Thesis

Yasmin Nazari

2024

Thesis

Comparative examination of the structure and function of the spleen in humans and small animal species

Az emberi és kisállatfajok (kedvtelésből tartott állatok) lépének szerkezetének és működésének összehasonlító vizsgálata

by Yasmin Nazari

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Abstract

This thesis presents a comparative analysis of the structure, function and pathology of the spleen in humans and small animals (dogs). The study begins with an exploration of the embryology, anatomy and histology of the spleen in both species, highlighting similarities and differences in their development and structural adaptations. It further examines the physiological roles of the spleen, such as blood filtration, erythrocyte storage and immune response and how these functions are adapted to the specific needs of each species. Pathological conditions, including splenic angiosarcoma in humans and hemangiosarcoma in dogs, are discussed in detail, emphasizing their aggressiveness, diagnostic challenges and poor prognoses. The thesis concludes that while the spleen in both species shares fundamental roles, its unique adaptations reflect the diverse requirements of each organism. These findings help to improve our understanding of the spleen's complexity and underline the importance of comparative research for practical advances in human and veterinary medicine.

Absztrakt

A dolgozat az emberi és kisállatok (kutya) lépének szerkezetét, működését és patológiáját hasonlítja össze. A kutatás az embriófejlődés, anatómia és szövettan vizsgálatával kezdődik, kiemelve a két faj fejlődési és szerkezeti különbségeit és hasonlóságait. Továbbá elemzi a lép élettani szerepét, mint például a vér szűrését, a vörösvértestek tárolását és az immunválaszok elősegítését és azt, hogyan alkalmazkodnak ezek a funkciók az egyes fajok igényeihez. A patológiás állapotok, beleértve az emberi lép angiosarcomáját és a kutyák hemangiosarcomáját, részletesen tárgyalásra kerülnek, hangsúlyozva azok agresszivitását, diagnosztikai kihívásait és rossz prognózisát. A dolgozat arra a következtetésre jut, hogy bár a lép alapvető funkciói hasonlóak, egyedi adaptációi tükrözik az egyes fajok eltérő igényeit. Ezek az eredmények elősegítik a lép összetettségének jobb megértését és kiemelik a komparatív kutatások fontosságát az emberi és állatorvosi gyakorlat fejlődésében.

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Abbreviations

C: Colon

CA: Central Artery

Cma: Greater curvature of the stomach

CT: Computer Tomography

D: Duodenum

DIC: Disseminated Intravascular Coagulopathy

G: Stomach

GC: Germinal Center

HMS: Hyperreactive Malarial Splenomegaly

HSPCs: Hematopoietic Stem and Progenitor Cells

IgM: Immunoglobulin M

Md: Mesogastrium dorsale

Mi: Spleen (German: Milz)

Mn: Monocytes

MRI: Magnetic Resonance Imaging

MZ: Marginal Zone

Oe: Oesophagus

Om: Omentum majus

PALS: Periarteriolar Lymphoid Sheath

PAMPs: Pathogen-Associated Molecular Patterns

PAS: Periodic acid-Schiff (PAS) stain

PT/PTT: Prothrombin Time/Partial Thromboplastin Time

Py: Pylorus

RBCs: Red Blood Cells

RP: Red Pulp

Sp: Spleen

TLRs: Toll-Like Receptors

VL: Visceral Leishmaniasis

1. Introduction

The spleen is known as the largest secondary lymphatic organ in the body of humans and small animal species. It has a significant physiological importance. Its importance is related to functions like blood filtering, storage of erythrocytes during periods of increased demand and responding immunologically to antigens in the blood stream (Onkar and Govardhan, Comparative histology of human and dog spleen 2013., Al-Salem, A. H. The Spleen: Anatomy, Physiology and Diseases, 2023.).

This Thesis deals with the comparison of the embryological, anatomical and physiological variations of the spleen in humans and small animal species (dogs).

Through this comparative examination, I would like to demonstrate the complex mechanisms of the spleen, both as a physiologically functioning organism and pathologically.

After exploring the general functions, this study will focus on one specific disease in each species: angiosarcoma in humans and hemangiosarcoma in dogs. By comparing these conditions, I hope to demonstrate the spleen's role in health and disease in both human and small animal species.

2.1. Embryology of the spleen in humans

From an embryological point of view, the spleen, a lobulated organ in the human fetus, develops from mesenchymal tissue. It starts to develop from the 5th week of the prenatal life. The mesenchymal tissue starts to compact between the two layers of the dorsal mesogastrium, close to the pancreas. It begins to shift to the left side as soon as the stomach changes position, where the spleen is now behind the stomach and in close contact with the left kidney.

The development of the spleen is fundamentally divided into two main stages.

During the first stage, which lasts up to the 14th week of pregnancy, the spleen is mostly mesenchymal (Fig. 1a). In Figure 1a a homogenous and light spleen is adhered to the mesenchyme of the posterior part of the stomach. A general framework of the spleen develops during this period. The red and white pulp show their first signs of differentiation. Erythrocytes, macrophages and normoblasts appear and the beginning of erythropoiesis occurs. The second stage is characterized by further differentiation or transformation. Structural changes in the spleen occur around the 15th week of embryonic development (Fig. 1b). During the developmental stages the splenic lobules begin to form and the trabeculae differentiate into larger veins. The red pulp starts to develop at the edges of these lobules, while the central part contains the main artery. In Figure 1b, in contrast to Figure 1a, the development of the red pulp is visible, characterized by the dark-coloured demarcated spleen. The differentiation into white pulp occurs slightly later, around the 18th week of gestation and is closely linked with the colonization of lymphoid tissue inside the spleen. The two pulps are separated by the marginal zone and by the 23rd week primary follicles accumulate at the periphery of the periarterial lymphoid sheaths, marking the beginning of the B-cell region formation. (Al-Salem, A. H. The Spleen: Anatomy, Physiology and Diseases, 2023).

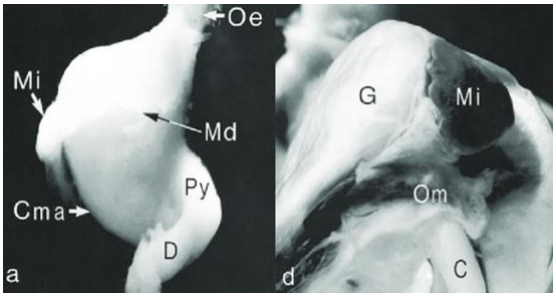

Fig. 1 Spleen (Mi) in a human embryo a) approx. 6 weeks b) approx. 15-16 weeks

Mi: spleen; G: Stomach; Oe: Oesophagus; Md: Mesogastrium dorsale; Cma: Greater curvature of the stomach; Py: Pylorus D: Duodenum; Om: Omentum majus; C: Colon

https://www.researchgate.net/figure/Spleen-in-human-embryology-a-Embryo-14-mm-approximately-week-6-the-homogeneous_fig2_340317608

2.2. Anatomy of the spleen in humans

The human spleen is located in the peritoneum on the left side under the diaphragm between the 9th and 11th ribs and over the left kidney, see in Figure 2.

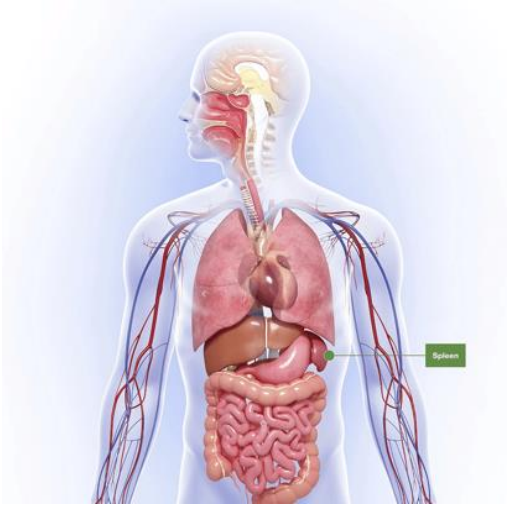

Fig. 2 Location of the spleen in the human body

https://www.researchgate.net/figure/Location-of-spleen-in-the-body-PIXOLOGICSTUDIO-SCIENCE-PHOTO-LIBRARY_fig1_356876272

There are 2 distinct borders (*margo*) in the spleen: margo anterior, margo posterior. The anterior border of the spleen possesses a notch on the anterior end. In addition, the spleen has two different surfaces, the visceral and diaphragmatic. The diaphragmatic surface is convex and smooth, while the visceral surface is concave and irregular with several imprints. The most concave imprint on the spleen is a resultant of the fundus of the stomach. The left kidney leaves an imprint on the intermediate and caudal borders. The colic imprint is from the splenic flexure of the colon. The pancreas tail creates an impression between the hilum and colic impression sites. On the inferomedial aspect, the gastric imprint contains the hilum of the spleen (Fig. 3).

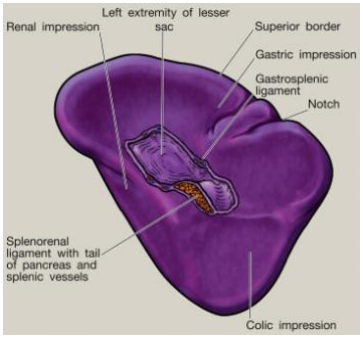

Fig. 3 Visceral surface of the spleen with imprints

https://www.sciencedirect.com/science/article/pii/S026393191930095X#fig5

The hilum of the spleen serves as an “entrance and exit gate” for nerves, splenic vessels and as attachments for the ligamentum splenorenale and ligamentum gastrolienale.

