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Histological Study of Uterine leiomyoma in Asian Elephants (*Elephas maximus*)

Presented by : **TOUCHEN Abderrahman**

Publicly defended on : 08-07-2024

Before the jury :

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En conséquence je m'engage à citer toutes les sources que j'ai utilisées pour écrire ce mémoire.

Signature
TOUCHEN Abderrahmane

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Abstract

Uterine leiomyomas or fibroids are benign tumors that arise from the smooth muscle of the uterus and are frequent in both captive and wild animals. They are also highly common in managed Asian elephants (*Elephas Maximus*). Our case describes a 62-year-old female elephant who died in Ben Aknoun National Park in Algiers. Autopsy revealed a larger-than-normal uterine size with a pale pinkish-white multinodular solid mass. Histopathological examination of the tumor revealed a pattern of well-differentiated, cells within a large stroma of finger-like collagenous connective tissue. The results of our study compared to other archival studies indicate that female reproductive tract neoplasia are common in adult Asian elephants and are not limited to leiomyomas, which can affect fertility and cause obstacles to conservation in managed care.

Keywords: Elephant, leiomyoma, tumor.

Résumé

Les léiomyomes ou fibromes utérins sont des tumeurs bénignes qui naissent du muscle lisse de l'utérus et sont fréquents chez les animaux en captivité et sauvages. Ils sont également très fréquents chez les éléphants d'Asie (Elephas Maximus). Notre cas d'étude décrit une femelle d'éléphant de 62 ans, morte dans le parc national de Ben Aknoon à Alger. L'autopsie a révélé une taille utérine plus grande que la normale avec une masse solide multi-nodulaire de couleur blanc pâle. L'examen histopathologie de la tumeur a révélé un motif de cellules bien différenciées au sein d'un grand stroma de tissu conjonctif collagène en forme de doigt. Les résultats de notre travail, comparé à d'autres études similaires, indiquent que les néoplasies utérines sont courantes chez les éléphants d'Asie adultes et ne se limitent pas aux léiomyomes, qui peuvent affecter la fertilité et constituer des obstacles à la conservation dans les soins gérés.

Mots clés : Éléphant, léiomyome, tumeur.

الملخص

الأورام الليفية الرحمية هي أورام حميدة تنشأ من العضلات الملساء للرحم وهي شائعة في كل من الحيوانات الأسيرة والبرية. وهي شائعة أيضًا في الأفيال الآسيوية المدجنة (Elephas Maximus). تصف هذه الحالة أنثى فيل تبلغ من العمر 62 عامًا توفيت في منتزه بن عكنون الوطني بالجزائر بعد اكتشاف ورم رحمي غير متوقع بعد عدة أسابيع من الاعتقاد بأنها حامل. كشف تشريح الجثة عن حجم رحم أكبر من الطبيعي مع كتلة صلبة متعددة العقيدات بيضاء وردية شاحبة. كشف الفحص النسيجي للورم عن نمط من الخلايا المتمايزة جيدًا داخل سدى كبير من النسيج الضام الكولاجيني الشبيه بالإصبع. تشير نتائج هذه الدراسة والعديد من الدراسات الأرشيفية الأخرى إلى أن أورام الجهاز التناسلي الأنثوي شائعة في الأفيال الآسيوية البالغة ولا تقتصر على الأورام الليفية الرحمية، والتي يمكن أن تؤثر على الخصوبة وتسبب عقبات أمام الحفاظ عليها في الرعاية المدارة

الكلمات المفتاحية :الفيل، الورم العضلي الأملس، الورم .

List of Abbreviations

E. : *Elephas*

E. m: Elephas Maximus

E. coli: Escherichia coli

E.g. : Exempli gratia

EEHV: Elephant Endotheliotropic Herpes virus

ENSV: higher national school of veterinary

EMC: Encephalo myocarditis

FMD: Foot and Mouth Disease

FMDV: Foot and Mouth virus

FFPE: Formalin-Fixed Paraffine-Embedded

HE: Hematoxylin and eosin

L: Loxodonta

TB: Tuberculosis

TP: tumor protein

PNET: peripheral neuroectodermal tumor.

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Introduction

The uterine leiomyoma, commonly referred to as fibroids, is a benign smooth muscle tumor that occurs within the uterus. While extensively studied in humans, its occurrence and pathology in non-human species, particularly in Asian elephants (*Elephas maximus*), remain less understood. The Asian elephant, an endangered species, presents unique physiological and reproductive challenges that necessitate comprehensive research to enhance conservation and veterinary efforts. Leiomyomas are not cancerous and do not spread to other parts of the body (metastasize), but they can be large and disfiguring, and can also cause mobility and health problems in elephants. Asian elephants reported in our study developed benign and malignant neoplasms at higher rates than African elephants,

Histological examination of uterine leiomyomas in Asian elephants offers crucial insights into the tumor's cellular composition, growth patterns, and potential implications on the reproductive health. Such tumors, although benign, can have significant impacts on fertility, pregnancy, and overall well-being. Understanding the histopathological characteristics of uterine leiomyomas in Asian elephants is therefore essential for developing effective diagnostic, therapeutic, and management strategies.

This study aims to fill the existing knowledge gap by providing a detailed histological analysis of uterine leiomyomas in Asian elephants. Our case study describes a 62-year-old female elephant who died with unexpected uterine tumor, being found several weeks after she was thought to be pregnant

By examining tissue samples through various histological techniques, we seek to identify specific morphological features, cellular dynamics, and potential etiological factors contributing to the development of these tumors.

Additionally, this research will compare the histopathological findings with those observed in other species, to uncover any possible similarities or distinct differences

Ultimately, the findings from this study will not only contribute to the veterinary literature on Asian elephant health but also support conservation efforts by improving reproductive management practices.

Enhanced understanding of uterine leiomyomas in Asian elephants will aid veterinarians and conservationists in ensuring the longevity and reproductive success of this endangered species.

BIBLIOGRAPHY

Chapter I: overview on Asian elephants

1 Some information on elephants

1-1 taxonomy and Origin of elephants

Elephants belonging to the family of Elephantidae a large family containing both elephants and mammoths appeared in the fossil record around 9 to 10 million years ago (H.Saegusa et *al.*, 2014)

Species classification:

Kingdom: **Animal**

Phylum : **Chordate**

Sub-phylum: **vertebrate**

Class: **Placental mammel**

Sub-class: **Theria**

Order: **Proboscidean**

Family: **Elephantidae**

Most species of the Elephatidae family being extinct only three remain roaming today the African bush elephant (*Loxodonta africana*), the African forest elephant (*L. cyclotis*), and the Asian elephant (*Elephas maximus*).

Elephas Maximus is also divided into four shown in the table below:

Table 1: sub species of Asian elephant

E. maximus Asian elephant	*E. m. maximus* "Sri Lankan elephant" *E. m. indicus*"indian elephant" *E. m. borneensis* "Borneo elephant" *E. m. sumatranus* "Sumatran elephant"

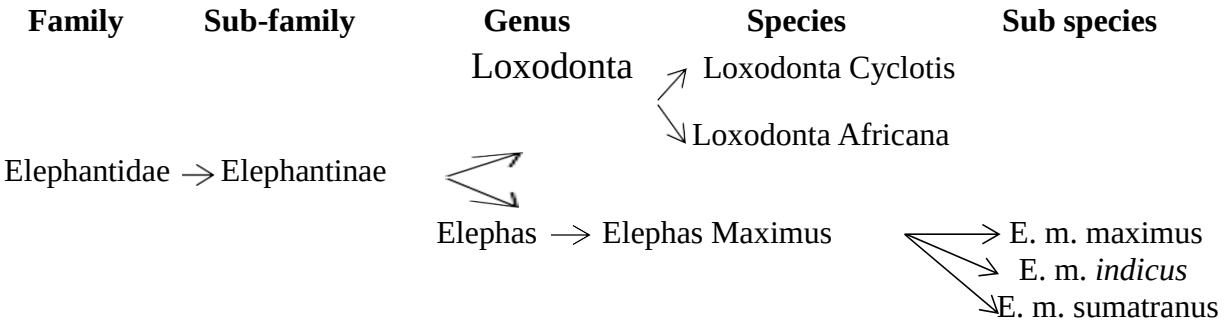


Figure 1: a partial and a simple Classification of the subspecies of elephants (Shoshani, 2006)

Note: The number of subspecies of Asian elephant is controversial: the distinction of subspecies is currently based on different distribution areas (DELNATTE 2008)

The Asian elephant (*E Maximus*) is the lone survivor of Genus Elephas was originally from Africa and found during the early Pliocene epoch 5 to 6 million years ago(Haynes,G,1993), and migrated to Asia around 3.6 milion years ago (lannucci 2023)

1-2 history of Asian elephants

The Asian elephant has a domestication history dating back to around 6000 BC, the Asian elephant has played a significant role in Asian societies.

Their impressive size and strength made them invaluable assets in warfare, where they were often mounted with armored riders and used to charge enemy lines. (Havelange. A 2020) Beyond the battlefield, Asian elephants were also employed as beasts of burden, particularly in the timber industry. Their ability to haul heavy logs through dense forests and transport goods over long distances made them indispensable for trade and construction. Today, the role of Asian elephants has evolved, with their primary involvement in tourism industry and, to a lesser extent, forestry (Havelange. A 2020).

Figure 2: Female Sri Lankan elephant with calves, Yala National Park, Sri Lanka

1-3 Geographical Distribution of the Asian Elephant

The Asian elephant was present over a very large part of the Asian continent, from the Iranian coasts and further inland to China via India and the South-Eastern countries, but that was before the 20th century, with area approximately 9 million km².(Havelange. A 2020)

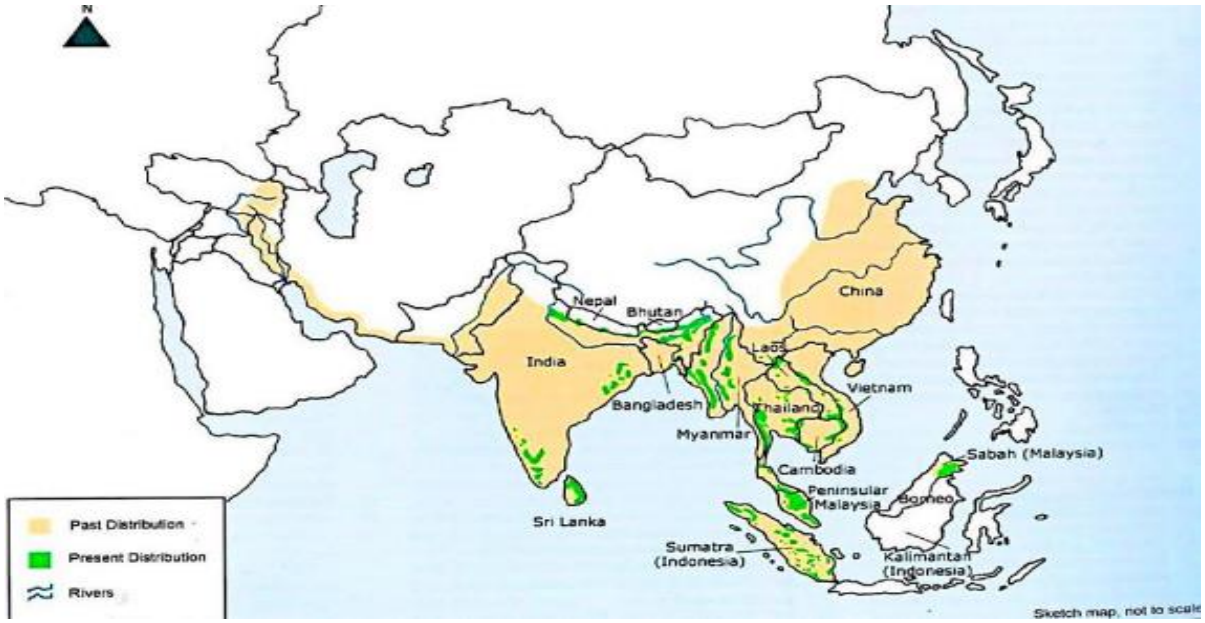


Figure 3: distribution of *Elephas Maximus* in today (in green and in the past (yellow) (Sukumar, R. (2011).

