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An Overview about Anatomy and Development of Spleen

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Abstract: Background: The spleen is a wedge shaped (44%) ,tetrahedral (42%) ,or less commonly a triangular (14%) soft tissue friable organ. It is situated in the left hypochondriac region , but its superior extremity extend into the epigastric region ; it lies between the fundus of the stomach and the diaphragm , It is the largest of the ductless glands. It generally weighs 150 gm in adults. The spleen is about the size of a clenched fist and residue in the shelter of ribs 9 ,10,11. In adult it is about 12 cm. in length, 7 cm. in breadth ,3-4 cm. in thickness . It has 2 surfaces diaphragmatic (convex) surface and visceral (concave) surface. It has 2 ends anterior (lateral) and posterior (medial).The diaphragmatic surface is convex, smooth surface , and is directed upward , backward, and to the left , except at its upper end , where it is directed slightly medially . It is in relation with the under surface of the diaphragm , which separates it from the ninth ,tenth , and eleventh ribs of the left side ,and the intervening lower border of the left lung and pleura. The spleen develops entirely from mesoderm, although the ultimate formation of the organ is dependent on cross-talk between hematopoietic and stromal cells and the establishment of the unique vascularization of this organ. Splenic development is initiated by the condensation of mesenchymal cells that form thickenings in the coelomic epithelium of the dorsal mesogastrium near the dorsal pancreatic bud and is dependent on activity of the transcription factors BAPX1, HOX11, TCF21 and WT1. Splenic development can be identified in human development by the 6th gestational week.

Keywords: *Spleen, Anatomy, Development*

Introduction

The spleen is a wedge-shaped (44%), tetrahedral (42%), or less commonly a triangular (14%) soft tissue friable organ. It is situated in the left hypochondriac region, but its superior extremity extends into the epigastric region; it lies between the fundus of the stomach and the diaphragm. It is the largest of the ductless glands [1,2]. It generally weighs 150 gm in adults. The spleen is about the size of a clenched fist and resides in the shelter of ribs 9, 10, 11. In adults, it is about 12 cm in length, 7 cm in breadth, 3-4 cm in thickness. It has 2 surfaces: diaphragmatic (convex) surface and visceral (concave) surface. It has 2 ends: anterior (lateral) and posterior (medial). The diaphragmatic surface is convex, smooth, and directed upward, backward, and to the left, except at its upper end, where it is directed slightly medially. It is in relation with the under surface of the diaphragm, which separates it from the ninth, tenth, and eleventh ribs of the left side, and the intervening lower border of the left lung and pleura [2].

The visceral surface is divided by a ridge into an anterior or gastric and a posterior or renal portion. The gastric surface, which is directed forward and upwards, is in contact with the posterior wall of the stomach; and below this with the tail of the pancreas. It presents near its medial end a long fissure, termed the hilum. The renal surface is directed medially and downwards. It is flattened and considerably narrower than the gastric surface, and is in relation with the upper part of the anterior surface of the left kidney and occasionally with the left suprarenal gland [3].

The superior extremity is directed toward the vertebral column, where it lies on a level with the eleventh thoracic vertebra. The lower extremity or the colic surface is flat, triangular in shape and rests upon the left flexure of the colon and the phrenicocolic ligament, and is generally in contact with the tail of the pancreas [2].

Fig(1): Picture of the visceral surface of the spleen. [2]

The superior border is free, sharp, thin and is often notched; it separates the gastric surface from the diaphragmatic surface. The posterior border is more rounded and blunter than the anterior, separates the renal from the diaphragmatic surfaces. The intermediate margin is the ridge which separates between the gastric and the renal surfaces. The inferior border, which separates the diaphragmatic surface from the colic surface [2].