As mentioned above, the spleen is variable in both size and weight. The normal weight in humans is 150 g with a range of 50 to 250 g. The weight of the spleen is due largely to the blood contained within the splenic tissue. In healthy adults, the spleen measures about 11 centimeters in length. Furthermore, the spleen is, as mentioned, attached by several ligaments. These not only support it but also offer protection and maintaining it in its position. There are three ligaments that arise from surrounding structures and attach to the spleen. Two of these attaches to the splenic hilum and are traversed by the splenic vessels. The third is a fold of the peritoneum that extends between the spleen and the diaphragm. The ligamentum gastrolienale extends from the hilum to the greater curvature of the stomach. It contains the arteriae gastricae breves and venae gastricae breves, arteria gastroomentalis sinistra and vena gastroomentalis sinistra and the associated lymphatics and sympathetic nerves. The ligamentum splenorenale extends from the hilum of the spleen to the anterior surface of the left kidney. It transmits the arteria lienalis and vena lienalis and contains the tail of the pancreas. The ligamnetum phrenicocolicum is a horizontal fold of the peritoneum extending from the splenic flexure of the colon to the diaphragm.

The spleen receives its blood supply mainly by the arteria lienalis, a branch of the arteria coeliaca. To ensure that the parenchyma is also supplied, the arteria lienalis divides further into smaller branches.

These initially lead through the trabeculae and, when they enter the parenchyma, become small arterioles. At this point, the arterioles are surrounded by a lymphatic sheath. In the center of this area, there is also an artery, which is called the central artery because of its location.

This artery also divides and runs through the marginal zone to the white pulp and from there into the red pulp. The branches are surrounded by B lymphocytes, which form the lymphoid follicles of the spleen.

The venous sinuses flow into trabecular veins and then pass into the splenic vein, through which the venous blood finally leaves the spleen.

Furthermore, the spleen contains efferent lymphatic vessels, which transport the lymph outside the spleen. The lymph is collected and directed from the spleen to the lymph nodes by the lymphatic vessels (Fig. 4 and 5) (Al-Salem, A. H., The Spleen: Anatomy, Physiology, and Diseases, p.28-29, 2023, Shazia R. et al. Anatomy, Abdomen and Pelvis, Spleen, 2023).

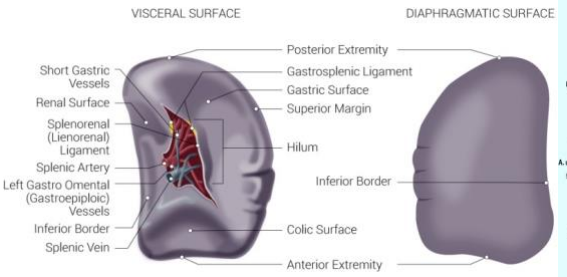

Fig. 4 Blood supply and ligaments of the spleen in humans https://www.ncbi.nlm.nih.gov/books/NBK482235/figure/article-29374.image.f1/

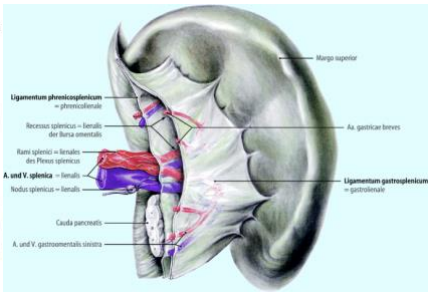

Fig. 5 Blood supply and ligaments of the spleen in humans https://link.springer.com/chapter/10.1007/978-3-642-36979-7_15

2.3. Histology of the spleen in humans

The spleen is made up of the stroma (supporting tissue), the white pulp, the red pulp and the vascular system. The stroma is fibroelastic, causing the spleen to significantly expand and increase its size when it is necessary. It forms the capsule of the spleen, a reticulum and coarse trabeculae.

The so-called trabeculae are different septa in the spleen (Fig. 6A). The white pulpa is formed from lymphatic tissue and consists of lymphocytes (Fig.6A). A distinction is made between B- and T- lymphocytes, which settle around the arteries in the spleen. In the germinal center (GC), shown in Fig. 6A and 7, the B-cells proliferate, differentiate and produce antibodies. The red pulpa, on the other hand, consists of venous sinuses and splenic cords. Splenic cords refer to connective tissue that contain erythrocytes, as well as macrophages and lymphocytes. However, splenic venous sinuses are cavities within the tissue and are filled with blood.

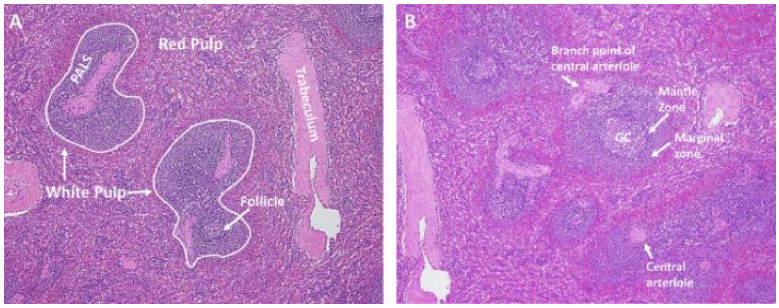

Fig.6 Histological section and schematic representation of the functional and structural compartments of the human spleen: white pulp, marginal zone and red pulp (GC= Germinal center) https://www.sciencedirect.com/science/article/abs/pii/S0740257020300605

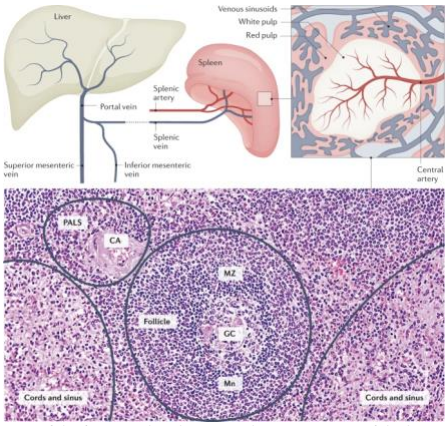

Fig.7 Histological section and schematic representation of the functional and structural compartments of the human spleen (CA= Central artery, MZ= Marginal Zone, GC= Germinal Center, Mn= Monocytes)

https://www.nature.com/articles/s41572-022-00399-x

2.4. Embryology of the spleen in small animals (dogs)

From an embryological point of view in small animal species, the spleen develops from local mesenchym that originates from the mesoderm. The development of the spleen takes place between the two serosal layers of the dorsal mesogastrium, which becomes the omentum majus in adult animals, as can be seen in Fig. 8. As the spleen enlarges, the outer layer of the mesogastrium proliferates until the entire organ is enveloped. In this manner, the spleen receives its peritoneal covering and forms close relations and connections with the omentum majus and the stomach. The spleen plays different roles throughout life: during embryonic development, it is responsible for producing erythrocytes, while in adulthood, it produces lymphocytes and later takes on the function of destroying erythrocytes and storing iron in the form of hemosiderin. From the 13th week of gestation, the vascular structure of the red pulp has formed. After the spleen has been infiltrated by macrophages, dendritic cells and lymphocytes, the white pulp is formed, following the red pulp (Nickel et al., The viscera of the domestic mammals, 1979., Hyttel et. al., Domestic Animal Embryology, 2010).

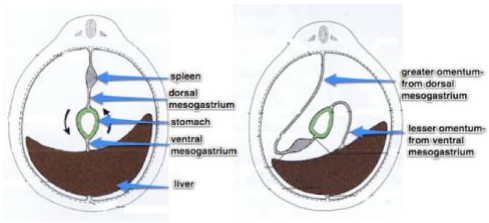

Fig. 8 Development of the spleen in dogs

http://bvetmed1.blogspot.com/2013/03/development-of-gastrointestinal-tract.html

2.5. Anatomy of the spleen in small animals (dogs)

In small animals such as dogs, the spleen is a reddish-brown, boot-shaped (in carnivores) organ located caudal to the diaphragm in the left cranial area of the abdominal cavity and entirely located within the peritoneum, see in Figure 9. The shape of the spleen variable between different mammals because, unlike carnivores, horses, for example, do not have a boot shape but instead have a falciform shape. It is important to remember that the consistency, color, size and weight are highly dependent on the amount of blood in the spleen. Other important influencing factors are the age of the animal, the sex, the breed and the level of nutrition (König, H. E., & Liebich, H.-G., Veterinary Anatomy of Domestic Animals, Textbook and Colour Atlas (7th ed.), 2020).

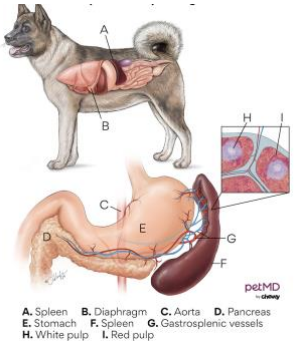

Fig. 9 Location of the spleen in dogs

https://www.petmd.com/dog/procedure/splenectomy-in-dogs

The extremitas dorsalis is rounded and wedge-shaped, it lies ventral to the crus sinistrum of the diaphragm between the fundus of the stomach and the cranial pole of the left kidney. Due to the relatively fixed position of the left kidney, the position of this part of the spleen is the least variable. The extremitas ventralis, is the most variable in both position and shape. When the spleen is maximally extended, it is related to the colon at its middle and to the mass of the small intestine ventrally (*facies intestinalis*).

The position of the spleen in carnivores depends on the degree of gastric filling. If the stomach is distended in carnivores the position of the spleen shifts caudally to the flank. The spleen is an elongated and on the lateral side flattened organ with a parietal (*diaphragmatic*) and visceral surface. The margo cranialis and margo caudalis (borders) are narrow and irregular in shape and shallow deep fissures are possibly present.