As depicted in the accompanying figure, the once expansive territory of the Asian elephant (Elephas maximus) has undergone a substantial reduction, now encompassing less than half a million square kilometers. This fragmented range spans across 13 Asian countries: Bangladesh, Bhutan, Vietnam, Nepal, Sri Lanka, Cambodia, China, Indonesia, Laos, Malaysia, Myanmar, Thailand, and India (Figure 3) (Havelange. A 2020)

The exact number of elephants in Asia is considered controversial topic more than in Africa. In 2005 there were 50,000 wild elephants living on Asian soil [J. Livet and J. Torsten, 2004.].with the exact number for wild elephant being between 44 281 et 49 107 (CITES, 2017),There are about 15,000 domesticated Asian elephants [D. Olson, 2004.] it is India today that has the largest number of elephants , almost 57% of the total population it was estimated to be 27,000–29,000 individuals. (Sukumar, R. 2011)

The oft-repeated global population “estimate” of about 30,000 to 40,000 or 50,000 Asian elephants is in reality no more than a crude guess, which has been accepted more or less unchanged for a quarter of a century despite major loss of Asian elephant habitat (Table 2). With few exceptions, all we really know about the status of Asian elephants is the location of some (probably most) populations, with in some cases a crude idea of relative abundance. For some large parts of the species range we do not even know where the populations are, or indeed if they are still extant .A major effort to address this ignorance is long overdue

Table 2: Status of Asian Elephant Populations in 2003

Country	Status
India	Distribution well known. Some valid population estimates, but majority of population estimates are less rigorous. No national population estimate possible.
Nepal	Distribution moderately well known, probably three main populations. No population estimates available, no national population estimate possible.
Bhutan	Distribution poorly known or published. Resident populations exist, but many elephants shared with India. No population estimates available, no national population estimate possible.
Bangladesh	No recent studies of distribution. No population estimates available, no national population estimate possible.
China	Distribution moderately well known. Crude information on relative abundance; no population estimates, no national population estimate possible.
Myanmar	Distribution moderately well known. Crude information on relative abundance. No population estimates, no national population estimate possible.
Thailand	Distribution well known. Crude information on relative abundance; no population estimates, no national population estimate possible.
Laos	Distribution well known. Crude information on relative abundance; no population estimates available no national population estimate possible.
Vietnam	Distribution of relic populations generally well known. Crude information on relative abundance available. No population estimates, but most recent guesses suggest fewer than 150 elephants remain.
Malaysia	Distribution moderately well know. Crude information on relative abundance on peninsula. Few if any high-quality population estimates available, no national population estimate possible.
Cambodia	Distribution moderately well known, some crude information on relative abundance; no population estimates available, no national population estimate possible.
Indonesia	In the mid-1980s, 44 discrete elephant populations were known to exist in Sumatra's 8 provinces. Some crude information about relative abundance exists for other sites, but no national population estimate possible.
Sri Lanka	Distribution well known. Crude information about relative abundance; no population estimates available, no national population estimate possible.

2-Morphological characteristics and difference between Asian and African elephants

Elephants are unique animals with many identifiable traits: their prehensile trunks, their ivory tusks, intelligence with long-term memory, and the fact that they are among the largest land mammals both living and extinct (Shoshani 1998).

Given their long lifespan; i.e., 65 years for African elephants (*Loxodonta africana*) (Moss 2001), and 80 years for Asian (Chapman et al. 2019) and with a lengthy gestation periods of 18 to 22 months.

However The Asian elephant is very distinguished from the African elephants(*Loxodonta africana*) by some morphological characteristics, they differ in various aspects such as the size of their ears, trunk, and tusks, as well as the shape of their forehead and back. As shown in the table below.

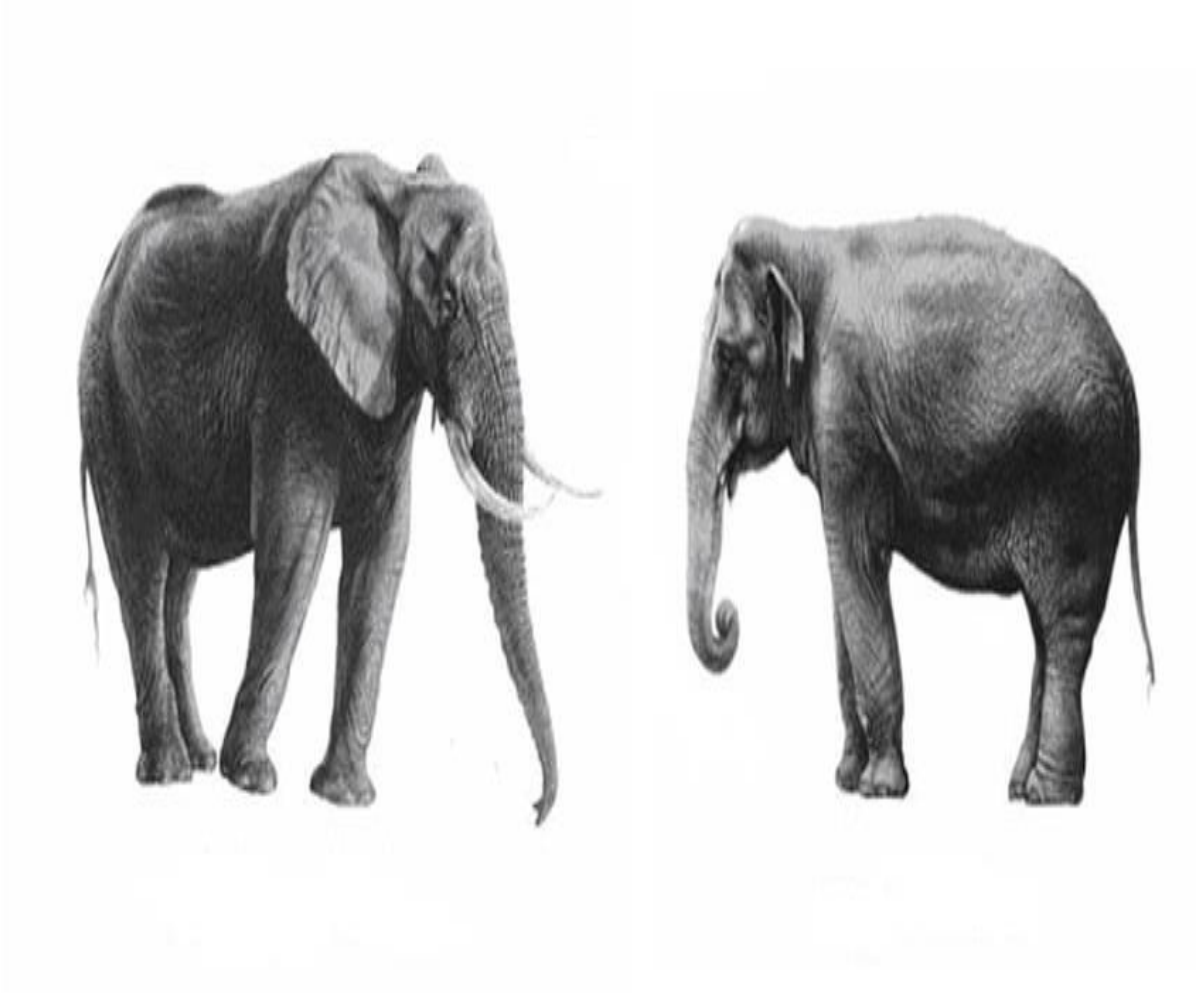
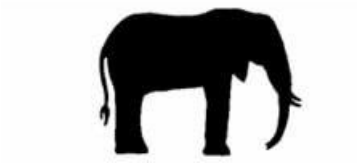
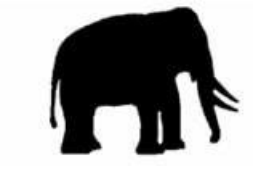


Figure 4: A photo of African elephant (*Loxodonta africana*),(left) and Asian elephant (*Elephas Maximus*) (right) (M. F. Stevenson 2006.)

Table 3: morphological Difference between Loxodonta africana and Elephas maximus (Shoshani, 2006)

	African elephant 	**Asian elephant** 
Weight	4000 to 7000 kilograms	2000 to 5500 kilograms
Height	3 to 4 meters	2 to 3.5 meters
Skin	Wrinkled	Smoother
Number of ribs	21 pairs	20 pairs
Highest point	Top of the shoulder	Top of the head
Size of ears	Larger exceeding height of the neck	Smaller
Shape of back	Concave	Convex
Shape of head	No compression No dish No bulges 	Compressed Dished forehead Dorsal bulges 
Teeth	Lozenge shaped 	Narrow compressed 
Food	Browser	Grazer
Tusk	Both sexes carry tusks but larger in males	Usually only males carry tusks while females ones are absents or vestigial
Trunk	Has more rings (annulations)	Less annulation but more rigid
Tip of trunk	Two fingers	One finger
Number of nail like structure	Forefeet 4 or 5 Hind feet 3 or 4	Forefeet 5 Hind feet 4 or 5

3 different pathologies in Asian elephants

From the medical standpoint, it is noted that generalized mammals (e.g., insectivores) are better adapted than specialized mammals (e.g., horses) to cope with living in different habitats. It could be argued that generalized mammals may be better adapted to fight diseases than specialized mammals. To test this hypothesis a survey of diseases known to occur in the African versus the Asian elephant should be conducted. (Fowler, M.E, 2006)

It is predicted that the African species (*L. Cyclotis* and *L. Africana*) would be more resistant to diseases including communicable and zoonotic diseases than the Asian species (*E. Maximus*). (Fowler, M.E, 2006)

3-1 Elephant Gross Examination Checklist (Murray_E_Fowler2006).

01. General exam (physical and nutritional condition, skin, body orifices, superficial lymph nodes).

02. Musculoskeletal system (bones, marrow, joints, muscles).

03. Body cavities (fat stores, pleura, thymus, lymph nodes and spleen.).

04. Respiratory system (trunk passages, pharynx, larynx, trachea, Bronchi, lungs, regional lymph nodes; submit lung lesions

For TB culture; bronchial lymph nodes should be cultured for TB even if normal in appearance).

05. Cardiovascular system (heart, pericardial sac, great vessels, myocardium, valves, chambers; be sure to examine abdominal aorta closely for subtle or obvious aneurysms).

06. Digestive system (mouth, teeth, tongue, esophagus, stomach, small intestine, cecum, large intestine, rectum, liver, pancreas, mesenteric lymph nodes).

07. Urinary system (kidneys, ureters, bladder, urethra).

08. Reproductive system (urogenital canal, testes/ovaries, placenta, uterus and cervix, penis/vagina, prostate, seminal vesicles, bulbourethral gland, mammary gland). Uterine

Masses/tumors are extremely common in Asian elephants, and multiple tumor types may be present.

9. Endocrine system (thyroids, parathyroids, adrenals, pituitary).

10. Central nervous system (brain, meninges, spinal cord).

11. Sensory organs (eyes, ears) (Murray_E_Fowler2006).

3 -2 Most important infectious diseases

3-2-1 Elephant Endotheliotropic Herpes virus (EEHV) Infection

Asian elephants are uniquely threatened by an acute hemorrhagic disease resulting from infection with elephant (EEHV) (Long et *al*. 2016). With mortality rates being much higher for Asian elephants then that of African elephants, suggesting a genetic component for increased EEHV lethality. Characterized by generalized hemorrhages in the heart, liver, intestine, and tongue and is the cause of abortion in captive Asian elephant populations

Clinical signs in elephants are sudden death with Initial signs being lethargy, accompanied by mild colic and anorexia. (Ossent, P.et *al* 1990), the presence of edematous swelling (head, neck, trunk, thoracic limbs) as the disease progresses. A sign that is often seen is cyanosis of the tongue, beginning in the tip and progresses caudally. (Richman,et *al*, 1996) Abortion has occurred with evidence of herpesvirus infection in fetal tissue. (Fowler, M.E, 2006) and ulcers may be observed in the oral and laryngeal cavities and the intestines. ((Richman,et al, 1996) Hematologic findings in three Asian elephants, included leukopenia, thrombocytopenia, and a low erythrocyte count. (Richman,et al 1996) the opposite of elephant that got treatment successfully in Missouri, where there was alymphopenia and a monocytosis. (Schmitt, 2000) The virus may be detected early, during the viremic stage in blood, by polymerase chain reaction (PCR) (Fowler, M.E, 2006) Microscopic findings include micro hemorrhages in the heart and tongue. Interstitial edema and some hepatocellular degeneration are observed in the liver. Treatment has been attempted and successful in at least two elephants. (Fowler, M.E, 2006) but No vaccine is available for this herpes virus. Since there is concern that the African elephant may be the source of infection for Asian elephants, it would be prudent to avoid housing African elephants with Asian elephants, particularly with young elephants. (Fowler, M.E, 2006).Lack of facilities may make this difficult. Asian elephants naive to earlier exposure could be of risks of transmission of EEHV may be higher during transportation of elephants to new facilities. (Murray E Fowler 2006)Serological tests for the identification of potential carriers or previous exposure to EEHV are becoming available for elephants. (Fowler, M.E, 2006)