The spleen, with the exception of the hilum, is completely enveloped by the peritoneum arising from the dorsal mesogastrium whose thickenings hold the spleen in the left hypochondrium. The most important are the splenorenal, gastrosplenic, splenocolic, and phrenicocolic ligaments. The splenorenal ligament arises from the posterior portion of the dorsal mesentery, envelops the tail of the pancreas, the splenic artery and vein, and ends on the splenic hilum. The gastrosplenic ligament connects the greater curvature of the stomach with the splenic hilum; it is triangular in shape with the apex cranially and the base directed caudally, where the distance between the stomach and the spleen is the greatest. It is traversed by the small gastric vessels in the upper portion and by the left gastroepiploic vessels in its inferior wider portion. The uppermost part of the gastrosplenic ligament attaches to the inferior left hemidiaphragm and is called the splenicophrenic ligament. The splenocolic ligament represents a secondary attachment of the spleen to the colon. The phrenicocolic ligament is not a direct splenic ligament but an attachment of the splenic flexure of the colon to the left hemidiaphragm, at the transition between the midgut and the hindgut, and constitutes a floor on which the spleen rests. Other ligaments such as the pancreaticosplenic ligament, the spleno-omental fold and the presplenic fold have little importance in holding the spleen in its place [1].

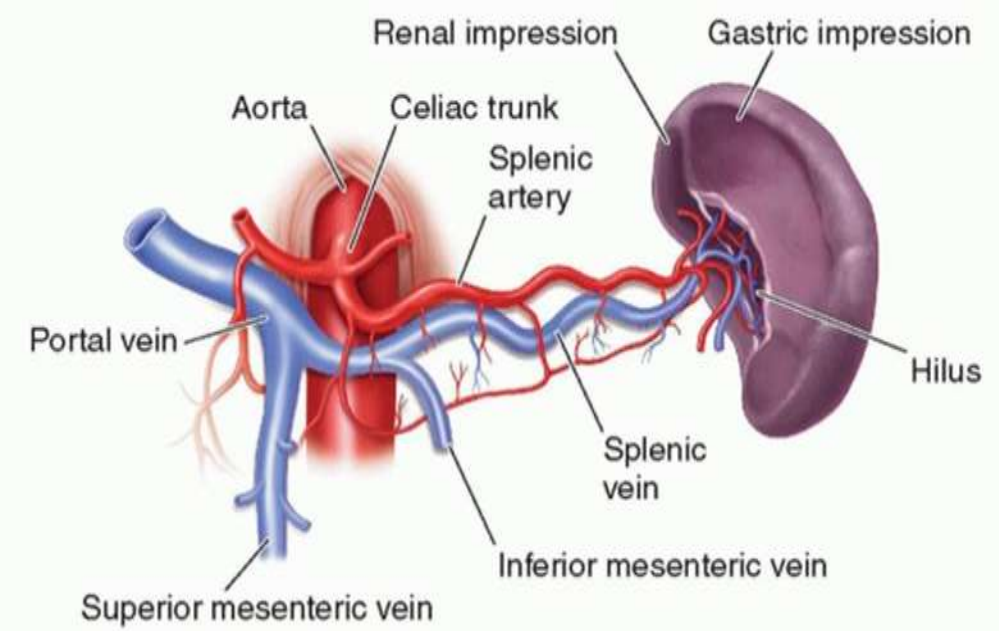
The adult spleen has no lobulations; however, the persistence of fissures separating the fetal spleen's lobules can indicate splenic lacerations in a trauma context. The ectopic spleen is a migration of the spleen from its normal anatomical location because its ligaments haven't developed properly. The spleen can migrate anywhere in the abdomen or pelvis. The accessory spleen can be found in 10% of the population; it is usually located near the hilum of the main spleen or the pancreatic tail. It can be located in many other places and be confused with a mass. Polysplenia is a complex congenital syndrome associating visceral heterotaxis and concomitant bilateral left-sidedness. The spleen is divided into many splenules of the same size [4].