Furthermore, the spleen is held in place by the ligamentum phrenicolienale, which is the part of the omentum majus, that leaves the crus sinistrum of the diaphragm between the hiatus oesophageus and the arteria coeliaca. From a caudal point of view, this part of the omentum widens and first connects to the hilus of the spleen, then to the curvatura ventriculi major (greater curvature of the stomach), forming an extensive ligamentum gastrolienale (Fig. 10 *Gastrosplenic ligament*). The spleen obtains its blood supply through the hilus from the arteria lieanlis (originated from the arteria coeliaca), as can be seen in Figure 10 (*Splenic a.)* and as Nr. 21 and 22 in Figure 11 (*Splenic a. and Celiac a.).* Venous blood leaves the spleen through the vena lienalis (Fig 11 Nr. 19 *splenic v.*), which is involved in the formation of the vena portae (Fig. 11 Nr. 2 *Portal vein*). In carnivores the spleen's lymphatics enter the splenic lymph nodes located at the hilus. The thick nerves of the plexus splenicus, originated from the plexus coeliacus, formed by the sympathetic and vagus (parasympathetic) nerves (König, H. E., and Liebich, H.-G., 2020., Nickel et al., The viscera of the domestic mammals, 1979., Evans and Lahunta, Miller's anatomy of the dog, 2013).

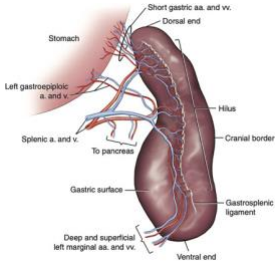

Fig. 10 Blood supply and ligaments of the spleen in dogs

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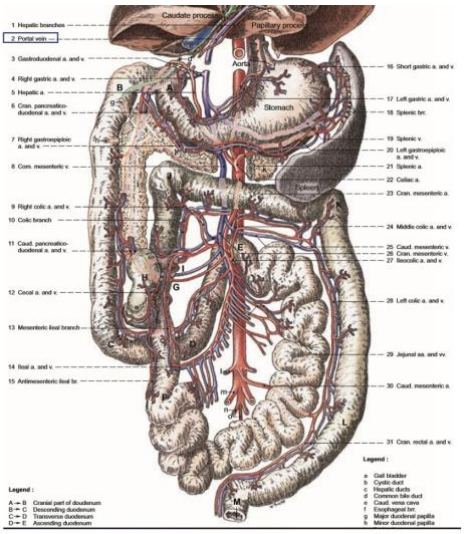


Fig. 11 Blood supply of the spleen and other organs in dogs

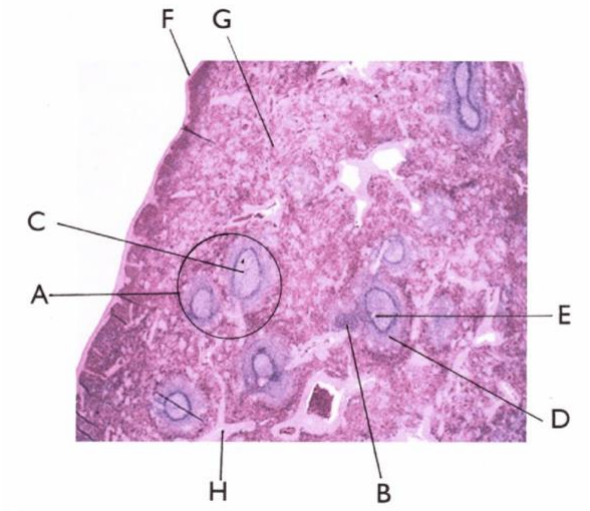
https://univet.hu/wp-content/uploads/2019/04/LIVER-PANCREAS-SPLEEN.pdf

2.6. Histology of the spleen in small animals (dogs)

The spleen is enclosed by a capsule (capsula) (Fig.12 F)., that contains fibromuscular trabeculae lienalis, which are made up of large, elastic and smooth muscle fibers (Fig. 12 H). The fibers of the trabeculae have a direct connection to the reticular fibers of the splenic pulp (Nickel et al., The viscera of the domestic mammals, 1979., Evans and Lahunta. Miller's anatomy of the dog, 2013).

The spleen's parenchyma is divided into red pulp and white pulp (*pulpa lienalis rubra et alba*), as can be seen in Figure 12 A and G.

The red pulp, which forms the majority of the organ, consists of venous sinuses and splenic cords (fine blood-filled meshwork), which merge into the white pulp. The cells of the cords include a lot of lymphocytes, megakaryocytes and macrophages. Between the red and white pulp the marginal zone is located, which consists of parietal lymphatic tissue and serves as a "border" (Fig. 12 D). In contrast, the white pulp, which makes up for approximately one-fifth of the splenic volume, is composed of diffuse and follicular (nodular) lymphoid tissue, see in Figure 12 B and C. The nodules (*lymphonoduli lienales)* have a germinal center, which is lighter in comparison, particularly under conditions of stress as during infections. The function of the nodules is to produce lymphocytes, and overall, the nodules are not visible to the naked eye.



Dog spleen. A: white pulp (PAS); B: primary folliculo-nodule; C: secondary folliculo-nodule; D: marginal zone; E: central arteriole; F: Thick capsule; G red pulp; H: thick trabeculae

Fig. 12 Histological section and schematic representation of the functional and structural compartments of the dog spleen

https://www.researchgate.net/figure/Dog-spleen-A-white-pulp-PAS-B-primary-folliculo-nodule-C-secondary_fig2_311882194

2.7. Function of the spleen in humans and small animal

The spleen plays different roles throughout the life: during embryonic development, it is responsible for producing erythrocytes, while in adulthood, it produces lymphocytes and later takes on the function of destroying erythrocytes and storing iron in the form of hemosiderin.

2.8. Comparison of the embryology and anatomy of the spleen of humans and small animals (dogs)

The spleen develops from mesenchymal tissue in both humans and small animals (dogs), though there are differences in the timing and structural development between the species.
In humans, the spleen begins to form from mesenchymal tissue during the 5th week of prenatal development. The first stage, up to the 14th week of gestation. The second stage begins around the 15th week. By the 23rd week, the spleen is fully colonized by lymphoid tissue.
In small animals like dogs, the spleen also develops from mesenchymal tissue, originating from the mesoderm. This process takes place between the serosal layers of the dorsal mesogastrium. By the 13th week of gestation, the vascular structure of the red pulp is formed, and shortly after, the white pulp develops. During embryonic life, the spleen in dogs is responsible for erythrocyte production, while in adulthood, its function shifts to lymphocyte production and the destruction of old erythrocytes.
In humans, the spleen is located in the peritoneum on the left side of the body, under the diaphragm, between the 9th and 11th ribs, and above the left kidney. It has two main surfaces: the diaphragmatic surface and the visceral surface. The spleen is encased in a fibroelastic capsule. The organ is attached to surrounding structures by several ligaments, including the ligamentum splenorenale and ligamentum gastrolienale, which support its position and function. The spleen's blood supply comes from the arteria lienalis, and its venous drainage occurs through the splenic vein.
In dogs, the spleen is a boot-shaped, located in the left cranial area of the abdominal cavity, caudal to the diaphragm. In dogs its position is influenced by the degree of stomach filling. The spleen has a parietal (diaphragmatic) surface and a visceral surface, similar to humans, and is held in place by the ligamentum phrenicolienale and the ligamentum gastrolienale.

The spleen is also covered by a capsule made up of fibromuscular trabeculae. Like in humans, the spleen's parenchyma is divided into red and white pulp. The spleen is supplied by the arteria lienalis and venous blood will be drained via the vena lienalis.

Although the development and structure of the spleen in humans and small animals (dogs) share common features, such as their origin and division into red and white pulp (Fig. 13 RP= Red pulp and GC= Germinal center of the white pulp), there are differences in the timing of development and the anatomical position and shape of the spleen. In humans, the spleen is closely associated with the surrounding organs and plays a role in immune defense, blood filtration and storage. In dogs, while similar in function, the spleen is boot-like shaped and its movement depends on stomach filling are distinct characteristics, reflecting species-specific adaptations.

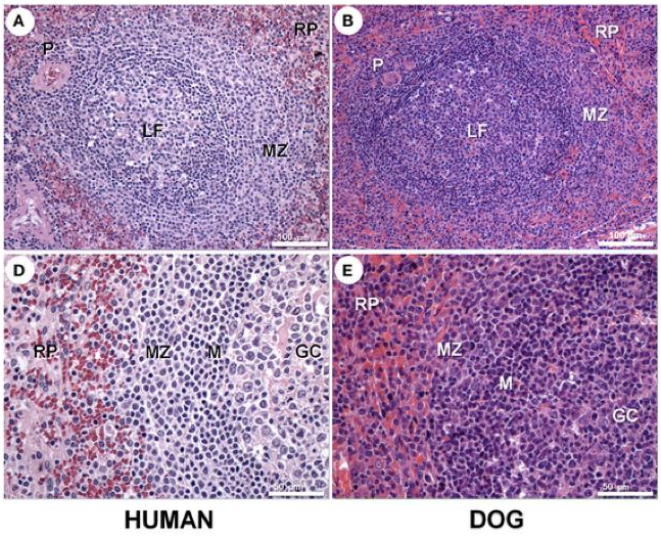


Fig. 13 Histological section of the human (left) and dog spleen (right)

https://www.researchgate.net/figure/Spleen-compartments-in-human-A-D-dog-B-E-and-hamster-C-F-spleen-Spleen-in-all_fig1_328915897

