

Histological and immunohistochemical characterisation of uterine adenocarcinoma in an Asian elephant (*Elephas Maximus*)

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*A 56-year-old nulliparous female Asian elephant (*Elephas maximus*) living at the zoological garden of Naples (Italy), with a clinical history of recurrent colic, was found in agonal state and humane euthanasia was elected. At necropsy the uterine body was moderately increased in size and the lumen was reduced due to a poorly demarcated and infiltrative neoplasm. Furthermore, multiple, whitish, firm nodules were present in both lungs. Histological examination of the uterine mass revealed epithelial cells arranged in tubular or solid pattern infiltrating the endometrium and the muscular layer. Immunohistochemical examination showed immunoreactivity of neoplastic cells to oestrogen receptors antibody. Pulmonary lesions were histologically and immunohistochemically superimposable to the epithelial uterine neoplasm. A definitive diagnosis of uterine adenocarcinoma with pulmonary metastases was made. (Folia Morphol 2018; 77, 4: 771–774)*

Key words: uterine adenocarcinoma, elephant, *elephas maximus*, uterus

INTRODUCTION

Endometrial cancer is the most common women pelvic malignancy [2], and is rare in domestic animals other than rabbits [3, 11], cattle and Wistar rats [3]; it is exceptionally reported in other species, such as cats and dogs [9, 15]. Cases of uterine adenocarcinoma are also described in rhinoceroses [10, 18] and many captive and wild animals [12, 16]. In the female genital system of the elephant, several cases of leiomyomas are described [5, 14] but, to our knowledge, no cases of uterine adenocarcinoma have been ever diagnosed. The present study reports the first case of uterine adenocarcinoma in an *Elephas maximus*.

CASE REPORT

A 56-year-old nulliparous female Asian elephant (*Elephas maximus*) living at the zoological garden of

Naples (Italy), with a clinical history of recurrent colic, was found in lateral recumbency (agonal state) and given the lack of response to the emergency medical treatments, humane euthanasia was elected and a complete necropsy was requested to find out the cause of the illness of the animal.

At necropsy the uterine body was moderately increased in size and firmer than normal. The lumen was reduced due to a poorly demarcated and infiltrative neoplasm showing papillary and soft luminal projections and multiple brownish necrotic areas. Furthermore, multiple, disseminated, whitish to grey, well demarcated neoplastic nodules, ranging from 2 to 5 cm in diameter, involving both uterine horns and the uterine body, were also observed. Multiple, whitish, firm nodules, 1 to 4 cm in size were present in the lungs. Bulging into the right cardiac ventricle, and