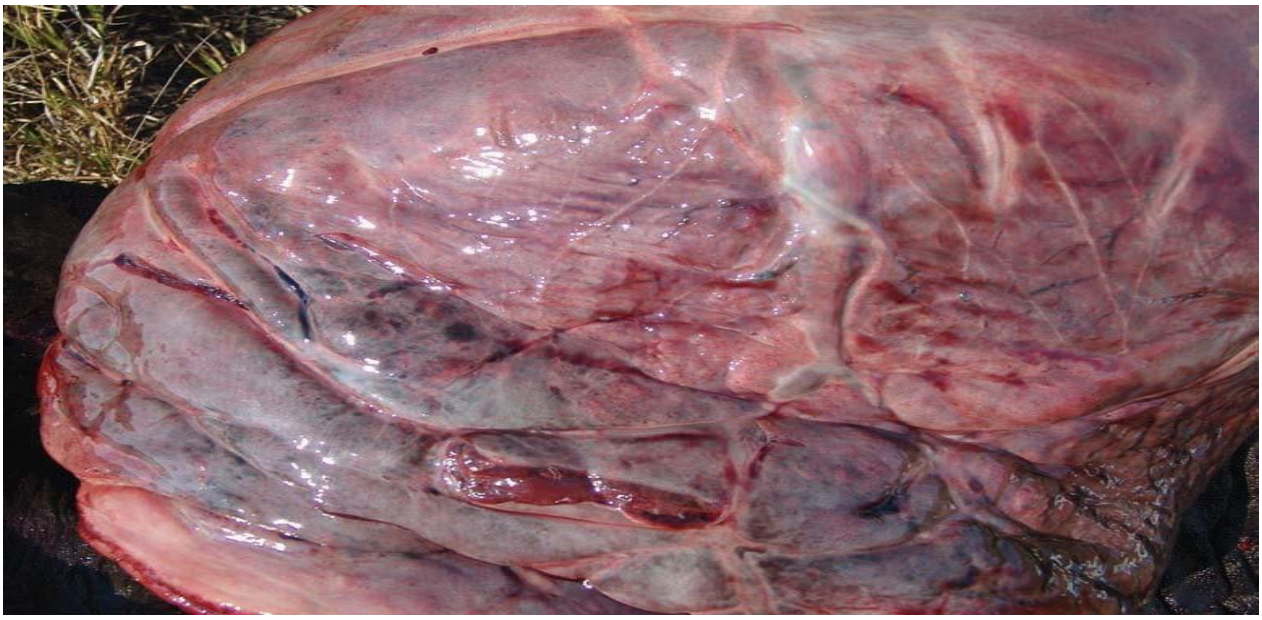


Figure 5: Epicardial hemorrhages in the heart of an Asian elephant that died of encepahlomyocarditis virus (courtesy of D. F. Keet).

3-2-2 Elephant Tuberculosis

in addition to increased susceptibility to EEHV compared with African elephants, Asian elephants were also significantly more vulnerable to TB infection (Marc Tollis ;Elliott Ferris 2021).Tuberculosis (TB) is an infectious bacterial disease affecting numerous species in elephants was first described more than 2000 years ago and was the subject of publications in the 20th century the 1996 was once considered a critical year, with the discovery of large numbers of infected elephants in the United States and Europe and the realization that the disease could be a zoonosis. (Fowler, M.E, 2006) In fact, the most common tuberculosis strain in elephants is Mycobacterium tuberculosis the same in humans transmition is primarily done by through infected respiratory droplets during trunk greeting or spraying .(Fowler, M.E, 2006)

The most common symptom is chronic weight loss anorexia and exercise intolerance, the prevalence of TB in captive elephants has not been evaluated, but it is likely due to the intermingling of sick and healthy elephants and humans during festivals, and the high prevalence in the human population. There is no standardized testing for TB in elephants. (Fowler, M.E, 2006)

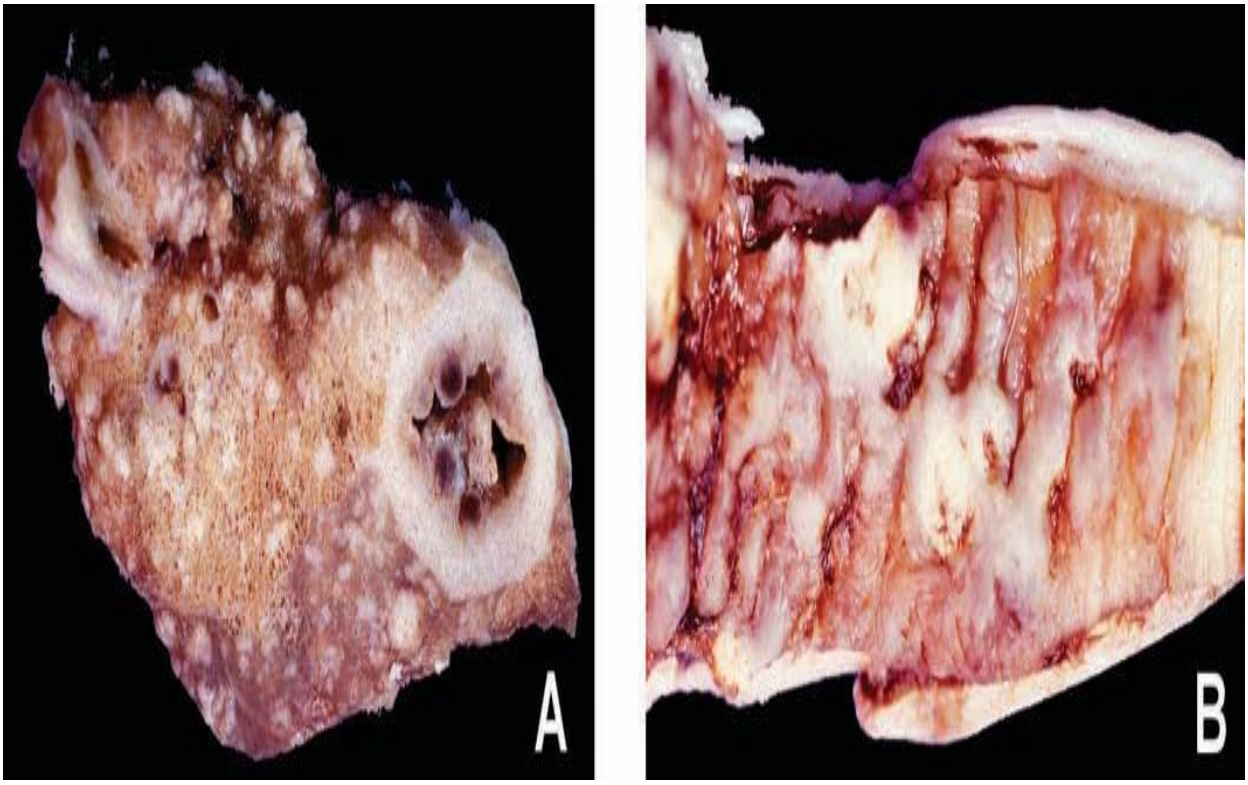


Figure 6: Mycobacterium tuberculosis infection in an Asian elephant. A) lung segment with small bronchial and parenchymal tuberculous granulomas, B) tracheal segment with tuberculous mucosal plaques.(Fowler, M.E, 2006)

3-3 Other common diseases

3-3-1 Colibacillosis

Colibacillosis refers to a group of diseases caused by pathogenic strains of Escherichia coli. Although there is only one species of E. coli but there are hundreds of strains. It may be an invasive bacterial infection or an enterotoxemia.

With The transmission of the organism from one animal to another Spreading via fecal-oral route (Fowler, M.E, 2006)

Nonpathogenic strains are often found as normal flora andinhabitant of the large intestine of animals. (Hirsh, D.C. 2004) It

One causes an enterotoxic diarrhea. Another produces an invasive disease, which results in generalized infection and septicemia. A third form is a non-enterotoxigenic diarrhea (Mathew, E.S. 1990). Laboratory tests are crucial for identifying and Isolation of strains, as clinical signs alone are insufficient for diagnosis. (Chakraborty, A. and Sarma, D.K. 1995.)

It can be difficult to diagnose colibacillosis without conducting laboratory diagnostic tests to identify the strain isolated. (Chakraborty, A. and Sarma, D.K. 1995.)Escherichia coli is a ubiquitous, gram-negative, mobile, non–spore-forming enteric bacterium that excrete at least five Pathogenic products; enterotoxins, siderophores, shigalike toxins, cytotoxic/necrotizing factors and hemolysins. (Fowler, M.E, 2006) and it leads to diarrhea, hypovolemia, and metabolic acidosis, and develops to be hyperkalemia. Clinical signs in elephants. There are multiple forms of colibacillosis. (Mathew, E.S. 1990)

3-3-2 Encephalomyocarditis:

While Encephalomyocarditis (EMC) is a natural infection in rodents without causing disease, sporadic outbreaks can occur in various domestic and wild animals, elephants. (Murname 1981).EMC virus is in the genus Cardio virus of family Picornoviridae. With Both African and Asian elephants have developed EMC with Cases occurring sporadically in eight zoos in six states of the United States. And also in South Africa and Australia, however Infection doesn't spread between elephants.(Fowler, M.E, 2006)

Clinical signs in elephants being Sudden death as the predominant sign or, development of anorexia and lethargy with moderate dyspnea and pulmonary edema resulting from congestive heart failure. (Fowler, M.E, 2006)

Infections in elephants do not always translate into clinical disease, there appears to be a sex bias toward clinical infection in males. It is known that testosterone enhances susceptibility to EMC infection. (Friedman, 1972).

The infection progresses so rapidly with Sudden death or signs associated with heart failure plus myocarditis. (Murray E Fowler, 2006) Virus particles may be visible on electron microscopy.

Prevention by rodent control is crucial as there is no specific treatment for EMC, population monitoring would reveal the use of rigorous control methods if there was a Rodent population buildup.(Murray E Fowler, 2006)

Inactivated vaccines were used in outbreaks in the United States with no conclusions reached as to effectiveness in elephants. (Murray E Fowler, 2006)

3-3-3 Foot and Mouth Disease

Foot and mouth is a highly contagious but rarely fatal viral disease, FMD is characterized by vesicular lesions and, subsequently, erosions of the oral mucosa and skin of the feet. (Fowler, M.E. 1985.)FMD is caused by Aphtho virus sp of family Picornoviridae, with seven immunologically distinct types of FMD virus (FMDV) are known (A, O, C, Asia 1, SAT1, SAT 2, SAT3) (Fowler, M.E, 2006))

Examination of the feet revealed hot, swollen, and tender skin around the toenails. (Fowler, M.E, 2006) The illness lasting for 10–20 days in uncomplicated cases most elephants with FMD will survive and pose no threat to other animals, providing soft feed to counter reluctance to eat. (Fowler, M.E, 2006)t

The transmission may be by respiratory, exposure to contaminated food and water and direct contact with infected animals. Humans may contribute to the spread of FMD by inhaling in aerosol droplets when working around infected animals. (Fowler, M.E, 2006) Clinical signs in elephants are noted to be anorexia and lameness, with mild fever, and vesicles on the tongue, cheeks, and mucous membranes of the trunk,

3-3-4 Rabies:

Rabies is one of the oldest diseases known to man, being first described over 4000 years ago. It is characterized as a uniformly fatal encephalomyelitis except in reservoir hosts. Caused by a Lyssavirus, serotype/genotype 1 of the family Rhabdovirus ,

There are only a few cases of rabies in elephants; Initial signs may be anorexia or behavioral changes (Fowler, M.E, 2006), but these progress to neurological signs that may vary depending on the precise location of the encephalitis. No treatment is available.

Elephants suspected of having rabies or other neurological conditions should be isolated and handled only in a no-contact mode. No vaccine has been validated for use in elephants.(Fowler, M.E, 2006)

Chapter II: tumors and cancers in Asian elephants

1- Different cases of Benign tumors of elephants

Tumors and cancer in elephants are considered uncommon and unusual, but it does sometimes occur, Elephants under human care or in the wild are sometimes diagnosed with it, more often in Asian elephants than in the two species found in Africa.

The longevity of elephants about 80 years and the huge cell numbers should have made elephants have higher rates of cancer but in reality they have low cancer rates and lower mortality then humans (Marc Tollis and Elliott Ferris 2021).

Fibromas and fibro sarcomas have been reported in both African and Asian elephants and may occur in young elephants. (Fowler, M.E, 2006)

Cutaneous Tumors on the trunk may be particularly annoying for the elephant and it is also noted that Mammary gland tumors have not yet been found (Murray_E_Fowler2006).

Figure 7: Fibro sarcoma in a 4-year-old Asian elephant (Fowler, M.E, 2006)

In an old case, an elephant of 54 years old developed a rapidly growing mass as large as a toenail with Metastases In the lung and lymph nodes were found during necropsy (Liu, C.H., Chang, 2004)

A surgical removal of an aural rhabdomyosarcoma from a wild-caught African elephant has also been described (Murray_E_Fowler2006).