3.1. Physiology and functions of the spleen in humans

The spleen performs numerous vital physiological functions within the human body. Of all functions, filtration of blood is a significant one, whereby only the old and damaged erythrocytes are removed from the circulation. In the red pulp, these are recognized and destroyed by macrophages through the process of phagocytosis. The hemoglobin of the destroyed erythrocytes, following their destruction, is used for the extraction of iron, which in turn gets recycled and stored by the bone marrow. Besides hematopoiesis, the spleen produces blood cells until about the 22nd week of the gestation. After birth, the active hematopoiesis takes place only in the bone marrow. Exceptional cases are serious bacterial infections or diseases such as leukemia, in which the spleen produces blood cells in adults too (extramedullary hematopoiesis). In contrast, lymphocytes are produced and mature in the spleen throughout life (lymphopoiesis), which underlines the spleen's critical role in the immune system. T-lymphocytes, which originate from the thymus, take part in cell-mediated immunity, while B-lymphocytes, derived from bone marrow stem cells, are responsible for antibody production. In the spleen, B-lymphocytes develop into plasma cells, which produce immunoglobulins such as Immunoglobulin M (IgM) that are vital for antigen neutralization. The white pulp of the spleen is made of periarteriolar lymphoid sheaths (PALS) and lymphoid follicles, which are involved in the uptake of antigens from the bloodstream. In the white pulp the lymphocytes and antigens interact with one another leading to the activation of immune responses. This function is crucial for the body’s defense against blood-borne pathogens, especially encapsulated bacteria such as Pneumococci. Furthermore, natural antibodies produced by memory B cells in the spleen are important for antibody opsonization and phagocytosis, ensuring the clearance of pathogens and preventing infections.

In addition, the spleen also serves as a storage site for platelets and erythrocytes. In emergency situations such as severe blood loss, the stored blood can be released via the blood vessels as a compensatory mechanism. (Al-Salem, A. H., The Spleen: Anatomy, Physiology, and Diseases. 2023).

3.2. Physiology and functions of the spleen in small animals (dogs)

The spleen has numerous vital physiological functions in the body of small animal species (dogs). Of all the functions, filtration of blood is significant, whereby only the old and damaged erythrocytes are removed from the circulation. The erythrocytes are phagocytized by macrophages in the red pulp and the breakdown products, such as iron from hemoglobin, are stored in the bone marrow and can be reused. This process helps maintain the balance of red blood cells in the body and prevents the accumulation of old or damaged cells in the blood stream. Similar to humans, besides hematopoiesis, intrauterine the spleen's primary function is to produce erythrocytes (hematopoiesis). After birth, the hematopoiesis takes place only in the bone marrow. In exceptional cases like bone marrow metastasis, the spleen is able to produce erythrocytes even in adult animals (extramedullary hematopoiesis).

Primarily the red pulp act as a storage for erythrocytes and platelets, which are released into the blood stream during times of increased demand, such as exercise or blood loss. This storage function is supported by the presence of smooth muscle fibers in the splenic capsule, which contract to release stored blood cells when it is necessary. The spleen's ability to store and release platelets is pronounced in dogs compared to other species.

The spleen holds a significant amount of blood platelets, which are essential for blood clotting. During periods of increased demand or in response to blood loss, the spleen can release these platelets as a compensatory mechanism. In addition, the spleen in dogs also has a role in maintaining the blood volume and pressure. It acts as a blood reservoir, storing up to 16% of the total blood volume.

The white pulp, on the other hand, consists of lymphoid tissue that supports the spleen's role in the immune system. It is divided into periarteriolar lymphoid sheaths (PALS) and lymphoid follicles, which are responsible for the production of lymphocytes and the initiation of an immune reaction.

The spleen also serves as a storage for monocytes, which can be activated in response to inflammatory processes or tissue injuries.

The spleen's immune function is important in small animals (dogs), as it filters pathogens in the blood and presents antigens to immune cells. The marginal zone of the white pulp, which serves like a "border" between the red and white pulp, plays an important role in this function by collecting antigens and allowing them to interact with B- and T-lymphocytes.

This interaction leads to the activation and proliferation of lymphocytes, which are then released into the bloodstream to deal with infections or other foreign substances.

This immune response is vital for small animals (dogs), as they are exposed to environmental pathogens through activities such as contact with other animals or consuming contaminated substances.
(Nickel et al., The viscera of the domestic mammals, 1979., P. K., Sejian, V., Mukherjee, J., & Banerjee, D., Textbook of Veterinary Physiology., 2023., Fischer et. al., Extramedullary Hematopoiesis in the Spleen with Special Reference to Bone Marrow Metastases, 1970).

3.3. Comparison of the physiology and functions of the spleen in humans and small animals (dogs)

The spleen has several important physiological functions in both humans and small animal species (dogs).
In both humans and small animals (dogs), the spleen plays an important role in filtering the blood by removing old and damaged erythrocytes. Macrophages in the red pulp of the spleen break down these erythrocytes by phagocytosis and the iron is stored in the bone marrow for reuse.
During fetal development, the spleen in both humans and dogs is responsible for erythrocyte production (hematopoiesis). After birth, this is the primary function of the bone marrow, in both species. Exceptions are for example special cases like severe infections in humans or for example bone marrow disease in dogs. Then the spleen can resume its role in producing blood cells. This process, known as extramedullary hematopoiesis, shows that the spleen in both species can adapt to unusual demands.
Yang and colleagues observed that hematopoietic stem and progenitor cells (HSPCs) in the bone marrow are able to sense peripheral inflammation or infection. This sensing can occur either directly or indirectly. It leads to an increase in proliferation and differentiation to fulfill the need for innate immune cells. Furthermore, mature immune cells detect pathogen-associated molecular patterns (PAMPs) through Toll-like receptors (TLRs), triggering the production of inflammatory cytokines and cell activation. HSPCs expressing TLRs can directly respond to inflammation, adapting their differentiation toward myeloid cells at the expense of other lineages (Yang et al. , 2020) This is illustrated in Figure 14.

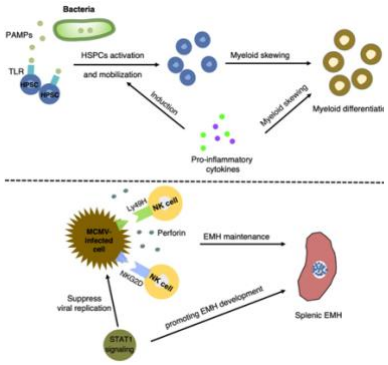


Fig. 14 Extramedullary hematopoiesis during an infection

https://pmc.ncbi.nlm.nih.gov/articles/PMC11104806/pdf/18_2020_Article_3450.pdf

In both humans and small animals (dogs), the spleen plays a key role in the immune system by filtering pathogens in the blood and supporting lymphocyte production. The white pulp in both species contains lymphoid tissue, which interacts with antigens and activates immune responses.

In humans, B-lymphocytes in the spleen develop into plasma cells, which produce antibodies such as IgM. These antibodies are important for neutralizing antigens.

Similarly, in small animals (dogs), the spleen also filters pathogens and presents antigens to immune cells, leading to the activation of B- and T-lymphocytes.

This immune response is important for the animals, as they are even more in a direct contact with pathogens from their environment, compared to humans.

One of the major differences between the spleen in humans and dogs is its role in storing blood. In humans, the spleen stores blood and can release it during emergencies such as severe blood loss. However, this function is more pronounced in dogs.

In dogs, the spleen stores up to 16% of the total blood volume and it also plays an important role in storing and releasing platelets as needed. These reserves can be released during physical exertion or blood loss, helping to maintain blood volume and pressure. While humans have a similar function, the spleen in dogs is much more specialized for this purpose.

In summary, in both humans and small animals (dogs), the spleen is from significant importance for their organisms, related to functions such as blood filtration, immune response and blood storage. However, the spleen in dogs is more specialized in storing and releasing large amount of blood and platelets. These differences show how the spleen uniquely supports the health of each species.

4.1. Pathophysiology of the spleen in humans

As mentioned in the previous section about the physiology of the spleen in humans, the organ has several important functions that contribute to the body's health. These include the filtration of the blood, hematopoiesis and the immune defense. If these functions are impaired, pathophysiological changes can occur that can lead to various diseases of the spleen.

One of the most important functions of the spleen is blood filtration. During phagocytosis in the red pulp, macrophages remove the old or damaged erythrocytes from the circulation. This activation and proliferation of the macrophages can lead to hypersplenism. Hypersplenism is a secondary process that can arise from splenomegaly for a variety of reasons. If there is, for example, a blockage of the cell passage through the open circulation, which can happen to humans suffer from malaria or sickle cell disease, it can result in hypersplenism. One example is Hyperreactive Malarial Splenomegaly (HMS), a condition marked by significant splenic enlargement that is common in malarious regions of the Old World, particularly in Africa. It is associated with a high mortality rate, although its natural history remains poorly documented (Alkadarou et al., 2013). Another cause of hypersplenism can be an increased pressure in the vena portae. Referring again to the function of blood filtering, this also includes blood cells with defects such as cells covered with antibodies or in sickle cell anemia (hemolytic anemia). For the spleen, this requires significant effort, causing an increase in reticuloendothelial cells, which can lead to splenomegaly as a consequence. In addition, the significant effort of the spleen producing antibodies also relates to increased immunological activity, for example in the fight against various infections, that are described as the most common cause for splenomegaly. In humans, infectious causes can be viral infections such as infectious mononucleosis, parasitic infections like malaria or bacterial infections such as a bacterial endocarditis. Furthermore, non-infectious causes like liver cirrhosis, neoplasms or traumas, for example due to a car accident, can lead to splenomegaly as well. Since the average human spleen has a length of about 11 centimeters and a weight of 250g, a length of 12cm or more and a weight of more than 400g is referred to as splenomegaly. There are no characteristic symptoms of splenomegaly. The patient may experience a feeling of heaviness, pain and distension of the abdomen, especially in the region of the spleen.