Blood supply of the spleen:

The splenic artery is the main arterial supply to the spleen. This artery is the largest branch of the celiac trunk and reaches the spleen's hilum by passing through the splenorenal ligament. It divides into multiple branches at the hilum. It divides into straight vessels called penicilli, ellipsoids, and arterial capillaries in the spleen. The splenic circulation is adapted for the separation and storage of the red blood cells. The spleen has superior and inferior vascular segments based on the blood supply. The two segments are separated by an avascular plane. Its terminal branches aside, the splenic artery also gives off branches to the pancreas, 5-7 short gastric branches, and the left gastro-omental (gastroepiploic) artery [5].

The splenic vein provides the principal venous drainage of the spleen. It runs behind the pancreas (after forming at the hilum) before joining the superior mesenteric vein behind the neck of the pancreas to form the portal vein. The short gastric, left gastro-omental, pancreatic, and inferior mesenteric veins are its tributaries.

Proper splenic tissue has no lymphatics; however, some arise from the capsule and trabeculae and drain into pancreaticosplenic lymph nodes [3].



Gross anatomy of rat spleen:

The spleen of the rat is a parenchymatous organ with the shape of an elongated bean. It is surrounded by a capsule from which fibrous trabeculae emerge. Five to seven arterial vessels accompanied by nerves reach the spleen at the hilus and enter the organ through the trabeculae. Veins collect the blood from the venous sinuses and leave the spleen at the hilus. The ratio of splenic weight to body weight in rats is typically 0.2% [6].

Moreover, in the rat spleen, the splenic arteries leave the trabeculae, they become the central arteries which are surrounded by lymphocytes and a concentric sheath of flattened reticular cells together they form the white pulp. The central artery gives off several arterial terminals. Part of these arterial terminals give rise to the meshwork of the white pulp capillaries. The terminal branches of this meshwork end in the follicles in the marginal sinus surrounding the white pulp or directly in the marginal zone. After passage through the reticular meshwork of the marginal zone, the blood is collected in the venous sinuses. Another part of the smaller branches of the central arteriole traverse the different compartments of the white pulp, including the marginal zone, toward the red pulp. The central artery leaves the white pulp and then designated as a penicillar artery, which divides into several arterial terminals ending up in the splenic red pulp. These arterial terminals are tubular or funnel-shaped and open into the reticular meshwork of the splenic cord of the red pulp. Therefore, the rat has an "open end" vascular system in the spleen. Venous blood is collected by the red pulp sinuses which are surrounded by a discontinuous layer of endothelial cells and then transported by the trabecular veins toward the hilum. Lymphatics are recognizable after ligation of the thoracic duct and occur in the periarteriolar lymphatic sheath (PALS) close to the large central arteries [7]. There are three theories of circulation in the spleen: Closed circulation, open circulation, and a combination of the two theories [8].

Function of the spleen:

The spleen plays an important role in both innate and adaptive immune function and is particularly critical for protection against encapsulated bacteria, fungi, and other blood-borne pathogens (Table 1). It also has a unique role in the circulatory system in removal of aged or abnormal red cells, cellular debris, and circulating tumor cells. Due to this dual role in immune function and cell turnover, the spleen is central to the pathologic destruction of blood elements in autoimmune diseases such as idiopathic thrombocytopenic purpura (ITP). [9]

Function Target Mechanism

Function	Target	Mechanism
Adaptive immunity (white pulp and marginal zone)	Bacterial, viral, tumoral or self antigens	Largest secondary lymphoid organ with extensive exposure to circulating antigens
Innate immunity (red pulp and marginal zone)	Bacteria, viruses, fungi, foreign material and tumor cells	Specialized macrophages recognize, engulf and/or inhibit growth of pathogens; produce cytokines/ inflammatory molecules to stimulate further immune response
Filtration (red pulp)	Remove aged and abnormal blood cells (culling) Intraerythrocytic inclusions (pitting)	Phagocytosis may relate to decreased deformability of abnormal/aged red cells and prolonged transit time in the spleen or changes in surface marker expression Non-deformable portion of red cell gets caught in rigid sinusoidal inter-endothelial slits and Phagocytized
Cellular reservoir (red pulp)	30% of platelets; red cells in some Mammals	Erythrophagocytosis by red pulp macrophages in conjunction with liver; released or stored as ferritin, which can aggregate into hemosiderin2 Release of platelets in response to stimuli, e.g. epinephrine
Hematopoiesis (red pulp)	Normal fetal development, pathologic Conditions	Pathologic: displaced precursors
Cell maturation (red pulp)	Reticulocytes	Mature in sinusoids prior to release