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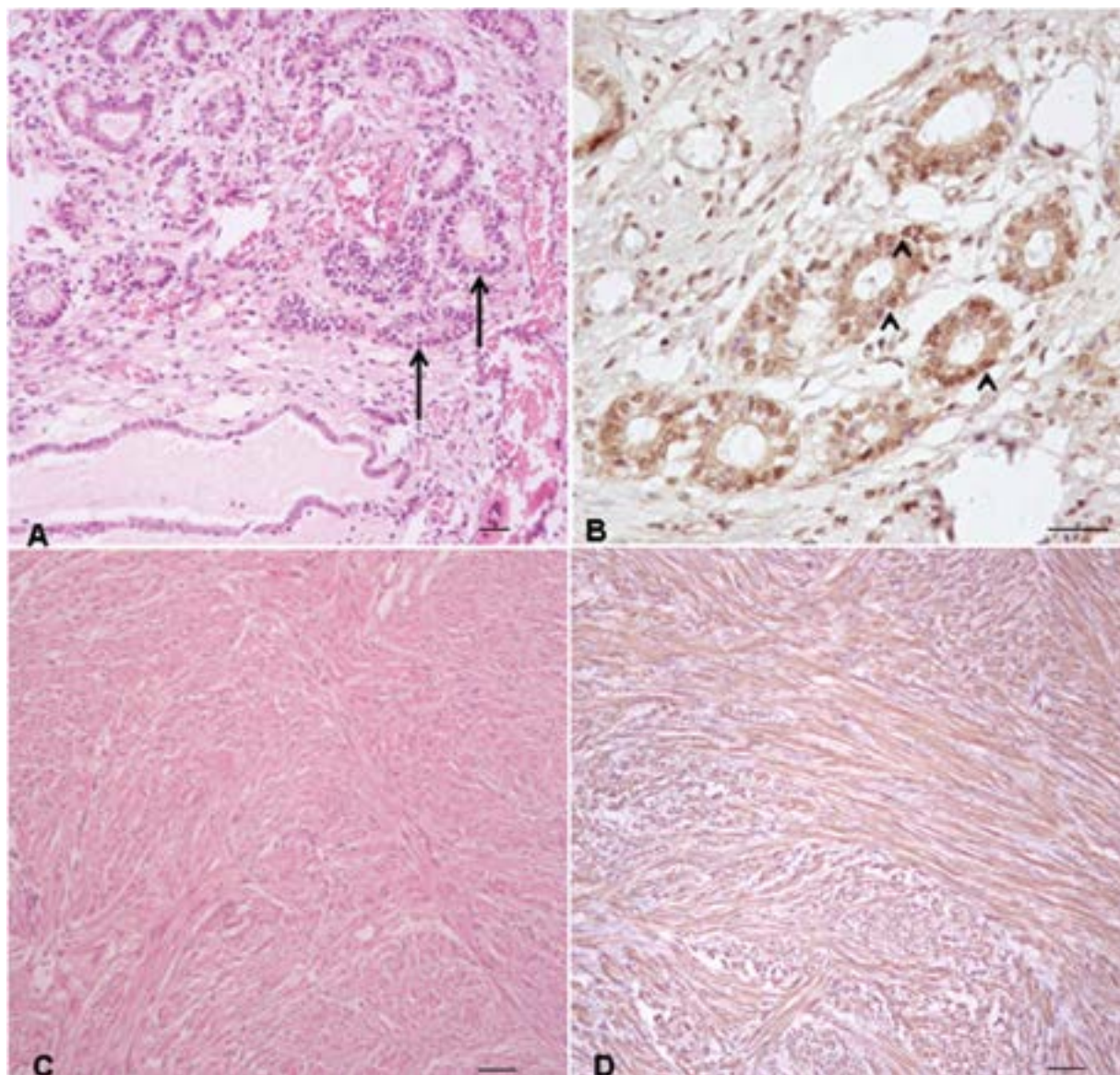


Figure 1. Microscopic images of uterine adenocarcinoma and leiomyoma in an Asian elephant (*Elephas maximus*); **A.** Uterine adenocarcinoma; neoplastic cells appear organised in acinar and tubular structures (arrows), with polygonal shape, distinct cell borders and eosinophilic to light basophilic cytoplasm; haematoxylin and eosin (H&E) stain; **B.** Uterine adenocarcinoma; neoplastic cells show a strong nuclear immunoreactivity (arrow-head) to oestrogen receptor antibody; immunohistochemistry (IHC) stain; **C.** Uterine leiomyoma; the cells are arranged in interlacing bundles or whorls and are supported by a moderate amount of fibrovascular stroma; H&E stain; **D.** Uterine leiomyoma; neoplastic cells showing strong immunoreaction to smooth muscle actin antibody; IHC stain; scale-bar 100 microns.

adhering to the endocardium, a firm to elastic reddish thrombus, 3 cm in diameter, was present. Based on the macroscopic examination, a suspected diagnosis of uterine adenocarcinoma with pulmonary metastasis and multiple uterine leiomyomas was made.

Representative samples of all organs were collected for a full histopathologic examination; tissues were fixed in 10% neutral buffered formalin, paraffin embedded, sectioned at 4 micron and stained with haematoxylin and eosin (H&E). Histologically, the poorly demarcated and infiltrative neoplasm of the

uterus consisted of an infiltrative unencapsulated neoplastic proliferation composed of epithelial cells infiltrating the endometrium and the muscular layer. Neoplastic cells formed acinar and tubular structures or solid aggregates and were polygonal in shape, with distinct cell borders and moderate eosinophilic to light basophilic cytoplasm (Fig 1A). Nuclei were oval with marginated or granular chromatin with a single prominent nucleolus; cellular atypia consisted of marked anisokaryosis and anisocytosis and mitotic figures ranged from 2 to 4 per high power field

(HPF, 400× magnification). Multifocal aggregates of neoplastic cells were noted in myometrial lymphatic vessels. On histological examination a diagnosis of uterine adenocarcinoma was made and immunohistochemistry (IHC) for pancytokeratin, oestrogen receptors (ER) and progesterone receptors (PR) was performed. Neoplastic cells showed strong cytoplasmic immunoreaction to pancytokeratin antibody; the nuclei of tumour cells were intensely and diffusely labelled by marker for ER (Fig. 1B) whereas no expression of PR was found.