The blood count shows characteristic changes that reflect the function of the spleen as a blood storage and filtering organ. Examples include anemia, thrombocytopenia and leukopenia or even a combination of all of these.

Splenomegaly, as can be seen in Figure 15, as a result of one of the infectious or non-infectious causes mentioned above, increases the risk of further injury to the spleen.

Acute or chronic splenomegaly causes the capsule of the spleen to expand, making it thinner and more prone to tearing. This can lead to the rupture of the spleen.

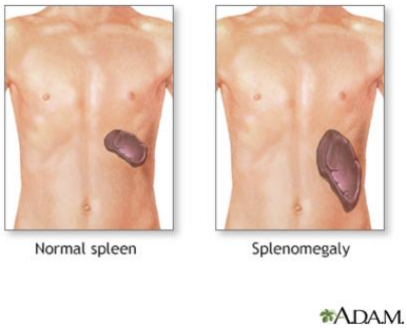


Fig. 15 Splenomegaly in humans

https://www.mountsinai.org/health-library/symptoms/splenomegaly

Another reason for a ruptured spleen is a trauma. This can be the result of blunt trauma, such as a car accident or penetrating abdominal trauma from a stab wound. Further, during an abdominal surgery that affects the pancreas, stomach or liver, a splenic rupture can occur.

A distinction is made between acute spleen rupture and delayed spleen rupture. The former is the more common type, in which the parenchyma and capsule of the spleen are injured, resulting in a splenic rupture. Intra-abdominal bleeding occurs, which can lead to hypovolemic shock. A delayed splenic rupture is a result from an injury of the parenchyma but an initially intact capsule. In this case, subcapsular or central hematoma occurs, with the intact capsule containing the bleeding. Symptoms often only appear after weeks, after the hematoma has continuously grown and the capsule finally ruptures, which then leads to intra-abdominal bleeding. In addition, there are several congenital diseases of the spleen, such as asplenia, polysplenia, accessory spleen or wandering spleen. Asplenia can describe a condition in which the spleen is either non-functional or completely missing. These patients are at an increased risk of infections because of the important role of the spleen in the immune system. In polysplenia, the human does not have just one spleen, but several small accessory spleens, as can be seen in Figure 16. These are not restricted in their function, which means that there is a sufficient immune function of the spleen.

Pretorius investigated that polysplenia involves the presence of two to fifteen small nodules of splenic tissue, which are usually located in the right or left upper abdominal quadrant.

This condition is linked to bilateral left-sidedness and is often associated with additional anatomical abnormalities. These include non-cyanotic cardiac septal defects, an interrupted inferior vena cava with azygos vein continuation and bilateral trilobed lungs. Other features commonly found are hyparterial bronchi, where the main bronchus lies below the pulmonary artery (as is typical of the left lung), a midline liver and an underdeveloped pancreatic body and tail (Pretorius, 2011).

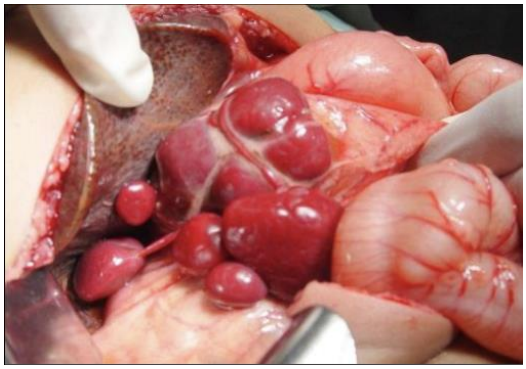


Fig. 16 Polysplenia in a human

https://www.researchgate.net/figure/ntraoperative-photograph-showing-polysplenia_fig2_273202956

An accessory spleen is a nodule of splenic tissue that is structurally identical to the spleen and occurs single or multiple (Fig. 17). It is a relatively common congenital abnormality in humans. The size of the nodules varies, but they are on average 1cm in diameter.

It is assumed that they arise during fetal development in the second or third trimester from insufficient fusion of primary lobules. Finally, a wandering spleen is a spleen that lacks ligament attachments to the colon, diaphragm and peritoneum and therefore cannot be adequately maintained in its correct anatomical position, which results in a mobile spleen. The spleen can move freely in the abdomen and sometimes even reaches the right lower part of the abdominal cavity (Al-Salem, A. H., The Spleen: Anatomy, Physiology, and Diseases. 2023).

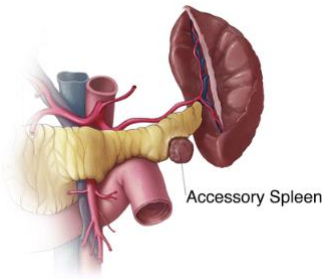


Fig. 17 Accessory spleen in a human

https://link.springer.com/article/10.1007/s00261-011-9830-x

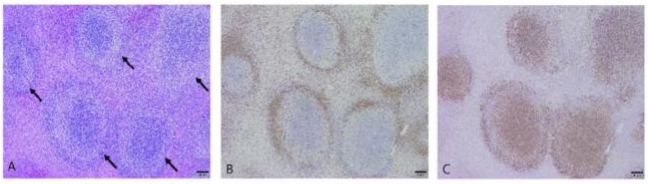
4.2. Pathophysiology of the spleen in small animals (dogs)

As mentioned in the previous section about the physiology of the spleen in small animals, the organ has several important functions that contribute to the body's health. These include the filtration of the blood, hematopoiesis and the immune defense. Similar to humans, pathophysiological changes in the spleen can occur if the function of the spleen is impaired. This can result in various diseases of the organ. The primary function of the spleen is to filter arterial blood, which may contain antigens, as well as other components. As previously discussed in the section on spleen physiology, macrophages located in the spleen perform phagocytosis to eliminate antigens and old or damaged erythrocytes. Due to this increased immunological activity, hyperplasia of the spleen can occur. This is particularly the case when pathogenic agents such as viruses, arthropods, protozoa or rickettsiae are in the organism for the first time and enter the bloodstream directly.

Silva-O'Hare and colleagues observed that the structure and cellular environment of the spleen can undergo significant changes during infections caused by various pathogens, including viruses, Plasmodium species and Leishmania. For instance, in visceral leishmaniasis (VL), the spleen initially shows an increase in lymphoid tissue (hyperplasia), but as the disease progresses, specific cell populations are lost, the structural integrity of the spleen deteriorates and the organ undergoes an atrophy (Silva-O'Hare et al., 2016).

A distinction must be made between pulpous and follicular splenic hyperplasia. What is characteristic of the former is that it occurs in acute and subacute infectious processes, whereas follicular hyperplasia tends to occur in chronic ones. Pulpous hyperplasia is characterized by a noticeable enlargement of the spleen, often with an increased accumulation of blood. This condition is referred to as hyperemic swelling. Pulpous hyperplasia of the spleen is particularly often associated with, for example, acute anaplasmosis, babesiosis, theileriosis, hepatozoonosis and other infections. In follicular splenic hyperplasia, however, the organ is only slightly enlarged.

Old dogs are more likely to have so-called nodular hyperplasia, illustrated in Figure 18 as a histological section. The nodules are the size of a lentil or plum, reddish-white in color and are usually seen on the surface of the spleen. They are often referred to as lymphomas but are just regenerative nodules or age-related hyperplasia.



Nodular hyperplasia in the spleen of a dog. (A) The proliferating lymphoid follicles were clearly separated from each other (arrows). Hematoxylin and eosin (H&E) at 40× magnification. Scale bar = 200 µm. (B) Immunohistochemical staining for CD3 with Mayer's hematoxylin counterstain. CD3 was expressed at the periphery of the follicles. 40× magnification. Scale bar = 200 µm. (C) Immunohistochemical staining for PAX5 with Mayer's hematoxylin counterstain. PAX5 was expressed within the follicles. 40× magnification. Scale bar = 200 µm.

Fig. 18 Histological section of nodular hyperplasia in the spleen of a dog

https://www.researchgate.net/figure/Nodular-hyperplasia-in-the-spleen-of-a-dog-A-The-proliferating-lymphoid-follicles-were_fig1_369571870

In felids, however, white lentil- to pea-sized nodules occur in the spleen, which consist of myeloid tissue and fatty marrow and are therefore also referred to as myelolipomatosis as a pathological change in the spleen. Furthermore, circulatory disorders, such as impaired blood flow via the vena lienalis or the vena portae or failure of the right heart, can cause a congested spleen.

Disturbances of blood flow via the vena portae or vena lienalis can occur in cases of gastric torsion, splenic torsion or splenic vein thrombosis.

Cardiac congestion of the spleen, on the other hand, is often associated with chronic congestion of the liver. A distinction is made between acute and chronic congested spleen.

In the acute form, the organ in dogs is greatly enlarged with an increased blood volume and multiple protrusions under the capsule, the size of beans or chicken eggs. These local congestions are often the result of diseases of a septicemic or toxemic nature.

In a chronic congested spleen, the organ is just as enlarged as in the acute form, but with a lower blood content. The connective tissue of the spleen is also pathologically altered and has a rough consistency. Bleeding of the spleen, caused by old or fresh hematomas under the capsule or in the parenchyma, is particularly common in dogs (Fig. 19).