Splenic development is initiated by the condensation of mesenchymal cells that form thickenings in the coelomic epithelium of the dorsal mesogastrium near the dorsal pancreatic bud and is dependent on activity of

the transcription factors BAPX1, HOX11, TCF21 and WT1. Splenic development can be identified in human development by the 6th gestational week. [11].

There is subsequent formation of independent lobules which eventually fuse into a multi-lobulated mass. Stray lobules that do not undergo fusion are the source of accessory splenic tissue, present in 10–30% of the population. [12]. While often located near the spleen, particularly the hilum, remote sites including the pelvis have been reported and can be similarly affected by disease processes. [13].

Rarely, splenogonadal fusion occurs during this period of embryonic life when the organs are in close proximity to each other. The majority of cases involve the testes, often in the setting of cryptorchidism, but may also present as a testicular mass mimicking a neoplasm. [14].

The gonad may fuse with the spleen (continuous type) or with accessory or ectopic splenic tissue (discontinuous type). [15]. Vascular structures first appear in the 8th week of gestation within the sponge-like reticular cell meshwork as thin-walled loops. [9].

Gradually, reticular cells and fibers form sheaths around the developing arterioles with distinct channels opening into endothelial-lined vessels by the 9th week. Hematopoiesis occurs in close association with the vasculature, and the fetal spleen, in addition to the fetal liver, appears to be a site of early hematopoiesis. [16].

While this has been best studied in animal models and has been controversial in human fetal development, hematopoietic progenitors can be identified in the developing human spleen during mid-gestation, with their numbers declining following the 5th gestational month when bone marrow hematopoiesis is established. [9].

In addition, mouse studies demonstrate that lymphoid-tissue-inducer cells (CD4+CD3-CD45+ cells) are seeded in the spleen during mid-gestation (embryonic day 13.5 in mouse) which can become natural killer, dendritic or follicular cells but do not appear to generate T or B lymphocytes. [10].

Colonization by these inducer cells is thought to play a role in the establishment of lymphoid architecture. [17].