This tumor was located on the anterior aspect of the pinna and over a period of 4 years, it had progressed slowly in size the mass extended ventrally to the zygomaticoauricularis muscle that controls ear movement (Lloyd, M 1993).

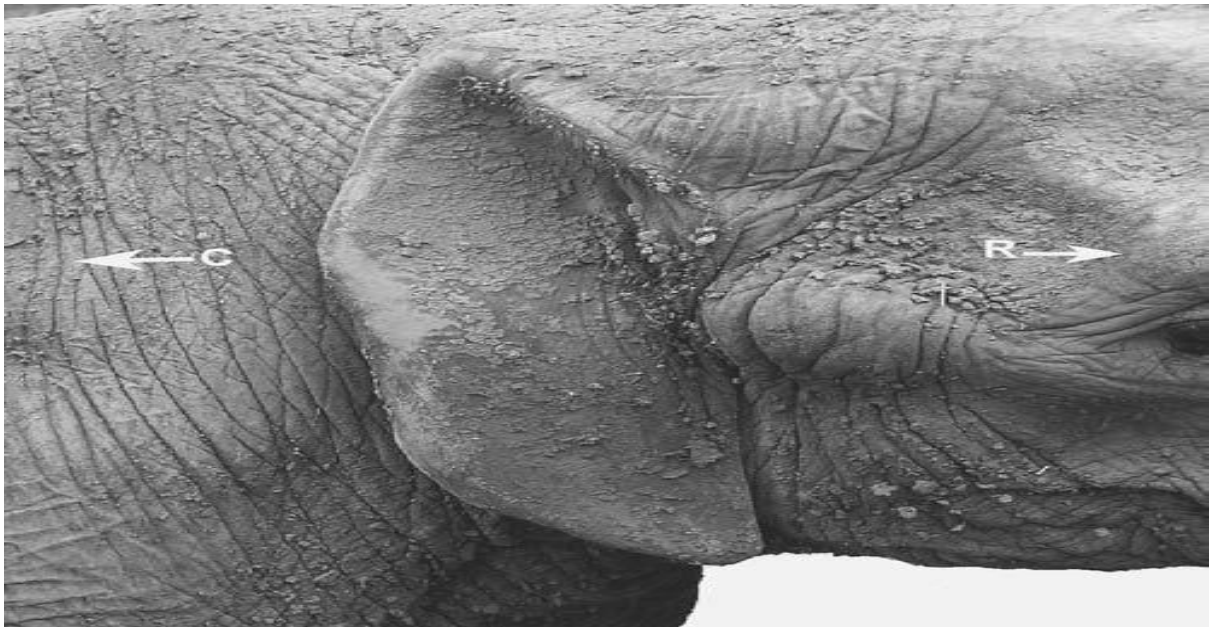


Figure 8. Post thromboembolic loss of 85% of the right ear of an African elephant. Rostral (R) and caudal (C) orientation are denoted. Necrosis of the pinna

1-1 Uterine tumors in both Asian and African elephants

Asian and African elephants exhibit clearly different uterine tumors. Asian elephants have the tendency to develop multiple benign uterine tumors in the myometrium (leiomyoma) after long non fertile reproductive periods approximately 10–15 years. (Fowler, M.E, 2006)

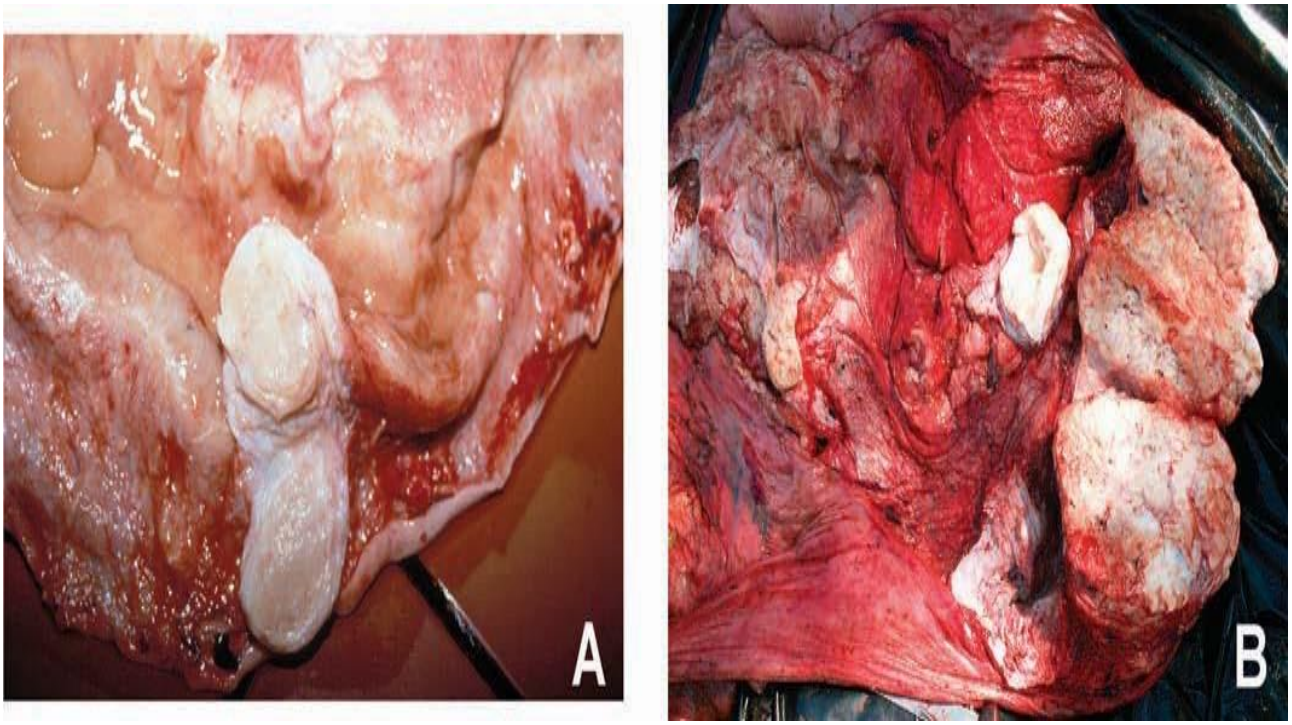


Figure 9: Elderly Asian elephant with uterine leiomyomas. A) Mild involvement with scattered tumor masses within the myometrium B) Massive uterine involvement in another elephant with large confluent fibrous-appearing tumor masses.

In contrast, African elephants have not been observed with these neoformations, but rather often develop only a cystic endometrial hyperplasia. (Fowler, M.E, 2006)

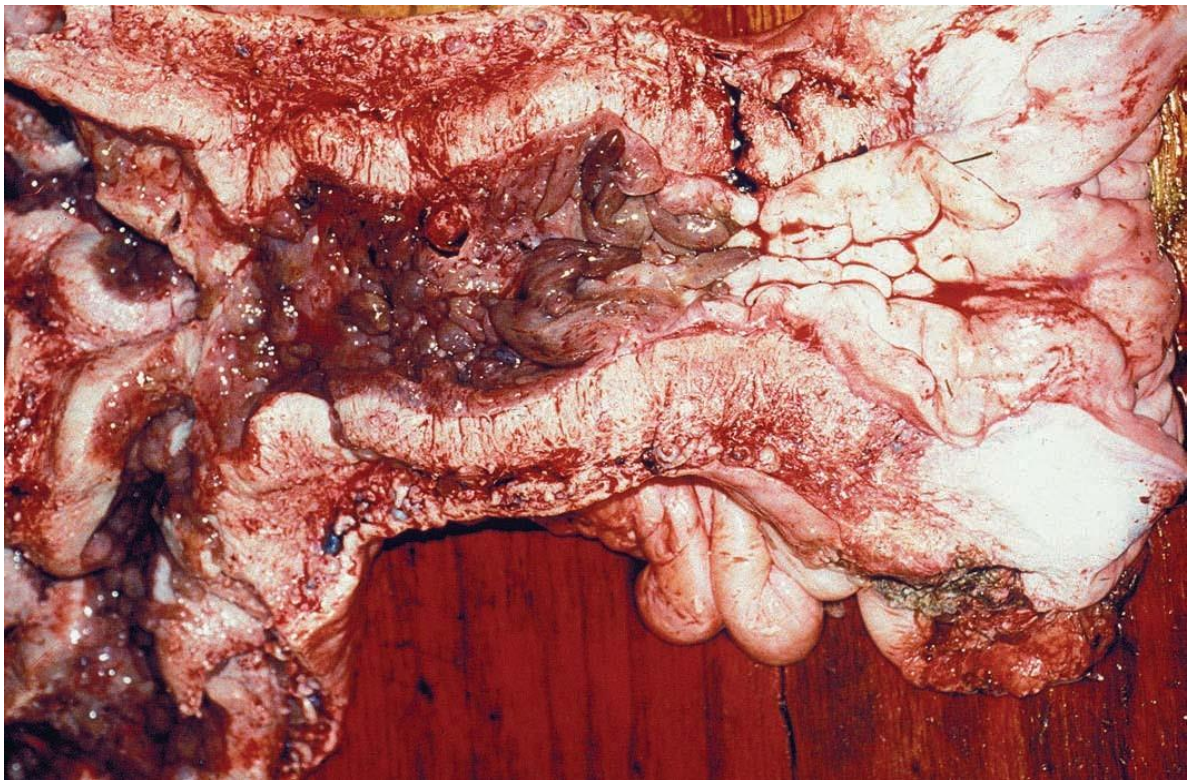


Figure 10: Uterus (body with cervix) of an elderly Asian elephant with cystic endometrial hyperplasia.

Cystic endometrial hyperplasia is also commonly found in Asian elephants. (Fowler, M.E, 2006) there has been only one identified case of a functional ovarian tumor where it produced levels of progesterone only seen in pregnancy for a period of over 3 years before the death of that Asian elephant as a consequence of the tumor .(Fowler, M.E, 2006)

1-2 Clinical and Pathological Aspects of Myometrial Leiomyoma in Asian elephants

Leiomyoma, also known as a uterine fibroid, is a benign tumor arising from the smooth muscle cells of the upper myometrium, the muscular layer of the uterus. Of Asian elephants (Elephas Maximus). [Landolfi 2020]. Leiomyomas are particularly prevalent, with studies reporting a staggering occurrence rate of 80-90% in adult females (Kidsadagon 2018). This high frequency stands in stark contrast to African elephants (Loxodonta Africana) which rarely, if ever, develop these tumors [Landolfi 2020].

Often appear as multiple tumors within the same uterus Can vary in size, but typically remain relatively small (a few centimeters) (Kidsadagon 2018).

Being generally asymptomatic the exact cause of Leiomyoma development in Asian elephants remains unclear. Several potential factors are being investigated:

- Hormonal Influences: Estrogen dominance during prolonged non-fertile periods is a suspected trigger, as these tumors are often hormone-sensitive. (Stewart, 1995).
- Genetic Predisposition: Asian elephants might possess a genetic susceptibility compared to their

African counterparts (Ryder, O. A. 2015)

Due to their typically asymptomatic nature, Leiomyomas in Asian elephants often don't require specific treatment.