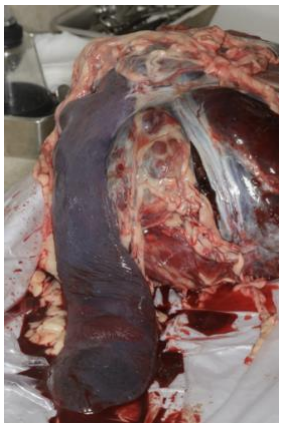


Fig. 19 Splenectomy / Splenic hematoma in a dog

https://lbah.com/feline/spleen-hematoma/

Necrotic changes can occur if an embolus leads to a blockage of the trunk of the splenic artery. However, more common is a blockage of the branches due to anemic splenic infarctions, caused by endocarditis of the left heart or in multiple hemorrhagic infarctions in dogs with parvovirus infections. Stenosis of smaller splenic vessels can often lead to hemorrhagic marginal infarctions of the spleen, especially in older dogs. If there is an acute, major blood loss in the animal's body accompanied by anemia, the spleen reacts by contracting and emptying itself to release the stored blood. As a result, it becomes flaccid and small. In contrast, in hemolytic anemia, the spleen enlarges due to the proliferation of its own pulp and the deposits of waste products in the blood. In chronic cases of anemia, histologically, metaplastic hematopoiesis foci are present in the spleen. Pathological changes in the spleen in small animals can also occur due to metabolic disorders. Atrophy of the spleen can occur as a result of cachexia, chronic congestion processes or in old animals. In this case, both the spleen capsule and the trabeculae are thickened, the lymphatic tissue regresses and the spleen becomes small and flaccid. Splenic amyloidosis (AA amyloidosis) can occur in dogs and cats as a consequence of a primary disease such as diabetes mellitus or chronic inflammation. Amyloid deposits are usually found macroscopically in the pathologically altered spleen.

In addition, yellowish-greyish to reddish, flat nodules, the size of a pinhead or a penny, are often found in the spleen capsule on the edge or on the visceral surface of the spleen, especially in dogs. These siderofibrous foci consist of collagen fibers with iron-calcium salt deposits and hematoidin and hemosiderin-containing macrophages in between.

There was a study about the processes leading to splenic infiltrations, focusing on abnormal cell accumulations and substance deposits during neoplastic changes. It includes primary and metastatic lesions, as well as splenic amyloidosis. According to the study, neoplasia-associated splenomegaly often results from the proliferation of resident cells such as lymphocytes, macrophages, fibroblasts, smooth muscle cells and endothelial cells. They form primary neoplastic lesions. The most common cause of generalized splenomegaly is myeloproliferative neoplasms, including lymphosarcoma and mastocytosis. Metastasis to the spleen, while relatively rare, typically presents as focal solitary or multifocal lesions, with lymphoma being the most frequently observed metastatic tumor in the spleen.

Rarely, conditions such as lysosomal storage diseases and splenic amyloidosis can lead to generalized splenomegaly. In cases of splenic amyloidosis, the organ typically appears pale beige, firm and waxy (Özer et al., 2020).

In this case, lacerations or complete ruptures of the capsule or parenchyma may occur, with simultaneous rupture of both the parenchyma and capsule being the most common. A distinction is made between traumatic ruptures and spontaneous ruptures.

The former refers to the separation of the initially unchanged spleen. These traumatic ruptures are particularly common in dogs. In this form, there is a chance of recovery due to scarring.

In the case of spontaneous ruptures, however, death often occurs due to internal bleeding. In this case, only a slight trauma is enough to cause a subsequent rupture of the spleen. This can be induced by, for example, leukosis, babesiosis or amyloidosis.

Moreover, positional and structural changes, as well as malformations, can also affect the spleen. A so-called accessory spleen, which refers to a lentil- to bean-sized nodule that occur in single or multiple forms, resembles the actual spleen in both shape and structure. In Figure 20, the white arrow indicates an accessory spleen next to the normal spleen (Sp) in an ultrasound examination of a dog.

Accessory spleens are often located in the peritoneum, ligamentum gastrolienale or in the omentum majus.

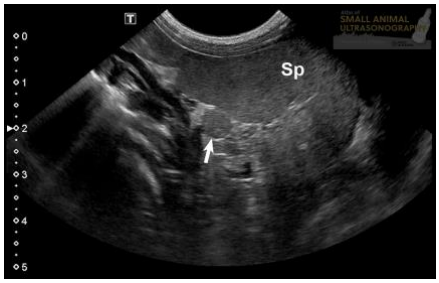


Fig. 20 Ultrasound image of a dog with the normal spleen (Sp) and an accessory spleen (arrow)

https://smallanimalultrasonography.com/ectopic-spleen-in-a-dog/

As a secondary consequence of, for example, a hernia diaphragmatica, the spleen may also be displaced into the thorax (ectopia).

Hypoplasia, aplasia or the presence of double spleens are rare in pets such as dogs and cats. In the case of double spleens, it is possible for them to develop postnatally as a result of a rupture. In addition, the spleen may exhibit changes in the form of folds, furrows or even notches, both in congenital and acquired forms.

Finally, in the well-known gastric volvulus in dogs, which frequently occurs in deep-chested and larger breeds, not only the stomach but also the spleen undergoes a torsion due to the connection through the ligamentum gastrolienale (Fig. 21).

This results in severe blood congestion, causing the spleen to assume a characteristic V-shape (E.Dahme, E.Weiss, Grundriss der speziellen pathologischen Anatomie der Haustiere. 2007).

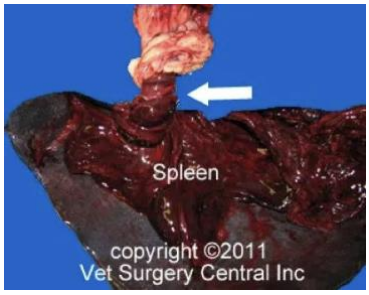


Fig. 21 Torsion of the spleen in a dog

https://www.animalsurgicalcenter.com/splenic-torsion

4.3. Comparison of the pathophysiology of the spleen in human and small animals (dogs)

Both humans and small animals like dogs have spleens that are crucial for blood filtration, hematopoiesis and immune defense. Pathophysiological changes in the spleen may lead to various diseases across species. Despite these similarities, notable differences exist in the specifics of pathophysiological processes, the progression of diseases and characteristic conditions affecting the spleen in each group.

In both humans and dogs, macrophages in the spleen are responsible for phagocytizing old or damaged erythrocytes. In humans, this process can lead to hypersplenism, especially when conditions like malaria or sickle cell anemia (Fig. 22) obstruct cell passage through circulation.

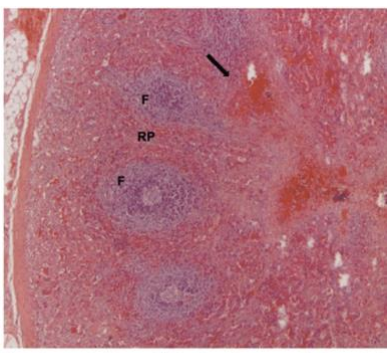


Fig. 22 Histological section of a spleen from a human affected by sickle cell anemia (black arrow: intense red blood cell congestion/hemorrhage)

https://www.researchgate.net/figure/Hematin-eosin-saffron-stained-spleen-sample-following-splenectomy-for-recurrent-acute_fig2_333786137

In dogs, however, this immunological activity often results in splenic hyperplasia. This hyperplasia is categorized as pulpous or follicular, with pulpous hyperplasia typically linked to acute infections (e.g., anaplasmosis, babesiosis or hepatozoonosis (Fig. 23)), while follicular hyperplasia corresponds to chronic infections.

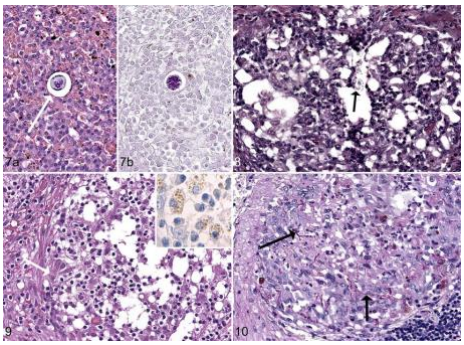


Fig. 23 Histological section of a dog spleen infected with Hepatozoon canis (7a arrow)

https://www.researchgate.net/figure/Figures-7-10-Spleen-dog-Figure-7a-Hepatozoon-canis-A-round-meront-arrow-in-the_fig2_304357064

Both humans and dogs can develop splenomegaly. However, the underlying causes and clinical manifestations vary between the two species. In humans, infectious causes of splenomegaly range from viral (e.g., mononucleosis) to bacterial infections, along with non-infectious causes like liver cirrhosis and trauma. In dogs, a similar condition, hyperemic swelling, arises during pulpous hyperplasia and may be accompanied by a noticeable enlargement and blood accumulation. Chronic splenomegaly in humans can increase the risk of splenic rupture, while in dogs, chronic congestion may alter the spleen's connective tissue, giving it a rough texture.

Human spleens may develop nodules, particularly in the form of congenital accessory spleens, which function similarly to the main spleen. Dogs, however, are more likely to develop nodular hyperplasia as they age, which, often confused with lymphomas, represents regenerative nodules.

Additionally, in felines, myelolipomatosis can occur, presenting as nodules of myeloid tissue and fatty marrow. In both species, accessory spleens can develop, they are structurally and functionally less impactful in dogs and other small animals compared to humans.

Both humans and dogs may experience vascular issues in the spleen. In humans, increased pressure in the vena portae may contribute to hypersplenism, while in dogs, congestion due to blood flow issues (such as splenic torsion) can lead to an acutely enlarged spleen with local congestions.

Chronic congestion in dogs is often linked with liver congestion and results in a significantly enlarged spleen with a lower blood content than its acute counterpart.