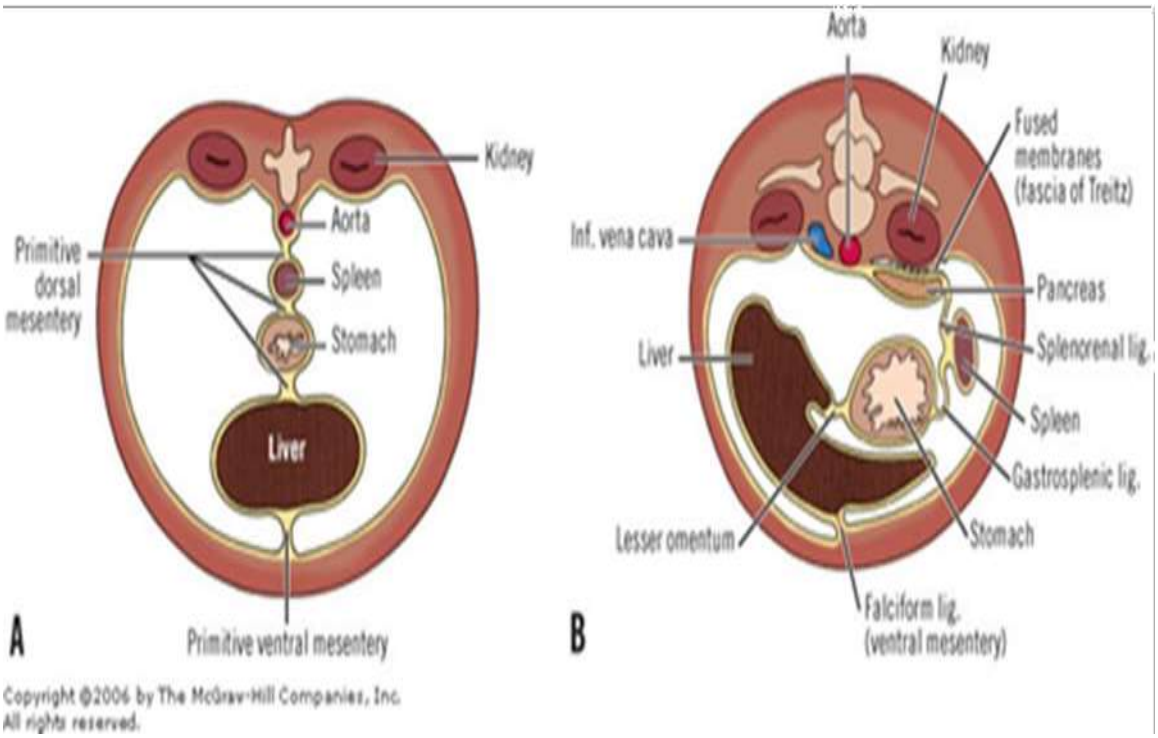
In humans, the first lymphocytes and monocytes/macrophages appear as early as 12–13 weeks of gestation and predominantly localize to the periarteriolar lymphoid sheath (PALS). Macrophages can also be found in the cords in fetal life, which appear to be derived from yolk sac precursors similar to other resident tissue macrophages. [18].

In contrast, specialized marginal zone macrophage populations may derive from circulating monocytes. The early splenic lymphocytes demonstrate a relative B-cell predominance with the first antibody production beginning in the third trimester. However, follicular dendritic meshworks do not appear until the postpartum period, with germinal centers soon following at approximately 2–4 weeks after birth. CXCL13, a chemokine produced by the follicular dendritic cells, is necessary for B-cell chemotaxis. B-cells express the CXCL13 receptor, CXCR5, guiding their migration into the follicles. [19].

Expression of lipid and chemokine receptors by marginal zone B-cells may enable them to overcome the attraction of CXCL13 and exit the follicle. [20].

In particular, receptors for sphingosine 1-phosphate are required, which also regulate the exit of T-cells from the thymus and lymph nodes [21].

It was once thought these marginal zone B-cells were largely stationary, but new evidence finds they shuttle continuously between the marginal zone and the follicles, potentially by altering expression of cell surface receptors. This shuttling may facilitate antigen delivery from the blood circulation to the follicle. [22].



Schematic cross-section of the upper abdomen of the embryo representing the development of the spleen during the embryonic stage.

A: Showing a cross-section of the spleen, stomach, and liver in the 5th week embryo.

B: Showing the movement of the liver to the right, rotation of the stomach, and its relation to the spleen [1].

The spleen develops during the fifth week of embryogenesis. In contrast to the gut organs, the cells of the spleen are mesodermal in origin. Multiple aggregations of mesodermal cells are found between the layers of the dorsal mesogastrium. At five weeks, the embryo's stomach is supported by a dorsal mesentery (dorsal mesogasterium) and a ventral mesentery (ventral mesogasterium). The spleen develops within the dorsal mesogasterium, while the liver is developed within the ventral mesogasterium. As the liver enlarges and turns to the right, the spleen and the stomach turn leftward to form the lesser peritoneal sac. The spleen divides the dorsal mesogasterium into the gastrosplenic ligament and the splenorenal ligament. The mesenchymal cells differentiate to form both the capsule and a connective tissue framework [23,24].