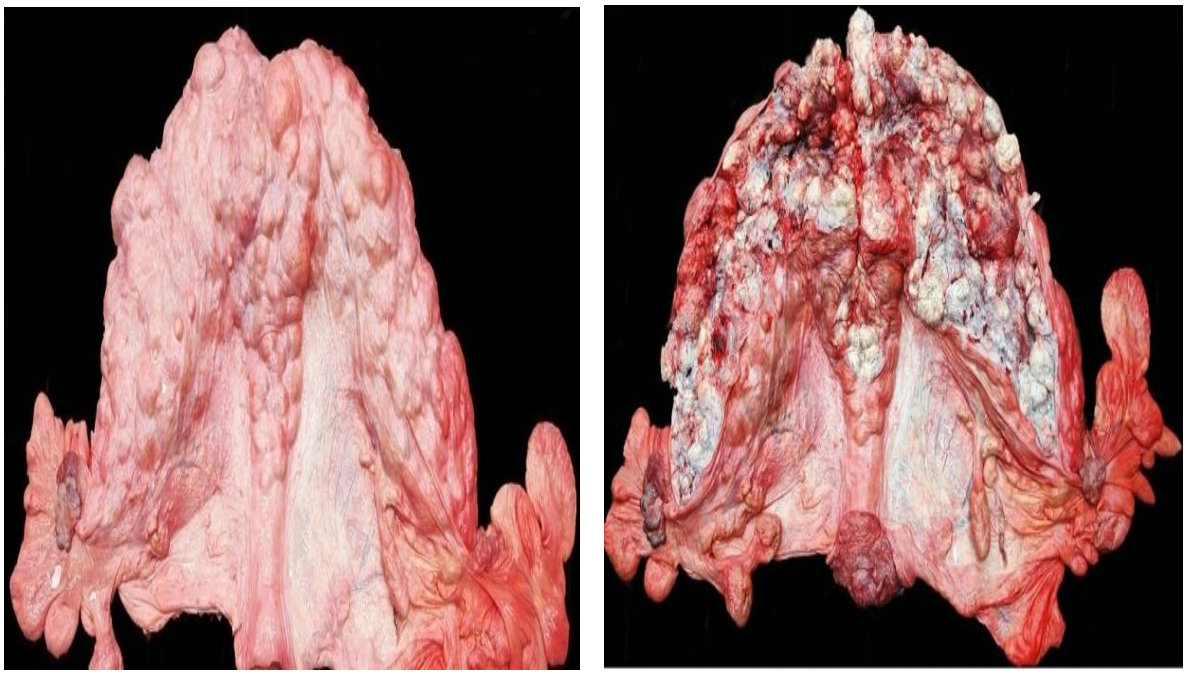


Figure 11: Uterine leiomyomas in Asian elephant (*Elephas Maximus*) (on the left), myometrium is distorted by numerous variably sized masses (on the right), masses are white on cut section (Jennifer A. Landolfi 2021)

Noted that leiomyomas were being discrete, encapsulated, firm, tan-white, nodular, masses that appeared to arise from the myometrium most were 1 to 10 cm (Jennifer A. Landolfi 2021). However in some cases, numerous coalescing masses could distort uterine architecture and and could result in the uterine lumen being obscured.

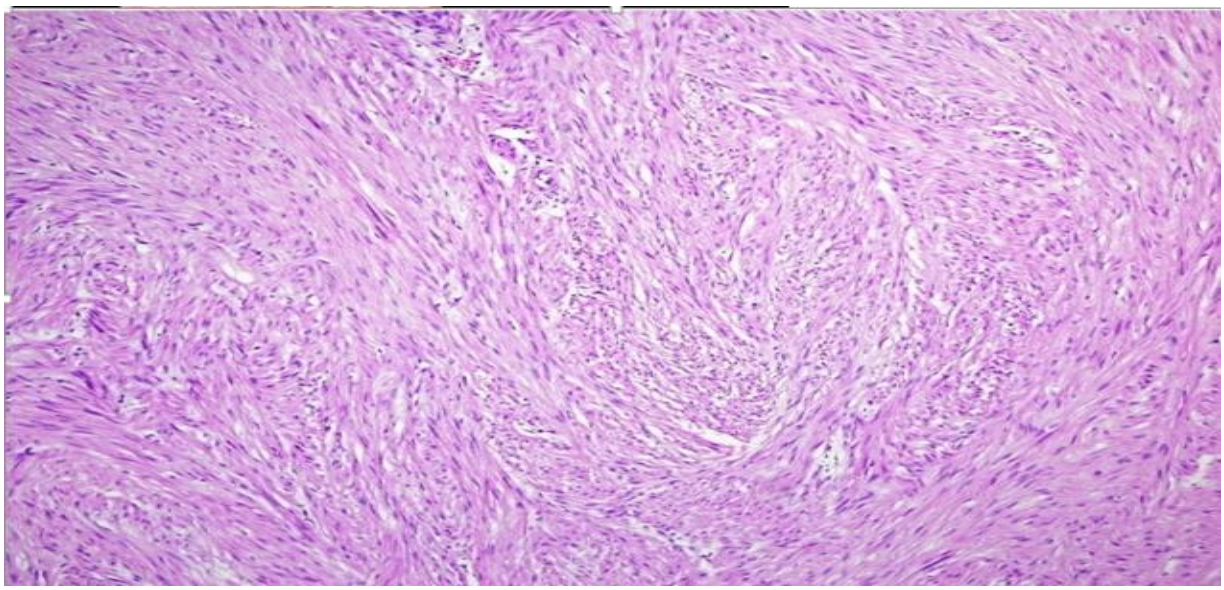


Figure 12 : Hematoxylin and eosin stain (HE). Neoplastic mesenchymal cells are arranged in haphazard, broad intersecting bundles. At 40x field (Jennifer A. Landolfi 2021)

Figure 13: Myometrial masses impinge upon the lumen of the uterus.Considering histologic features they were typical of benign smooth muscle neoplasms supported by variable amounts of fibrous stroma and consisted of long intersecting bundles of large spindyloid mesenchymal cells (Jennifer A. Landolfi 2021)

Leiomyomas could be detected via transrectal ultrasound. Since it could have important effects on reproduction, if the elephant is being considered for breeding then a careful evaluation is warranted.

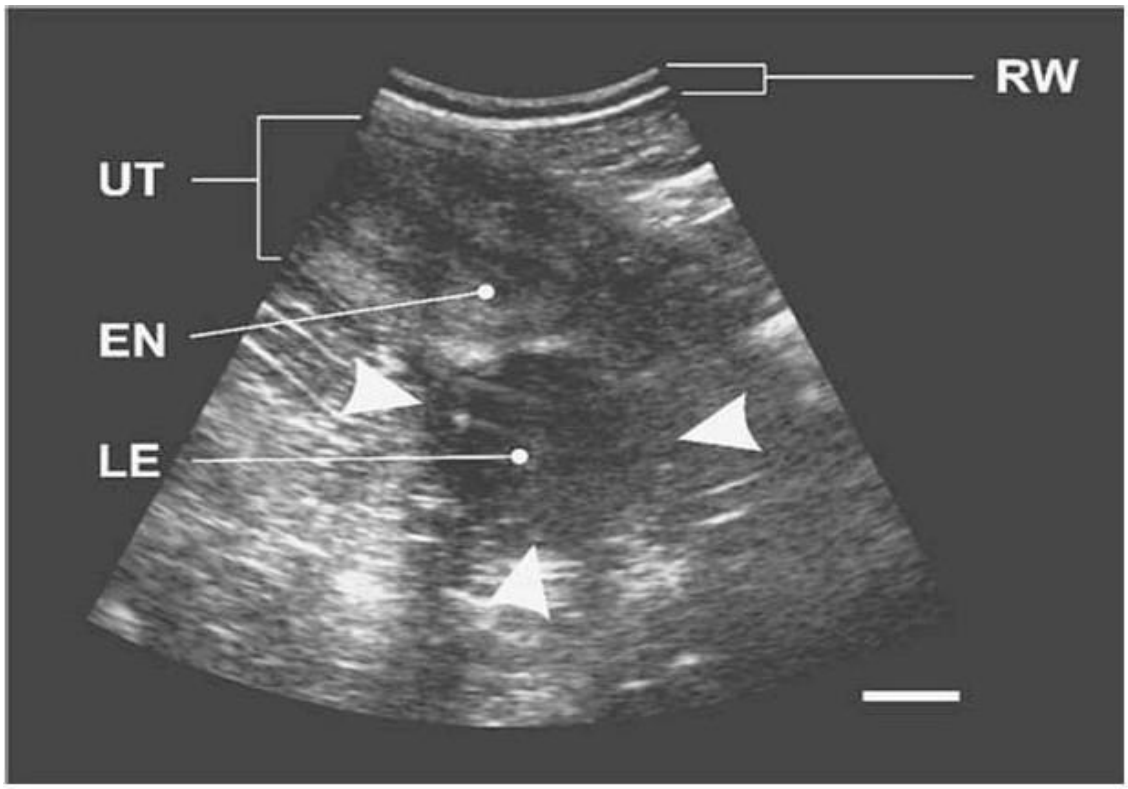


Figure 14: Transrectal sonogram of the uterine horn of asian elephant (UT) containing a large leiomyoma **(LE)** marked by the white arrow heads in the myometrium. **(EN)** The endometrium is not affected by this benign muscle tumor. **(RW)** The rectal wall appears as a moderate echoic strip on top of the sonogram. (Fowler, M.E, 2006)

2-Malignant uterine tumors of Asian elephants

Table 4. Malignant uterine neoplasms in 12 Asian elephants (*Elephasmaximus*) from United States managed care facilities.

Histologic type	Age	Reproductive history	Metastasis	Sites of metastases	Concurrent myometrial leiomyomas	Concurrent endometrial hyperplasia	Concurrent adenomyosis
Adenocarcinoma	59	Unknown	+	N/A	+	–	+
Adenocarcinoma	57	Unknown	+	Mesentery, kidney, lymph nodes	–	–	–
Adenocarcinomaa	53	Unknown	+	Lung, kidney	+	–	–
Adenocarcinoma	65	Unknown	–	N/A	+	–	–
Adenocarcinoma	Unknown	Unknown	+	Lung, adrenal gland, lymph nodes	+	–	–
Adenocarcinoma	53	Unknown	–	N/A	+	–	–
Adenocarcinoma	45	Nulliparous	+	Carcinomatosis, lymph nodes	–	+	–
Adenocarcinoma	51	Unknown	+	Carcinomatosis	–	–	–
Anaplasticcarcinoma	60	Nulliparous	+	Lymph nodes, kidneys, adrenal glands, adipose, vagina	+	+	–
Carcinoma in situ in endometrial polyp	57	Nulliparous	–	N/A	–	+	–
PNET	48	Nulliparous	+	Brain, lymphnodes	–	+	+
Angiosarcoma	50	Unknown	+	Lung, spleen, lymphnodes	+	–	–
Anaplasticsarcomab	53	Unknown	–	N/A	+	–	–

From the study in the table 4 cases of uterine adenocarcinoma where identified, rare malignant tumor .the uterine masses were all uniform and with similar gross characteristics of myometrial leiomyomas that they were grossly indistinguishable as described above. (Jennifer A. Landolfi 2021)In one case it had a large pelvic mass histologically categorized as an anaplastic sarcoma. In five of the eight cases of uterine adenocarcinoma they had additionally

many leiomyomas present in them with reported Distant metastasis in some but in the remaining 3 cases, adenocarcinomas were poorly demarcated, and ranging multi nodular asses that went from 12 to more than 30 cm in diameter.with distortion of the uterine wall and elevation of the endometrial surface. (Jennifer A. Landolfi 2021)

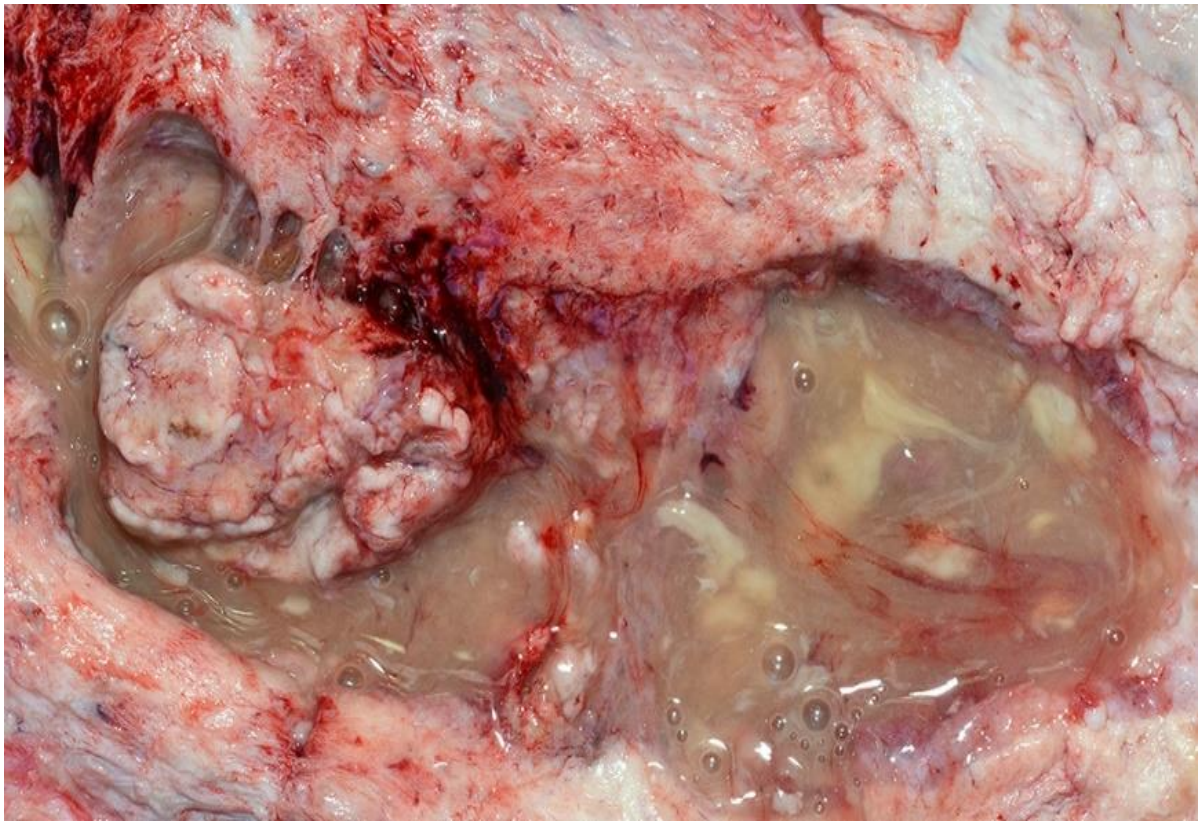


Figure 15: Asian elephant uterine adenocarcinoma, a firm, mottled, tan-pink, nodular mass protrudes from the endometrium (Jennifer A. Landolfi 2021)

It noted the masses were firm but with a rough, irregular endometrial surface after getting cut it contained yellow-tan, mucoid material from numerous small cystic cavitation.