Additionally, dogs may suffer from hemorrhagic splenic infarctions caused by embolic incidents, with infarctions potentially linked to endocarditis.

Both humans and dogs are susceptible to splenic ruptures, although their causes and consequences vary.

Human spleens may rupture due to blunt or penetrating trauma, with delayed ruptures sometimes occurring after initial hematoma formation. In dogs, trauma can similarly cause splenic rupture. However, spontaneous ruptures, especially in conditions such as leukosis or amyloidosis, have a significant risk. Dogs' spontaneous ruptures are often fatal due to internal bleeding, contrasting with the possible delayed presentation in humans.

In both species, metabolic changes can lead to splenic disorders. Humans may develop amyloidosis in the spleen due to chronic inflammation or diseases, on the other hand in dogs AA amyloidosis often follows conditions like diabetes or chronic inflammation. Structural changes are also present.

While humans may experience conditions like polysplenia or wandering spleen, dogs may develop siderofibrous nodules, often containing hemosiderin-containing macrophages and may exhibit ectopic spleens due to anatomical displacements, as seen in cases of diaphragmatic hernias.

5.1. Splenic angiosarcoma in humans

The spleen is a highly vascularized organ due to functions such as blood filtering described in section 3.2. "Physiology and functions of the spleen in humans". The good blood supply to the spleen makes it susceptible to benign and malignant tumors of the vascular endothelium. One of these is the malignant splenic angiosarcoma, a rare and aggressive neoplasia. Although uncommon in humans, this tumor grows quickly, spreads easily and has a poor prognosis. It is often diagnosed late because symptoms like abdominal pain or anemia are not specific to this condition.

The angiosarcoma of the spleen is most common in people between the ages of 50 and 60, but women are more likely to develop it at an older age compared to men. A link has been found between patients with angiosarcoma and exposure to certain environmental factors. (Al-Salem, A. H. The Spleen: Anatomy, Physiology and Diseases, 2023).

These include vinyl chloride, thorium dioxide and ionising radiation. One of the most common symptoms of angiosarcoma is splenomegaly. The significant expansion of the organ and structural changes associated with this condition can lead to splenic rupture. Additionally, this type of tumor carries a high risk of massive hemorrhages. Furthermore, more unspecific symptoms may occur such as fever, weight loss, weakness, fatigue and abdominal pain, especially in the left upper abdominal region.

Due to the non-specific nature of the symptoms, further diagnostic tests are required. These include blood tests with a particular focus on hematology. In cases of angiosarcoma of the spleen, blood counts may show leucopenia, thrombocytopenia and often normochromic normocytic anemia. Normochromic normocytic anemia describes a type of anemia in which red blood cells (RBCs) appear normal in both size (normocytic) and hemoglobin concentration, giving them a regular red color (normochromic). Despite their normal appearance, the overall number of RBCs is reduced, leading to anemia. This condition often appears as a secondary effect of underlying diseases, while cases caused by primary blood disorders are relatively rare (Yilmaz & Shaikh, 2023).

Further, increased Prothrombin Time/Partial Thromboplastin Time (PT/PTT) coagulation parameters can occur, which can indicate a coagulation disorder. Less frequently, leukocytosis or thrombocytosis may also be observed. Along with the blood test, an ultrasound of the abdomen may be performed, focusing particularly on the left upper quadrant where the spleen is located. An angiosarcoma typically appears on ultrasound as multiple complex heterogeneous masses.

Due to possible hemorrhages and necrosis within the tumor, it presents as a heterogeneous rather than homogeneous structure, as shown in Figure 24.

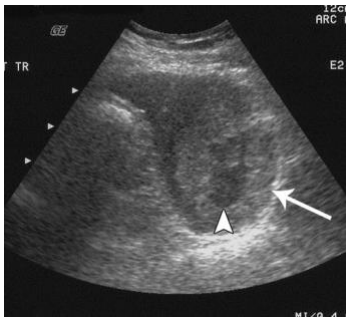


Fig. 24 Ultrasound examination of a splenic angiosarcoma in a human

https://pubs.rsna.org/doi/abs/10.1148/radiol.2351040308?journalCode=radiology

It is also possible to perform Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) scan. In a contrast-enhanced CT, an angiosarcoma typically appears as multiple hypervascular masses. On MRI, the tumor is visible as a heterogeneous mass, similar to its appearance on ultrasound. Both CT and MRI can also detect hemorrhages or hemoperitoneum, either within or surrounding the tumor.

When examining a histological section of the spleen affected by angiosarcoma under the microscope, mitotic figures and multinucleated tumor giant cells are characteristic features of this tumor type, despite its otherwise highly variable histological appearance (Fig. 25). Additionally, honeycomb-like or spongiform proliferations are often observed. Immunohistochemical studies are essential to confirm the vascular origin of the tumor.

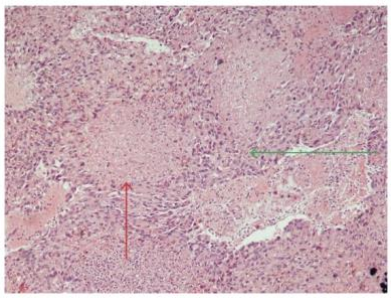


Fig. 25 Histological section of a splenic angiosarcoma in a human (red arrow: necrosis, green arrow: atypical area of endothelial cells with irregular hyperchromatic nuclei)

https://www.researchgate.net/figure/Microscopic-view-of-splenic-angiosarcoma-Hematoxylin-Eosin-stain-H-E-200-Area-of_fig2_264629744

Although, as previously mentioned, the prognosis is poor, chemotherapy and/or radiation therapy may be considered following surgical removal of the spleen. The poor prognosis is attributed to the high metastasis rate of 70–85%, which occurs early and frequently. Tumor size plays a significant role in prognosis. Patients with tumors smaller than 5 centimeters generally have a better outcome compared to those with angiosarcomas exceeding 5 centimeters.

Metastases most commonly occur in the bones, lymph nodes, liver and lungs, while those in soft tissues, the brain or adrenal glands are less frequent (Al-Salem, A. H. The Spleen: Anatomy, Physiology and Diseases, 2023).

5.2. Splenic hemangiosarcoma in dogs

Similar to humans, the dog's spleen is highly susceptible to both benign and malignant tumors originating from the primitive endothelial cells of blood vessels. However, unlike the rare splenic angiosarcoma in humans, the malignant hemangiosarcoma of the spleen in dogs accounts for approximately 40% of all abdominal tumors and 40–60% of all splenic tumors. Hemangiosarcoma is particularly common in certain breeds, especially large and medium-sized dogs, indicating a breed predisposition. German Shepherds are most frequently affected, but Boxers, Bernese Mountain Dogs and Golden Retrievers also show an increased tendency to develop this type of splenic tumor. On average, older dogs around 9–10 years of age are most commonly affected. As in humans, environmental influences can probably contribute to the development of this type of tumor, although, as previously mentioned, in dogs genetic factors also play a role. However, it is not known why the incidence of this tumor is so high in dogs compared to humans and other animals. In the early stages of the tumor, dogs often show no symptoms or only non-specific signs such as anorexia, lethargy, reduced performance, vomiting, dyspnea or polydipsia. In the later stages, the splenic tumor may rupture, leading to a hemoperitoneum. This often results in hypovolemic shock, which can have fatal consequences. Blood tests in dogs often reveal changes, particularly in hematology. The most characteristic finding is a non-regenerative or regenerative anemia (60%), which may result from bleeding into the peritoneum, hemolysis or a blood clotting disorder. Leukocytosis and thrombocytopenia are also common. Thrombocytopenia frequently occurs as a consequence of disseminated intravascular coagulation (DIC), also known as consumption coagulopathy. Clinically, DIC in dogs manifests as a tendency to bleed either locally or throughout the body.

Bruchim and colleagues explain that disseminated intravascular coagulation is a complex syndrome in which excessive clot formation within blood vessels (microthromboses) can impair organ function. At the same time, paradoxical bleeding occurs due to the overconsumption and inactivation of platelets and clotting factors (Bruchim et al. ,2012).

In addition to blood tests, an ultrasound examination can reveal tumorous changes in the spleen. However, it cannot definitively determine whether the tumor is benign or malignant. A mixed echogenic structure with cavernous formations is characteristic of hemangiosarcoma, as can be seen in Figure 26.

Additionally, contrast-enhanced Computer Tomography is useful for distinguishing hemangiosarcomas from other (benign) conditions, such as hematomas.

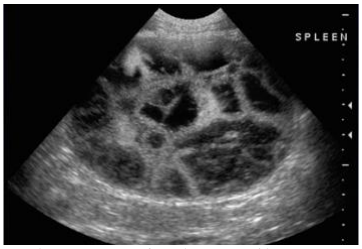


Fig.26 Ultrasound examination of a splenic mass/ hemangiosarcoma in a dog

https://slideplayer.com/slide/2406512/

Macroscopically, hemangiosarcoma of the spleen in dogs presents as a solitary or multiple dark red mass with a consistency ranging from soft and spongy to firm and nodular (Fig. 27). Upon incision, characteristic cavernous, blood-filled cavities are visible and the tissue appears spongy and fragile when palpated.