The spleen assumes an active role as a hematopoietic organ by the fourth month of gestation. The weight of the spleen increases in a linear fashion with the body weight, reaching its maximum at puberty after which it decreases [25].

In the fetus, the spleen begins as a collection of primitive reticular cells in the dorsal mesogasterium. The first cells that appear are hematopoietic, which are evident by gestation day 17 in the rat [6]. The first lymphocytes to appear are T-cells, which accumulate in the PALS regions [6, 26]. In rats, the appearance of lymphocytes begins at 2 days of age; by day 5, dendritic cell precursors appear, after which B-cell follicles begin to develop, and immunological function begins at 14 days of age when cell-to-cell contact of antigen-presenting dendritic cells becomes apparent [6].

In the first week of postnatal life, the capsule was rarely distinguishable. The capsule becomes slightly thicker and consists of two or three rows of cells at the end of two weeks. In adult animals, the capsule is relatively thick and in addition to its content of collagen and reticular fibers, it also contains smooth muscle cells and is covered with peritoneum. Extensive development of trabeculae, which formed a branched network of vascular cords extending through the spleen. In senile rats, an increase in the thickness of the capsule was noticed [27].

The reticular fibers are distributed in the capsule and trabeculae and forming the framework of the spleen. Its thickness distribution increases with increasing age. In the adult spleen, the reticular fibers were distributed in the PALS. Two areas can be distinguished; a central area largely devoid of reticular cells and a peripheral area where reticular cells are arranged in cylindrical shells and represented a transitional zone toward the red pulp, in which branched reticular cells with many processes are concentrically arranged. At the first day, the reticular fibers are very thin. However, in senile rats, there are very thick irregular reticular fibers that run through the parenchyma of the spleen [28].

The splenic parenchyma is formed of white pulp and red pulp. In the spleen of adult animals, the white pulp is formed of the periarterial lymphatic sheath and lymphoid follicle with pale stained germinal center. A marginal zone with many aggregations of darkly stained lymphocytes was observed, which differentiates the white pulp from the red pulp. However, in senile rats, the lymphatic follicles decrease in size [29].

By the twenty-first day, the adult appearance of PALS is clear with distinct separation into a central area populated with T-lymphocytes and a peripheral part with a mixed population of T and B lymphocytes [29].

Dijkstra et al. [30] reported that after the differentiation into an inner and outer periarteriolar lymphatic sheath, the T-cell-dependent area of splenic white pulp has attained its adult appearance and further changes are not to be expected. Before the T-cell organization, suggesting that IDC may play an essential role in the homing of T cells.

Namikawa et al. [31] stated that the ontogenic development of lymphoid and non-lymphoid cells in human splenic white pulp was studied histologically with an immunoperoxidase technique suggesting that the spleen is an important site for B-cell maturation. The organization of antigen-positive T cells around arterioles developed four weeks later than that of B cells. Interdigitating reticulum cells (IDC) stained with anti-S-100 protein serum appeared from week 14.

Plackett et al. [32] reported that aged dendritic cells are less able to stimulate T and B cells. The altered T-cell stimulation is a result of changes in human leukocyte antigen expression and cytokine production and lower B-cell stimulation is a result of changes in DC immune complex binding.

Labunets [33] investigated the 24-hour and seasonal fluctuations of cellularity of the spleen and antibody levels in rats of different ages. In adult rats, the peak of splenic cellularity was at night and during the daytime, respectively. In young rats, splenic cellularity was highest in autumn and spring, respectively. While in aging rats, the intrasystemic relations underwent changes (new relations appeared while the existing ones weakened or disappeared).

In the newborn, the splenic parenchyma was mainly red pulp, and the venous blood sinusoids are large, dilated, and filled with blood elements. In adult animals, sinuses were moderately enlarged. However, in senile rats, the red pulp of senile animals showed a conspicuous change consisting of its transformation from predominantly compact reticular type of tissue to a predominantly sinusoidal type of tissue [4].