Histologically, neoplastic cells were arranged in solid nests, acini or irregular, elongate, tortuous glandular structures, sometimes with luminal papillary projections (Fig. 14).

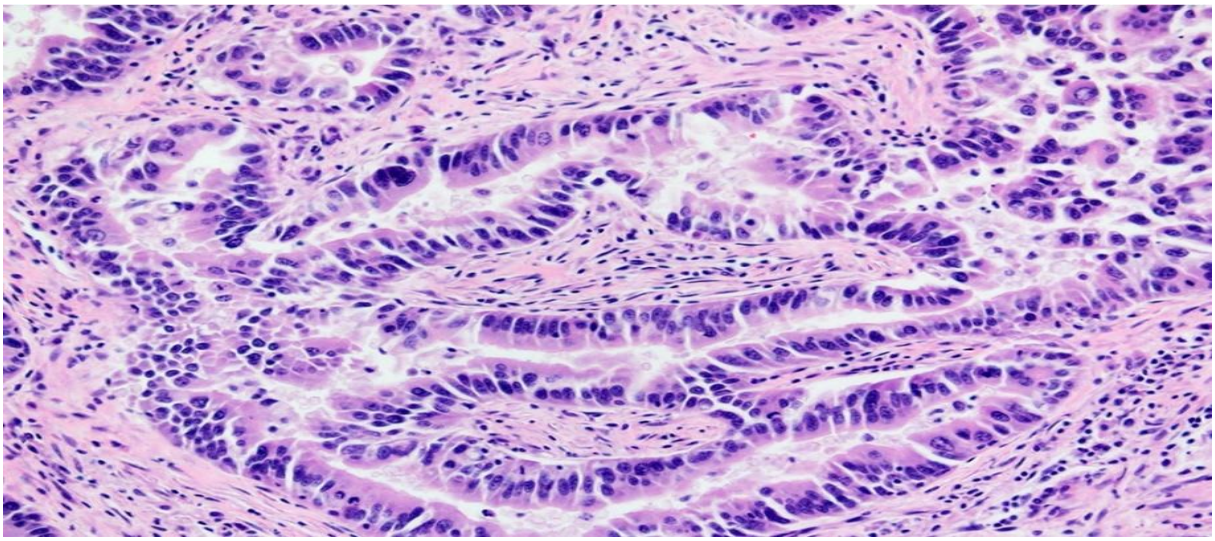


Figure 16: HE staining of adenocarcinoma. Cuboidal to columnar neoplastic epithelial cells are arranged in irregular, elongate, tortuous glandular structures supported by abundant fibrous densely collagenous stroma. (Jennifer A. Landolfi 2021)

Neoplastic cells were ranging from cuboidal to polygonal and had eosinophilia granular in moderate amounts with indistinct borders, basally oriented Nuclei with vesicular chromatin with one or more prominent nucleoli. (Jennifer A. Landolfi 2021)

The case of anaplastic carcinoma was largely evident as also poorly demarcated with the endometrium being irregular thickening and uterine wall becoming composed of friable, tan-brown tissue, this case had a uterine adenocarcinoma and a large mass was present at the pelvic inlet of uterine origin. (Jennifer A. Landolfi 2021)The pelvic anaplastic sarcoma was 59 cm in greatest diameter and weighed 48 kg. (Jennifer A. Landolfi 2021)

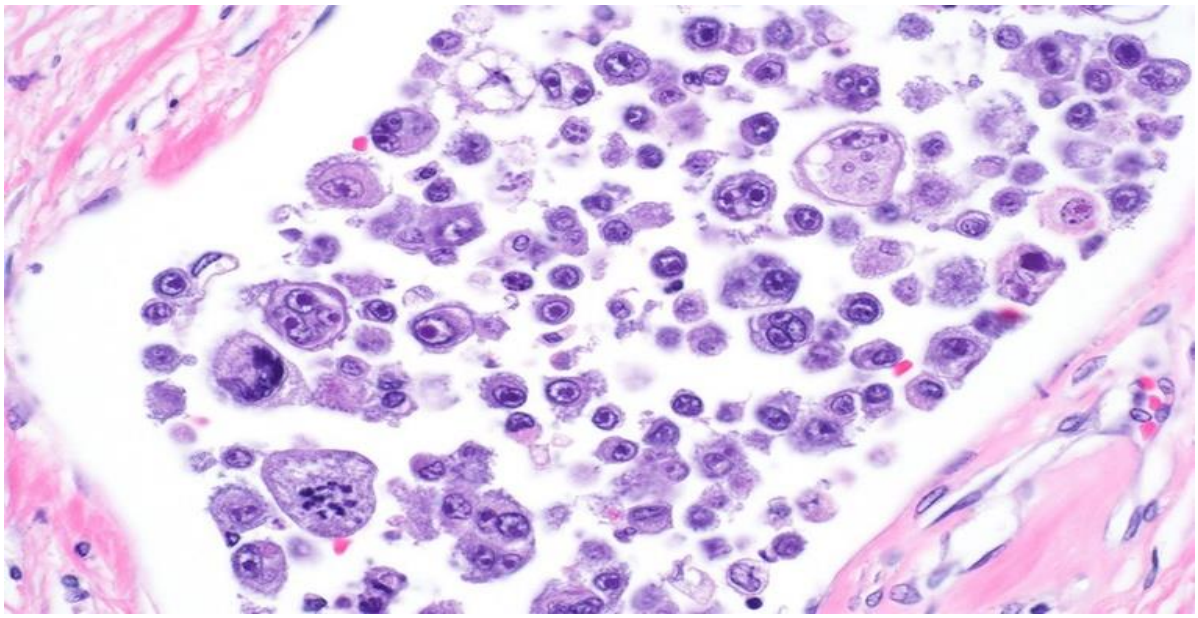


Figure 17. Anaplastic carcinoma, Asian elephant, uterus. A lymphatic vessel is filled with many pleomorphic neoplastic epithelial cells, and some contain multiple nuclei or have bizarre mitoses. Hematoxylin and eosin (HE).

The component of the neoplasm were dissociated individualized cells supported by fine fibro vascular stroma, they were also pleomorphic and ovoid to polygonal, abundant lacy **cytoplasm, round Nuclei and vesicular chromatin. (Jennifer A. Landolfi 2021)**

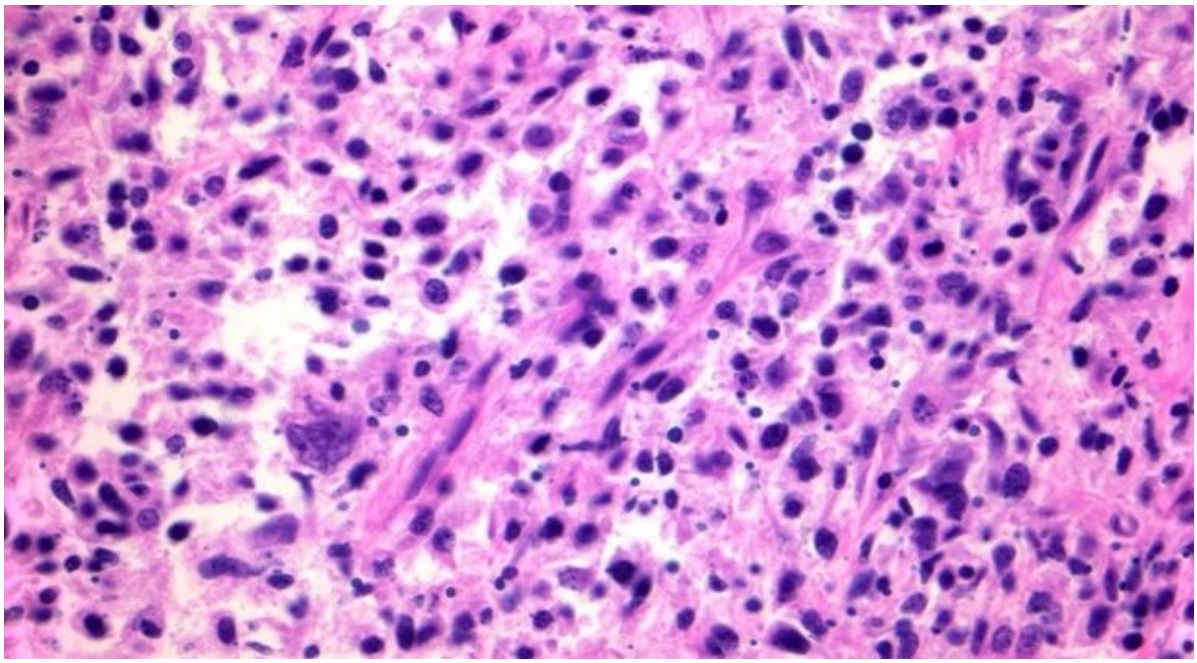


Figure 18: HE staining of Anaplastic sarcoma, Asian elephant, pelvic inlet. The mass contains round to spindyloid neoplastic cells with indistinct borders that are arranged in loose streams (Jennifer A. Landolfi 2021)

The neoplasm was densely cellular, non-encapsulated, and infiltrative. Cells were round to spindyloid with indistinct borders and arranged in streams supported by moderate amounts of fibro vascular stroma (Jennifer A. Landolfi 2021).

The PNET or Primitive neuroectodermal tumor it had marked infiltration found on the right uterine horn, forming a tan to pink, smooth, 44-cm-long mass that is firm, luminally occlusive which is blended perfectly with the uterine wall. (Jennifer A. Landolfi 2021)

