface, which was associated with edematous changes. Mature adipocytes with clear cytoplasm and paracentric nuclei were found in submucosal lesions, especially at the border between the endometrium and myometrium (Fig. 2). In addition, adipocytes were also seen in the myometrial region between the circularis and longitudinalis muscles. This resulted in the normal vasculature moving to the periphery. No smooth muscle cells or fibrous elements were seen within the proliferation zone of adipocytes, but the peripheral region of the myometrium was atrophic (Fig. 3). At higher magnification, smooth muscle cells in the myometrium near the lipomatous lesion were atrophic due to proliferation of mature adipocytes (Fig. 3, inset). According to these histopathological findings, the final diagnosis of the lesion was established as pure uterine lipoma.

The lipomatous lesion was further examined by performing immunohistochemistry (IHC) to identify the origin of the abnormal proliferative adipocytes, according to the previous report. The primary antibodies were anti-vimentin (DakoCytomation, A/S, Glostrup, Denmark), anti-desmin (DakoCytomation), anti-S-100 protein (Abcam, Cambridge, UK), anti-estrogen receptor (ER)-α (Santa Cruz Biotechnology, California, USA), and anti-ER-β (Santa Cruz Biotechnology).

Smooth muscle cells of the myometrium stained positively for desmin (Fig. 4a), vimentin (Fig. 4b) and S-100(data not shown); the adipocytic tumoral lesion also showed the same immune profile. In addition, lipomatous

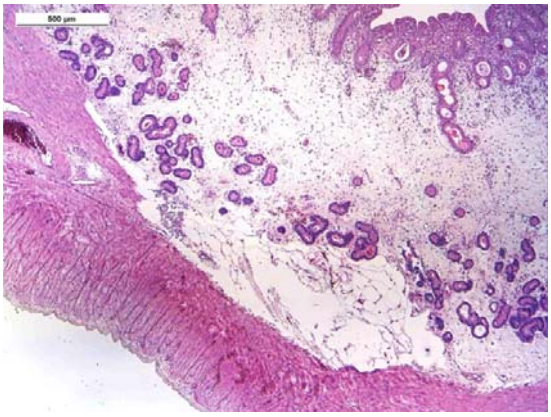

Fig. 2: Histopathological findings of uterus (endometrium & myometrium). The endometrial glands are displaced towards the lamina propria and the myometrium shows atrophy because of submucosal proliferation of mature adipocytes (hematoxylin & eosin stain, ×40).

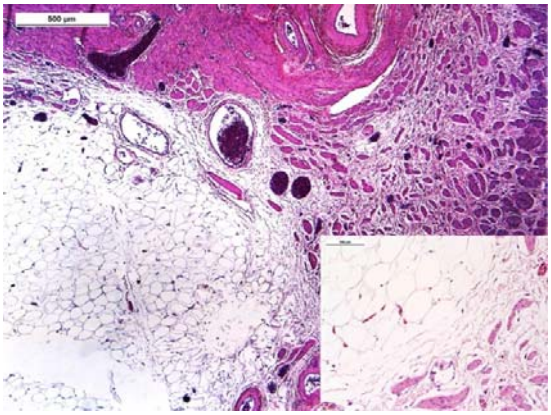

Fig. 3: Histopathological findings of the uterus between the circularis and longitudinalis muscles. Proliferation of adipocytes has caused the normal vasculature to move towards the periphery. Inset: myocytes atrophied due to the abnormal growth of mature adipocytes (hematoxylin & eosin, ×40, ×200 [inset])

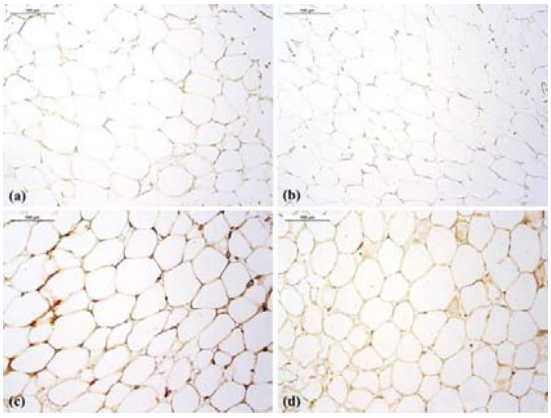

Fig. 4: Immunohistological characterization of tumor adipocytes. Neoplastic cells are positive for mesenchymal cell markers vimentin (a) and desmin (b) as well as estrogen receptors alpha (c) and beta (d) (Immunohistochemical stain, ×200).

tissue (Fig. 3), associated with degeneration of adjacent smooth muscle cells, was positive for estrogen receptors alpha (ER-α) and beta (ER-β), in contrast to the previous article (Fig. 4c & 4d).