Matsumura et al. [34] reported that the erythropoiesis in the splenic red pulp was examined histologically; in early life until day 20, erythroblasts constituted 91.5% to 96% of all hematopoietic cells and then decreased gradually in proportion, although they composed 71% even at 150 days of age. The total number of erythroblasts contained in the red pulp increased in early life until it reached a maximum at day 35. At 150 days of age, erythroblasts were half of those at day 35 in number.

In addition, Oseroff et al. [35] stated that the spleen of the neonatal rat was formed mainly of islands of hematopoietic tissue. The hematopoietic activity began to be noticeable in the spleen of the rat at the newborn, then gradually declined until the age of 60 days where granulopoiesis arrested in contrast to the continuous erythropoiesis and megakaryocytes formation throughout life. Moreover, there are a number of rounded cells with prominent nuclei scattered among the pleomorphic mesenchymal cells in the first few days of postnatal life. These cells are termed hematopoietic stem cells.

Cheung and Nadakavukaren [36] added that the spleen, however, it increased in weight with age. They also found that fewer cells were recovered from the spleens of old animals even though the weight of the spleen of the old animals was greater than the spleens from the younger ones. Moreover, the white pulp of the adult rats

contained a large number of small lymphocytes, and this number of cells was found to decrease with increasing age.

Linton et al. [37] studied the role of antigen in the changes that occur as T cells age. The aged T cells are relatively deficient in their ability to produce interleukin and they proliferate less. Thus, at least one component of aging must be antigen-dependent. The loss of optimal interleukin production may participate in the aging process and may represent the main independent defect in the T-cell population.

Haynes et al. [38] stated that memory cells generated from young T cells responded well to antigen even a year after generation, whereas memory cells derived from T cells from aged mice responded poorly. Memory cells generated from aged naive cells proliferate less, producing reduced levels of cytokines.

Kohut et al. [39] examined the effect of aging on macrophage function in male mice. Macrophages from spleens of older mice generally produced more cytokines than younger mice. Chronic moderate exercise tended to reverse age-associated changes in macrophage function in old mice.

Butcher and Lord [40] stated that in the elderly, the immune response is blunted as a result of the decline in several components of the immune system and shifting to a chronic pro-inflammatory status. Both stress and aging affect upon the innate immune system in which the age-related increase in the cortisol/sulfated dehydroepiandrosterone ratio “due to alteration in the hypopituitary-adrenal axis” synergizes with elevated cortisol during stress to reduce immunity in the elderly significantly.

Ahluwalia et al. [41] stated that aging is often associated with a dysregulation of the immune function. Iron deficiency may further impair immunity in older people. Iron deficiency is associated with impairment in the cell-mediated and innate immunity and may render older people more vulnerable to infections.

Mittler and Lee [42] reported that aging is associated with changes in the immune system that lead to decreased immunity in the elderly. They monitored the immune response in both young and old-aged microenvironments. The immune response is the same in both microenvironments and so, these changes are mainly intrinsic within the aged T cells (with defective T-cell activation and clonal expansion). Rather than to extrinsic influences associated with the aged lymphoid microenvironment.

Microanatomy of the spleen:

The spleen is surrounded by a fibroelastic connective tissue capsule occasionally housing smooth muscle cells and invested by visceral peritoneum. The simple squamous epithelium of the peritoneum provides a smooth surface of the spleen. The capsule is thickened at the hilum and where arteries and their accompanying nerve fibers enter and veins and lymph vessels leave the spleen. It has three-dimensional networks of reticular fibers and associated reticular cells. This reticular fiber network is attached to the capsule as well as to the trabeculae and forms the architectural framework of the spleen [43].

Its tissue composition of red pulp and white pulp explains the heterogeneous aspect when contrast medium is injected in the arterial phase. This can make it difficult to detect intrasplenic masses [4].