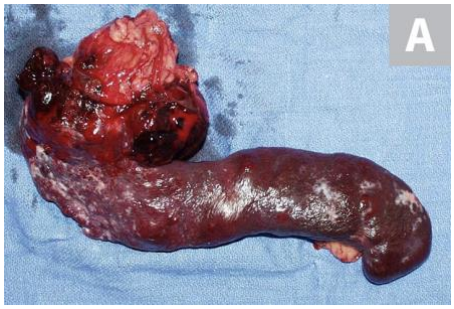


Fig.27 Surgically removed spleen of a dog with a hemangiosarcoma (left side)

https://tierarzt-karlsruhe-durlach.de/en/haemangiosarcoma-of-the-spleen-of-the-dog-hsa/

Histologically, hemangiosarcomas are made up of enlarged neoplastic endothelial cells that envelop the stromal tissue. These cells create irregularly structured and poorly defined vascular spaces, which are often filled with blood (Boes & Durham, 2017). In Figure 28, the irregularly organized blood-filled vascular cavities formed by neoplastic endothelial cells are visible as well as a mitotic figure (arrow).

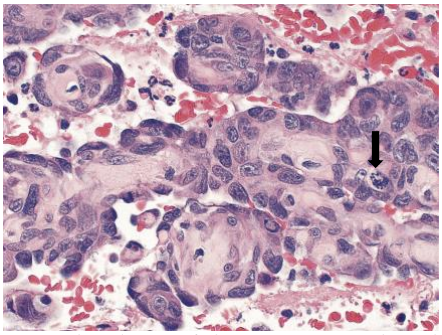


Fig. 28 Histological section of a hemangiosarcoma in a dog's spleen

https://www.sciencedirect.com/topics/medicine-and-dentistry/hemangiosarcoma

Similar to the splenic angiosarcoma in humans, the splenic hemangiosarcoma in dogs has a strong tendency to metastasize. Common sites of metastasis include the omentum majus, peritoneum, lungs, liver, heart, kidneys, adrenal glands and brain. Due to the high malignancy and metastasis rate, the prognosis for this tumor is poor. Therapy involves surgical splenectomy followed by chemotherapy, aiming to prolong life while prioritizing the patient's quality of life (M. Kessler Kleintieronkologie. Diagnose und Therapie von Tumorerkrankungen bei Hund und Katze, 2022).

5.3. Comparison of the splenic angiosarcoma in humans and splenic hemangiosarcoma in dogs

Splenic angiosarcoma in humans and splenic hemangiosarcoma in dogs share many similarities but have distinct differences, particularly in frequency, contributing factors and clinical manifestations. While splenic angiosarcoma is a rare and aggressive tumor in humans, the aggressive splenic hemangiosarcoma is significantly more common in dogs (accounting for 40% of all abdominal tumors and 40–60% of splenic tumors). This contrast may be due to genetic predispositions in dogs, particularly in breeds such as German Shepherds, Boxers, Bernese Mountain Dogs and Golden Retrievers, which are more susceptible to this type of tumor. In humans, environmental factors, such as exposure to vinyl chloride, thorium dioxide and ionizing radiation, play a major role in the development of splenic angiosarcoma. While environmental influences might also contribute to hemangiosarcoma in dogs, genetic factors are likely more significant. Although the exact reasons for the high incidence in dogs compared to humans remain unknown.

Both humans and dogs often show non-specific symptoms in the early stages of the disease, which contributes to delayed diagnosis. In humans, these symptoms include fever, weight loss, weakness, fatigue and abdominal pain. Similarly, dogs may present with anorexia, lethargy, reduced performance, vomiting, dyspnea or polydipsia. In the later stages, splenic rupture is common in both species due to the structural fragility of the tumor. It often leads to hemoperitoneum and hypovolemic shock with fatal consequences.

Hematological changes in the blood tests are observed in both species. In humans, splenic angiosarcoma often presents with normocytic normochromic anemia, thrombocytopenia and occasionally leukocytosis. Dogs frequently show non-regenerative or regenerative anemia (60%), leukocytosis and thrombocytopenia. The latter often resulting from disseminated intravascular coagulation (DIC). Diagnostic imaging techniques such as ultrasound, contrast-enhanced CT and MRI are used in both species to detect the tumor. On ultrasound, splenic angiosarcoma in humans and hemangiosarcoma in dogs share a heterogeneous appearance due to hemorrhages and necrosis. In dogs, a mixed echogenic structure with cavernous formations is particularly characteristic of hemangiosarcoma.

Histologically, both tumors consist of neoplastic endothelial cells forming irregular, blood-filled vascular spaces.

Mitotic figures and multinucleated tumor giant cells are characteristic in humans, while in dogs, irregularly arranged and poorly defined vascular spaces wrapped by plump endothelial cells are typical.

The prognosis for both splenic angiosarcoma in humans and splenic hemangiosarcoma in dogs is poor due to the high malignancy and metastasis rates. In humans, metastases most commonly affect the bones, lymph nodes, liver and lungs. In dogs, common sites include the omentum majus, peritoneum, lungs, liver, heart, kidneys, adrenal glands and brain. In both species, the prognosis improves slightly for smaller tumors (<5 cm in humans), but survival remains limited. Treatment involves surgical splenectomy, often followed by chemotherapy, aiming to prolong life while considering the patient's quality of life.

Despite the differences in frequency and contributing factors, the similarities in clinical presentation, diagnostic challenges and poor prognosis highlight the aggressive nature of splenic angiosarcoma in humans and splenic hemangiosarcoma in dogs.

6. Conclusion

The spleen is known as the largest secondary lymphatic organ in the body of humans and small animal species (dogs), fulfilling important functions such as blood filtering, storage of erythrocytes during periods of increased demand and responding immunologically to antigens in the blood stream. The anatomy and physiology of the spleen are adapted to the specific needs of each species, as demonstrated in this thesis.

The comparison of the spleen in humans and dogs highlights both similarities and differences. For example, while the spleen in both species serves as a blood filter and immune defense organ, dogs have a more pronounced capacity for blood storage and release. These differences underline the adaptive nature of the spleen and its importance in species-specific health maintenance.

Pathological conditions can affect the spleen in both species, such as splenic angiosarcoma in humans and hemangiosarcoma in dogs. They demonstrate how similar diseases can manifest differently between species. Splenic angiosarcoma is rare in humans and often linked with environmental factors. However splenic hemangiosarcoma is more common in dogs, particularly in certain breeds with genetic predispositions. Despite these differences, both diseases are aggressive, have unspecific early symptoms and are often difficult to diagnose and treat, with poor survival rates due to high metastasis rates.

From the research done in this thesis, comparative studies of the spleen in humans and dogs provide valuable insights into the complex structure and function in health and disease of the spleen.

Such comparisons can improve our understanding of shared physiological mechanisms and species-specific adaptations and it may contribute to a progress in both human and veterinary medicine.

With this deeper understanding of diseases like angiosarcoma and hemangiosarcoma, these studies also highlight the importance of research to improve possible diagnostic and treatment options for both species.

7. Acknowledgement

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9. Figures

Fig. 13: Histological section of the human (left) and dog spleen (right)

Source: https://www.researchgate.net/figure/Spleen-compartments-in-human-A-D-dog-B-E-and-hamster-C-F-spleen-Spleen-in-all_fig1_328915897

Fig. 14: Extramedullary hematopoiesis during an infection

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC11104806/pdf/18_2020_Article_3450.pdf

Fig. 15: Splenomegaly in humans

Source: https://www.mountsinai.org/health-library/symptoms/splenomegaly

Fig. 16: Polysplenia in a human

Source: https://www.researchgate.net/figure/ntraoperative-photograph-showing-polysplenia_fig2_273202956

Fig. 17: Accessory spleen in a human

Source: https://link.springer.com/article/10.1007/s00261-011-9830-x

Fig. 18: Histological section of nodular hyperplasia in the spleen of a dog

https://www.researchgate.net/figure/Nodular-hyperplasia-in-the-spleen-of-a-dog-A-The-proliferating-lymphoid-follicles-were_fig1_369571870

Source: *https://www.researchgate.net/figure/Nodular-hyperplasia-in-the-spleen-of-a-dog-A-The-proliferating-lymphoid-follicles-were_fig1_369571870*

Fig. 19: Splenectomy / Splenic hematoma in a dog

Source: https://lbah.com/feline/spleen-hematoma/

Fig. 20: Ultrasound image of a dog with the normal spleen (Sp) and an accessory spleen (arrow)

Source: *https://smallanimalultrasonography.com/ectopic-spleen-in-a-dog/*

Fig. 21: Torsion of the spleen in a dog

Source: *https://www.animalsurgicalcenter.com/splenic-torsion*

Fig. 22: Histological section of a spleen from a human affected by sickle cell anemia

Source: https://www.researchgate.net/figure/Hematin-eosin-saffron-stained-spleen-sample-following-splenectomy-for-recurrent-acute_fig2_333786137

Fig. 23: Histological section of a dog spleen infected with Hepatozoon canis

Source: https://www.researchgate.net/figure/Figures-7-10-Spleen-dog-Figure-7a-Hepatozoon-canis-A-round-meront-arrow-in-the_fig2_304357064

Fig. 24: Ultrasound examination of a splenic angiosarcoma in a human

Source: https://pubs.rsna.org/doi/abs/10.1148/radiol.2351040308?journalCode=radiology

Fig. 25: Histological section of a splenic angiosarcoma in a human

Source: https://www.researchgate.net/figure/Microscopic-view-of-splenic-angiosarcoma-Hematoxylin-Eosin-stain-H-E-200-Area-of_fig2_264629744

Fig. 26: Ultrasound examination of a splenic mass/hemangiosarcoma in a dog

Source: https://slideplayer.com/slide/2406512/

Fig. 27: Surgically removed spleen of a dog with a hemangiosarcoma

Source: https://tierarzt-karlsruhe-durlach.de/en/haemangiosarcoma-of-the-spleen-of-the-dog-hsa/

Fig. 28: Histological section of a hemangiosarcoma in a dog's spleen

Source: https://www.sciencedirect.com/topics/medicine-and-dentistry/hemangiosarcoma