DISCUSSION

Lipomatous or fatty tumors of the uterus are rare and benign neoplasms in humans and dogs (Vilallonga *et al.*, 2009). Uterine lipoma is extremely rare and often misdiagnosed as normal hyperplastic condition of adipose tissues due to the abundance of fatty tissue around the ovary and uterus in both species. Generally, uterine lipoma can be of pure or mixed type. In most cases, lipomatous tumors are of mixed type, such as lipoleiomyoma or fibrolipoma, which contain muscle cells and fibroblasts, respectively (Lau *et al.,* 2005). In the present case, only mature adipocytes were found in the submural region (the border between the endometrium and myometrium) and the interspace between circularis/longitudinalis myometrium. In addition, normal vasculature and smooth muscle cells were pushed to the periphery because of the abnormal growth of mature adipocytes.

The histogenesis of uterine lipoma is still controversial (Vilallonga *et al.,* 2009; Vamseedhar *et al.*, 2011). Various attempts have been made to explain histogenesis of abnormal adipocytes, including theories about mislocation of embryonal mesodermal cells, or implantation of lipoblasts during surgery. However, direct metaplasia of connective tissue or smooth muscle cells to adipocytes seems to be the most reliable theory in recent times. In agreement with the results of Mignogna *et al.* (2009), we found that the adipocytes at the tumor site were positive for vimentin, desmin, and S-100, supporting the hypothesis of direct transformation from smooth muscle cells to adipocytes. The positive immunoreactivity for ER-α and ER-β in our case suggests a correlation between estrogen hormone receptor signaling and adipocyte proliferation; estrogen may have an effect on adipocyte proliferation or abnormal growth of adipocytes can influence hormonal balance and receptor expression, although our study does not use any estrogen-specific hormonal assay.

According to recent articles, imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI) are good techniques for detecting these tumors (Wijesuriya *et al.,* 2011) in humans. However, the final diagnosis of primary pure uterine lipoma should be made histopathologically and only if the smooth muscle cells are confined to the periphery.

Most human patients who develop lipomatous tumors remain asymptomatic (Lau *et al.,* 2005, Vamseedhar *et al.*, 2011). Sometimes, an increase in lipoma size can cause signs and symptoms such as increased frequency of urination, uterine bleeding, and abdominal pain. We believe that the incidence of pure uterine lipomas in humans and dogs is different, because in most human cases, the patients were postmenopausal women; the estrogenic effect was therefore minimal (Erdem *et al.,* 2007; Chu *et al.,* 2012). In our case, the patient showed no effects indicating increased tumor size, but probable hormonal effects were seen in the ovaries and uterus. Multiple ovarian cysts of various sizes and hyperplastic lesions of luteal cells were found on histopathological analysis. Further immunohistochemical study revealed that abnormally growing adipocytes in the uterus showed strong positive immunoreactivity to ER-α and ER-β receptors. This suggested that in our case, estrogen might influence neoplastic proliferation of adipocyte, although the tumor did not reach the size at which it would have caused pressure symptoms in our patient similar to those seen in humans. Therefore, our case supports the pathogenetic hypothesis of pure uterine lipoma that describes direct smooth muscle metaplasia to abnormal adipocytes, and our immunohistochemical studies further suggest estrogenic effects in this transformation.

In conclusion, our case may bear similarities to immunohistopathological profiles of uterine lipomas from previous studies (Mignogna *et al.,* 2009), which show direct fatty metaplasia of connective tissue or smooth muscle cells. Additionally, the ER-α and ER-β immunoreactivity of the tumor cells suggests a possible estrogenic effect on growth of the pure uterine lipoma. However, further studies are needed to demonstrate the relationship between estrogen receptor signaling and histogenesis of pure uterine lipomas.

Author contributions: Han Jun Kim carried out most of the work in writing. Ji-Han Kim did the ovario-hysterectomy. Hye-Rim Lee and Sun Hee Do provided information to analyse the findings. All authors read and approved the final manuscript.

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