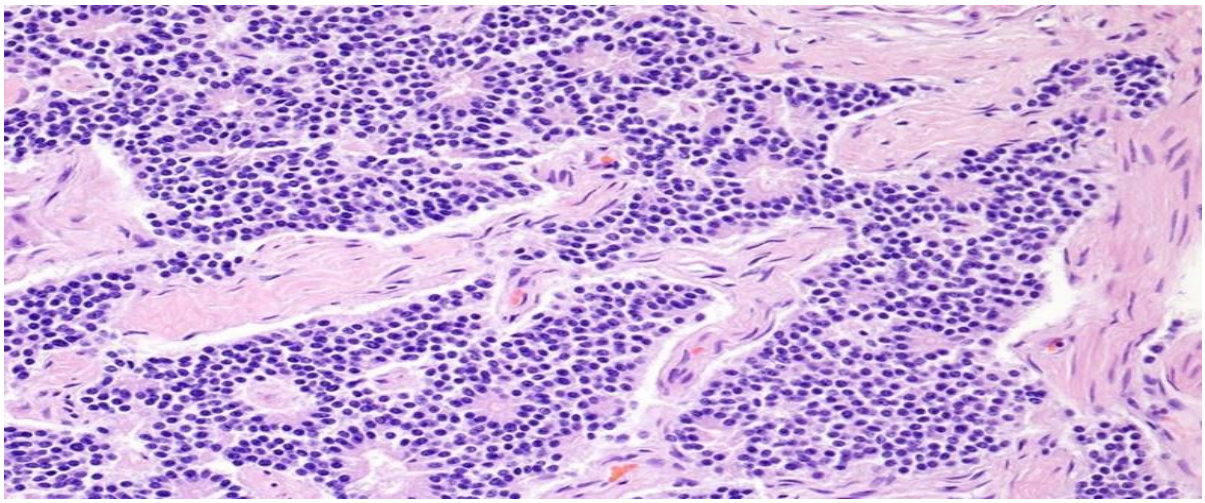
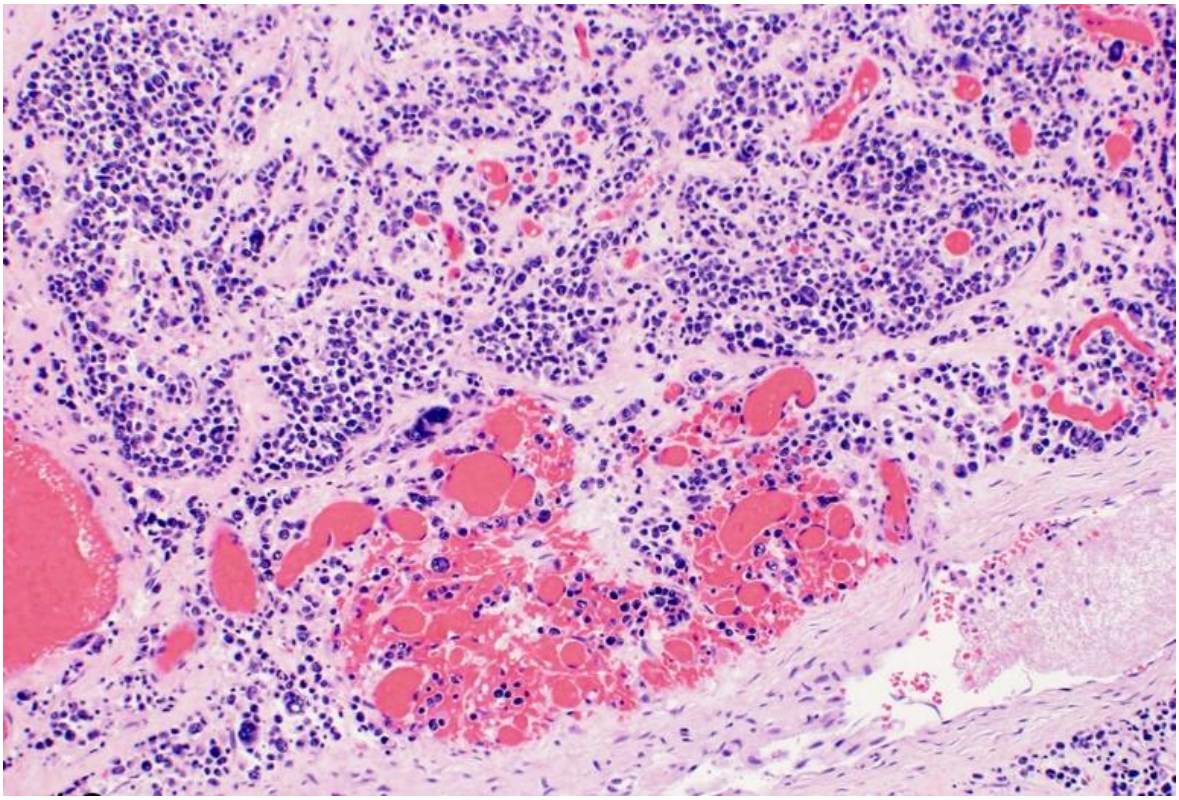


Figure 19: HE staining of Primitive neuroectodermal tumor in Asian elephant, uterus. Neoplastic cells separate smooth muscle bundles of the myometrium arranged in sheets with eosinophilia fibrillar material (Jennifer A. Landolfi 2021)

The uterine angiosarcoma was detected histologically within a large (81 × 81 × 101 cm) uterine leiomyoma that was firmly attached at the pelvic inlet, filled half of the peritoneal cavity, and obscured the entire reproductive tract. (Jennifer A. Landolfi 2021)

The leiomyoma contained a second, morphologically distinct population of neoplastic cells that is the angiosarcoma which was multifocal that is mixed with benign neoplastic cell population. (Jennifer A. Landolfi 2021)



Figures 20, 1. HE staining of Uterine angiosarcoma in Asian elephant neoplastic cells are round to polyhedral and arranged in sheets and rows within a fibro vascular stroma.(Jennifer A. Landolfi 2021)

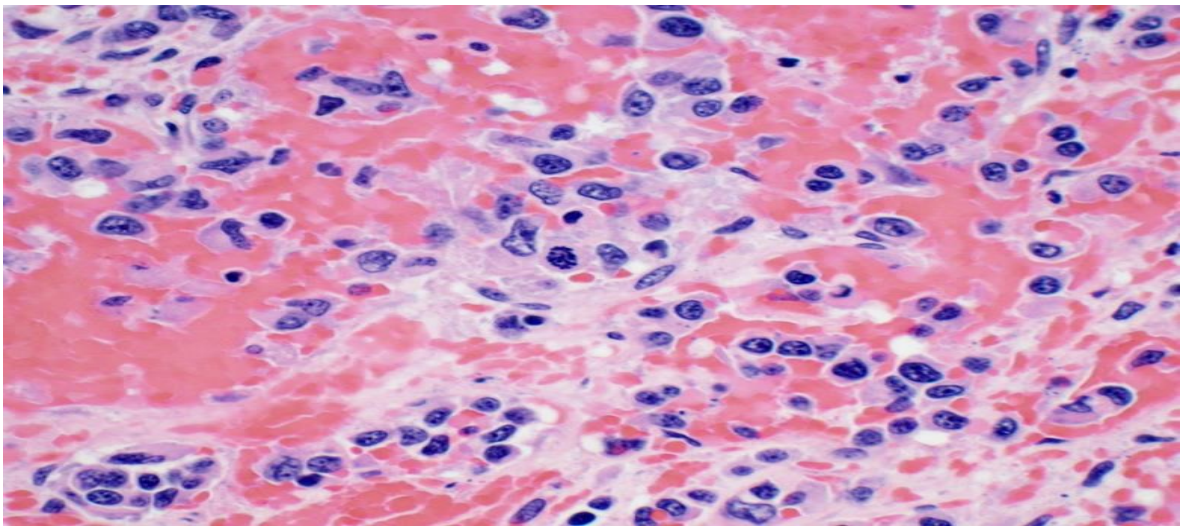


Figure 21, 2: HE staining of Uterine angiosarcoma, multifocal, cells form vague vascular channels containing erythrocytes. Hematoxylin and eosin. (Jennifer A. Landolfi 2021)

2- The tumor suppressor gene TP53

The longevity of elephants about 80 years and the huge cell numbers should have made elephants have higher rates of cancer but in reality they have low cancer rates and lower mortality then humans (Marc Tollis and Elliott Ferris 2021).

Cancer defenses in elephants are thought to be mediated by an enhanced apoptotic response of elephant cells to DNA damage, associated with extensive amplification of retro gene copies of the tumor suppressor gene TP53(Marc Tollis and Elliott Ferris 2021).

As Compared with other mammalian species, elephants appeared to have a lower-than-expected rate of cancer, potentially related to multiple copies of TP53 (Abegglen et al. 2015) TP53 began originally in a common ancestor of both Asian and African elephants, and continued throughout elephantid evolution.(Marc Tollis and Elliott Ferris 2021)

It was estimated Asian elephant genomes contain from 10 to 37 of the genome (Marc Tollis and Elliott Ferris 2021) while humans have only one copy of the TP53.

The highest numbers of TP53 copy were found in the smallest species of elephants, suggesting that during elephant evolution the copy number has not increased linearly with body mass as a response to increased cancer risk (Marc Tollis and Elliott Ferris 2021) of this gene prevents tumors from forming.

EXPERIMENTAL PART

CHAPTRE I:

MATERIALS and METHODS

Objectives

The objectives of this study are:

- The aim of this present work is the histological analyze of the uterine tumor mass of the elephant postmortem.
- Identify what caused the death of this female Asian elephant
- Check the effectiveness of the HE Stain protocol in determining if the tumor is benign or malignant
- Propose a different measure of histological analyze of this uterine tumor.

This study is the first of it is kind to be done in Algeria, it is review of reproductive uterine tumor in a 63-year-old adult female Asian elephant.

Ben Aknoun National Park of Algeria had two Asian elephants under it managed care with the female elephant being deceased in 2022.

Figure 22 Asian elephants in the Ben Aknoun National Park of Algeria by 06/2004 by Pierre Livet

The Asian elephant had a very large abdomen that the veterinary doctors of the zoo thought she was pregnant, but in fact she had a hypertrophied abdomen. The autopsy of this elephant was done at the Ben Aknoun zoological park revealed and a tumoral mass was found in the uterus, it was handed over for analyses at the pathological anatomy service in ENSV in 2 October 2022

Histological analysis

Samples for histological analysis must be taken within one hour of autopsy, During autopsy, the portion of the organ to be removed should be as fresh as possible, with as little soiling as possible, to avoid contamination during the procedure. Forceps should be applied to the non-necrotic part of the specimen.

Protocol for H&E staining:

This a Manual Protocol of Hematoxylin and Eosin (H&E) Staining From Baylor College of Medicine. This procedure is simple and valid for all kinds of tissue sections which are 10 μm or less. Thicker samples may require shorter staining times. The entire procedure will take 10 minutes

1. Tissue Preparation

- ✓ Frozen tissue:

1. Fix and rehydrate tissue
2. Fix tissue in 75 % ethanol for 30 sec

- ✓ FFPE tissue

• Place slides containing paraffin sections in a slide holder (glass or metal)

• Deparaffinize and rehydrate sections:

- 3 x 3 min Xylene (blot excess xylene before going into ethanol)
- 3 x 30 sec 100% ethanol
- 1 x 30 sec 95% ethanol
- 1 x 30 sec 80% ethanol
- 1 x 30 sec deionized H2O

• While sections are in water, skim surface of hematoxalin with a Kim wipe to remove oxidized particles. Blot excess water from slide holder before going into hematoxalin.

2. Hematoxalin staining:

- 1 x 3´ Hematoxalin Rinse deionized water
- 1 x 5´ Tap water (to allow stain to develop)
- *Dip 8-12x* (fast) Acid ethanol (to destain)
- Rinse 2 x 1´ Tap water
- Rinse 1 x 2´ Deionized water (can leave overnight at this stage)

(Blot excess water from slide holder before going into eosin)

3. Eosin staining and dehydration:

- 1 x 30 sec Eosin (up to 45 seconds for an older batch of eosin)
- 3 x 5´ 95% ethanol
- 3 x 5´ 100% ethanol (blot excess ethanol before going into xylene)
- 3 x 15´ Xylene

• Coverslip slides using Permount (xylene based).

• Place a drop of Permount on the slide using a glass rod, taking care to leave no bubbles.

• Angle the coverslip and let fall gently onto the slide.

• Allow the Permount to spread beneath the coverslip, covering all the tissue.

• Dry overnight in the hood

Reagents for H&E staining:

- Acid Ethanol: 1 ml concentrated HCl + 400 ml 70% ethanol
- Hematoxylin: hematoxylin with glacial acetic acid
- Eosin: Eosin Phloxine stain

RESULTS

CHAPTRE II:

RESULTS

The tumoral mass found in the uterus it was examined in 19 October 2022 at the pathological anatomy lab was determined to be subserous Leiomyoma based on its location, developing outside uterus under the serosa the smooth outer layer and present in the body of the uterus. Ranged in diameter from microscopic to over 10 cm, although most leiomyomas measured between 1 and 10 cm.

It was noted that there was also a large amount of blood (edema), this tumor mass was found without vascular invasion or metastasis.