Furthermore, multiple, well-demarcated nodular uterine masses consisted of a relatively uniform population of mesenchymal cells arranged in interlacing bundles or whorls and supported by a moderate amount of fibrovascular stroma, were observed (Fig. 1C). The neoplastic cells were spindloid, often showed cigar-shaped nuclei and a mild to moderate anisokaryosis and anisocytosis; mitotic figures were rare. At IHC, neoplastic cells showed strong immunoreaction to smooth muscle actin antibody (Fig. 1D).

Pulmonary lesions were histologically and immunohistochemically superimposable to the epithelial uterine neoplasm (Fig. 2). Aggregates of neoplastic cells were found in mediastinal lymph nodes. On histological and IHC data a definitive diagnosis of uterine adenocarcinoma with pulmonary metastases and multiple uterine leiomyomas was made.

DISCUSSION

The classification of the uterus tumours of the domestic animals follows the general scheme employed in the first International Histological Classification of Tumours of Domestic Animals based on histological criteria. The classification includes: epithelial tumours such as adenoma and adenocarcinoma of the endometrium and mesenchymal tumours that include fibroma, leiomyoma and leiomyosarcoma [4].

Histological and immunohistochemical characteristics of multiple uterine leiomyomas have already been described in domesticated Asian elephant, and our findings are similar to those previously reported [5]; the tumourigenesis of uterine leiomyoma remains unclear even if previous studies have pointed out that hyperoestrogenic state is relevant to the initiation of this tumour [5].

To the author knowledge this is the first report of uterine adenocarcinoma with distant metastases diagnosed in an Asian elephant (*Elephas maximus*). In contrast, endometrial carcinoma is the most common

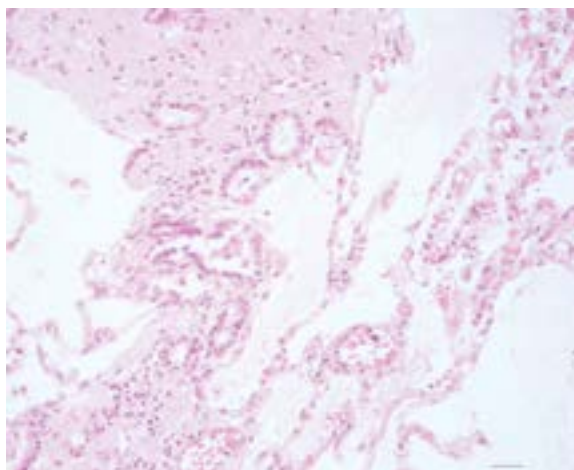


Figure 2. Lung; neoplastic cells appear organised in acinar and tubular structures, with polygonal shape, distinct cell borders and eosinophilic to light basophilic cytoplasm; haematoxylin and eosin stain; scale-bar 100 microns.

invasive neoplasm of the human female reproductive tract [2]. Chronic estrogenic stimulation has been associated with endometrial hyperplasia and carcinoma in women, and endometrial carcinoma tends to be most common in aging, nulliparous females with a history of menstrual irregularity consistent with anovulatory cycling [6]. This relation between sex hormones, especially oestrogens, and endometrial carcinoma is also described in rabbit [12].

To describe a case of uterus metastatic adenocarcinoma associated to multiple leiomyomas is extremely important also for epidemiological purpose considered that the elephants, despite their long life-span, seem to be at lower risk to develop cancer potentially related to multiple copies of TP53 gene. TP53 (encoding the protein p53 [RefSeq NM_000546]) is a crucial tumour suppressor gene, mutated in the majority of human and animal cancers [7]. Compared with human cells, elephant cells demonstrated increased apoptotic response following DNA damage [1].

CONCLUSIONS

Finally, the tumours described in this study seems to have the same histological pattern and biological behaviour already described in women and domestic animals [9, 17]. Considering that anthropogenic activities contribute to the development of neoplasia in wildlife species [8], and that endometrial cancer may be related to environmental pollutants [13] animals like elephants, living for long time in zoological gardens, could be considered sentinels of disturbed environments.

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