Figure 23,1the Asian elephant uterine tumor leiomyoma appearing large and irregularly shaped, It has a pale pinkish-white color, with areas of darker red .personnel foto

Figure 24: Massive uterine involvement with large confluent fibrous-appearing tumor masseshe from the died Asian elephant uterine leiomyoma

The official report of the tumor mass

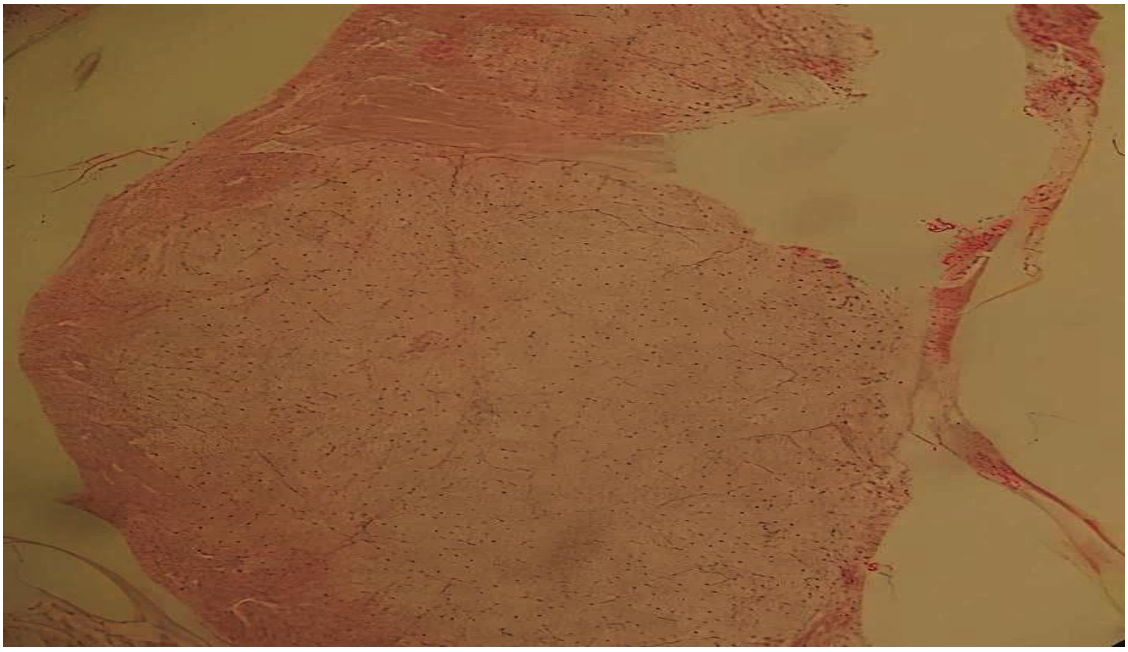
The result report from the pathological anatomy service show a purulent degeneration of the uterus

Uterus:

- ✓ characterized by the total absence of the endometrial layer and replaced by a uniform and homogeneous layer with the myometrial layer we note atrophy and diffuse degeneration of the smooth muscle fibers with significant purulent edema disseminated between the smooth muscle fibers and encysted in inter lacunae fibrillar

Tumoral mass:

- ✓ characterized by excessive tissue outgrowth of mesothelium phenotype with an enormous fibrillar formation secrete collagen forming multiple macro cysts whose epithelial membrane gives rise to mature and non-mature round cells of varied size with round nucleus occupies the entire cell and presents chromatins exclusively pale, sometimes yellowish.
- ✓ Presence of areas of necrosis with the formation of laminated basophilic deposits derives from the debris of the cystic apoptosis nuclei which are calcospheritized.
- ✓ Poorly vascularized tissue mass and low mitotic rate.



- ✓ **Figure 25:** One case of myometrial leiomyoma, among other grossly visible macroscopic cases, characterized by excessive tissue outgrowth of mesothelium phenotype with an enormous fibrillar formation secrete collagen forming multiple macro cysts whose epithelial membrane gives rise to mature and non-mature round cells of varied size with round nucleus occupies the entire cell and presents chromatins exclusively pale, sometimes yellowish. 4x

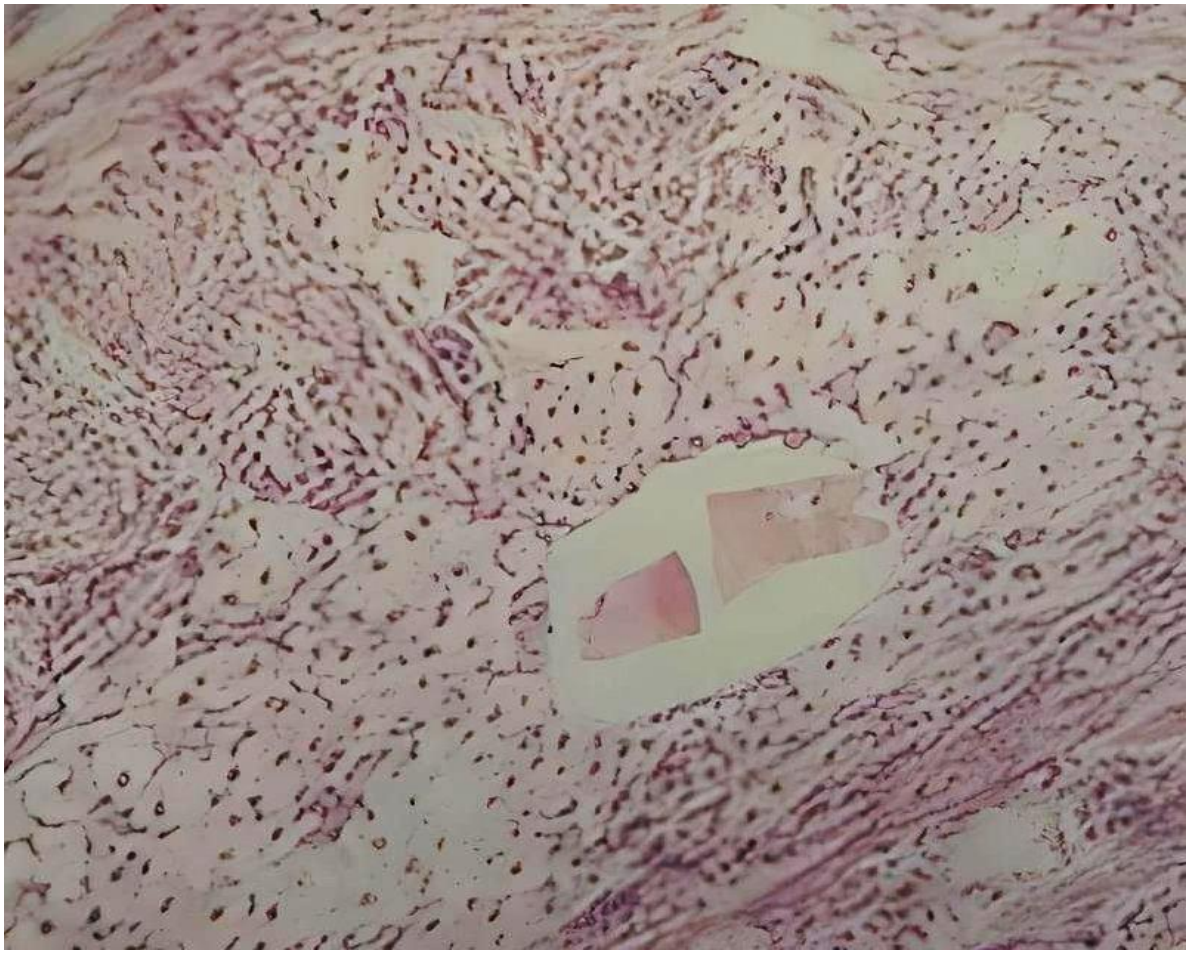


Figure 26: photo microscopic suggest a uterine tumor leiomyoma with proliferation of the smooth fiber with nuclei whose masses were subjected to hematoxylin-eosin-stained(HE) in histological sections at the ENSV pathological anatomy service. 10x

DISCUSSION

CHAPTRE III:
DISCUSSION

Asian elephants reported in our study developed benign and malignant neoplasms at higher rates than African elephants,
Histological examination of uterine leiomyomas in Asian elephants offers crucial insights into the tumor's cellular composition, growth patterns, and potential implications on the reproductive health.

The uterine leiomyoma in Asian elephants (*Elephas maximus*), commonly referred to as fibroids, is a benign smooth muscle tumor that occurs within the uterus. While extensively studied in humans, its occurrence and pathology in non-human species, particularly in Asian elephants, remain less understood.

One case of myometrial leiomyoma, among other grossly visible macroscopic cases, characterized by excessive tissue outgrowth of mesothelium phenotype with an enormous fibrillar formation secrete collagen forming multiple macro cysts whose epithelial membrane gives rise to mature and non-mature round cells of varied size with round nucleus occupies the entire cell and presents chromatins exclusively pale, sometimes yellowish

Our histological study is of a retrospective nature it was not possible by the authors to have confirmation of gross abnormalities in other elephants due to the limitation in the number of cases with uterine neoplasia in elephant and with few elephants here in Algeria in the first place, so the Analysis was achieved through review of archival postmortem records, and thus was reliant on the observations and interpretations of various veterinary clinicians and pathologists. The elephant was originally diagnosed by the Veterinary Pathology board-certified pathologists of the Ben Aknoun National Park of Algiers, many of which with extensive experience with zoo and wildlife species and the interpretations of the histological results were done by the pathological anatomy service of ENSV for more analysis of the uterine leiomyoma in the Elephas Maximus, a comparison was done between the histological findings at ENSV and other histological findings from retrospective study, directed by Jennifer A. Landolfi published in 2021.

Our study results are of one sample of a tumor mass taken from a dead adult female Asian elephant, and are in fact similar to the results from Jennifer A. Landolfi study, obtained for a total of 80 postmortem reports of adult, female Asian elephants from 26 different holding centers in the United States from 1988 to 2019. The study population of Asian elephants was considered representative of the managed population in the United States as a whole (reviewed cases comprised 85% of the total adult female Asian elephant mortalities for the time period)

Myometrial leiomyoma, were grossly visible in 57 cases with the neoplasms were multiple in 51 cases, and solitary masses in 6 cases, in which the masses were detected histologically. Leiomyomas were present in the uterine horns and body and ranged from microscopic to over 100 cm in diameter, though most were 1 to 10 cm, leiomyomas had metastasized in 67% of cases

In our study, Leiomyomas was detected histologically in the masses sample. The masses were also present in the uterine body and ranged from microscopic to over 10 cm in diameter, though most were 1 to 10 cm, but this tumor mass was found without vascular invasion. Previous studies have described a high prevalence of reproductive tract disease in aged Asian and, to a lesser extent, African elephants and with this study case too, all of them indicate that myometrial leiomyoma is another common uterine neoplasia in Asian elephants as it is also common in older women occuring in 77% of the cases. Importantly, benign uterine neoplasms affecting the uterus have the potential to impact fertility. Carcinogenesis is a complex process in which evolutionary, genetic, and epigenetic factors contribute. In the reproductive tract, the uterine tumors are associated with prolonged phases of both estrogen and progesterone influence, this hormones have profound and regulatory effects providing the principal mechanisms that lead to varying degrees of .proliferation, differentiation, and apoptosis. Estrogen stimulates endometrial proliferation via increasing production of insulin-like growth factor-1, while progesterone counterbalances these mitogenic effects by stimulating production of insulin-like growth factor binding protein-1

It was also found in these studies that Compared with other mammalian species, elephants do have a lower-than-expected rate of cancer, due to multiple copies of the TP53 gene. In Asian elephants this genome provides cancer resistance and plays a central role in cancer suppression and response to DNA damage through enhanced apoptosis and cell cycle arrest.

Though obesity was not described in any of the cases, it can lead to insulin resistance and hyperinsulinemia, increased bioavailability of steroid hormones and localized inflammation, all of which potentially contribute to carcinogenesis. Body condition at the time of death may not have been reflective of body condition prior to or during carcinogenesis. A high percentage of elephants housed in North American zoos have an elevated body condition score. Due to the physical constraints of the managed care environment, relative reduction in physical activity compared with free-ranging individuals likely contributes to over conditioning. Possibly, body condition and activity level could be factors impacting hormonal homeostasis and metabolism in elephants and are recognized contributors to cancer risk in women.

Histological analysis using hematoxylin and eosin (HE) staining revealed the presence of neoplastic mesenchymal cells, arranged in haphazard, broad intersecting bundles. These results are similar to those obtained by Jennifer A. Landolfi (2021).

Finally, by examining tissue samples with Hematoxylin and eosin stain (HE), through various histological techniques, we seek to identify specific morphological features, cellular dynamics, and potential etiological factors, contributing to the development of these tumors. Thus, Immunohistochemistry is the best histological technique for detecting Leiomyomas and uterine tumor masses in Asian elephants.

CONCLUSION

Conclusion

The examination of uterine leiomyomas in a 63-year-old Asian elephant (Elephas maximus), commonly known as fibroids, is the first examination of this type carried out in Algeria on Asian elephants. Our histopathological examination of the tumor revealed a pattern of well-differentiated cells within a large stroma of finger-like collagenous connective tissue.

The case of uterine leiomyoma was the most frequent tumor in Asian elephants in the world. Uterine leiomyomas is a benign tumor arising from the smooth muscle cells of the upper myometrium, the muscular layer of the uterus. Of Asian elephants (Elephas Maximus).

We suppose that the longevity of elephants, which is about 80 years, may have made elephants have higher rates of cancer, but in reality they have low cancer rates and lower mortality then other animals. Importantly, benign uterine neoplasms affecting the uterus have the potential to impact fertility.

Ultimately, our study showed that the tumor mass was a benign neoplasm, which caused the death of the Asian elephant, after several months of illness.

RECOMMENDATION

Recommendation

By examining tissue samples through various histological techniques, we seek to identify specific morphological features, cellular dynamics, and potential etiological factors contributing to the development of these tumors.

Thus, we recommend the introduction of immunohistochemistry to detect any forms of myometrial leiomyoma for benign uterine neoplasm in an Asian elephant (Elephas Maximus). Additionally, this research will compare the histopathological findings with those observed in other species, including humans, to uncover any commonalities or distinct differences.

We also recommend that whenever an abdominal over-mass is discovered in an elephant, a transrectal sonogram of the elephant's uterine horn should be performed, to distinguish pregnancy from the presence of a uterine leiomyoma.

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