The argentophil reticular cell network in the red pulp of the spleen is composed of three types of fixed cells: the primitive reticular cell (slightly argentophil), the small reticular cell, and the larger reticular cell (strongly argentophil and phagocytic). The large reticular cell may become free, constituting a fourth cell type, the free macrophage. A fifth reticular cell type is the dendritic cell found in the lymphatic follicles of the white pulp. The argentophil reticular cells of the red pulp join together to form the reticular cell network which maintains a relationship with the arterial terminal vessels of the red pulp, being responsible for the ellipsoid structure. These ellipsoids are formed by large argentophil cells arranged in concentric layers around its lumen that sometimes appear devoid of endothelial lining cells [44].

Splenic stromal cells mimic the immune microenvironment at which contact with stromal cells drive mature dendritic cells (DCs) to proliferate in a fibronectin-dependent way induced their differentiation into new regulatory cells (DCs). These differentiated DCs secrete nitric oxide that mediated the suppression of T-cell proliferation in response to antigen presentation by mature DCs [45].

The white pulp of the spleen consists of the periarteriolar lymphoid sheath (PALS) and splenic nodules. The splenic nodules contain germinal centers, which are due to a reaction with antigen and thus do not appear until

birth. They contain B lymphoblasts, T lymphocytes, macrophages, and reticular cells. Their number varies in the different animal species. The PALS surrounds the central artery branches to become the follicular arteriole in the splenic nodules. The PALS of lymphocytes is continuous with those comprising the splenic nodules. The central region of the PALS contains T lymphocytes, while the periphery of the PALS contains mainly B lymphocytes [28].

Veerman and van Ewijk [46] added that the PALS has a loose framework of reticular fibers with associated reticular cells. The meshes of this reticulum are occupied by small and medium-sized lymphocytes, sometimes associated with interdigitating cells. In the course of an immune response to blood-borne antigens, a great number of large lymphocytes, lymphoblasts, and immature plasma cells appear in the PALS and then become concentrated at their periphery. At the periphery of the sheath, the reticular fibers become arranged circumferentially and the flattened reticular cells associated with them form the concentric layers that establish the boundary between the lymphoid tissue of the sheath and the surrounding red pulp.

The perifollicular zone is a dynamic region of variable cellular and phenotyping composition, which can be regarded either as a part of the red pulp or of the follicles. In most cases, the perifollicular zone appears as a compartment of the red pulp containing erythrocyte-filled spaces that differ from the typical red pulp sinusoids. Similar to the splenic cords, the perifollicular zone mostly harbors scattered B and T lymphocytes. However, sometimes B lymphocytes clearly predominate in the perifollicular zone. In addition, macrophages form sheathes around the capillaries in the perifollicular zone. So, in humans, the perifollicular region is the compartment where antigen and recirculating lymphocytes enter the organ while in rats, the marginal zone represents this compartment [47].

The white pulp is surrounded by the marginal zone, which separates the white pulp from the red pulp. The marginal zone of the spleen forms an intriguing area in which a variety of cell types are combined. Many of these cell types seem to have a fixed position in the marginal zone, such as the marginal zone macrophages, the marginal zone macrophages, the marginal metallophilic macrophages at the inner border, and to a lesser extent, the marginal zone B cells. For other cell types, T lymphocytes, small B cells, and dendritic cells, the marginal zone is only a temporary residence. The marginal zone is a concourse of cell traffic through which cells migrate to the red pulp or white pulp. This unique combination of cells and functions cannot be found in any other lymphoid organ [48].

Infants are more susceptible to infections caused by T-cell-independent polysaccharide antigens of certain encapsulated bacteria. Immune responses against this type of antigen are related to the splenic marginal zone. So, an immature state of the spleen, and especially of the MZ during the early development, may contribute to the increased susceptibility to bacterial infections and sudden infant death [49].

In cross-section, the white patches are recognizable with the naked eye within the deep reddish organ. These patches are designated the white pulp and represent the lymphoid compartment of the spleen. They are surrounded by the red pulp, the compartment of the spleen which deals with the removal of foreign particles and aged erythrocytes [50].

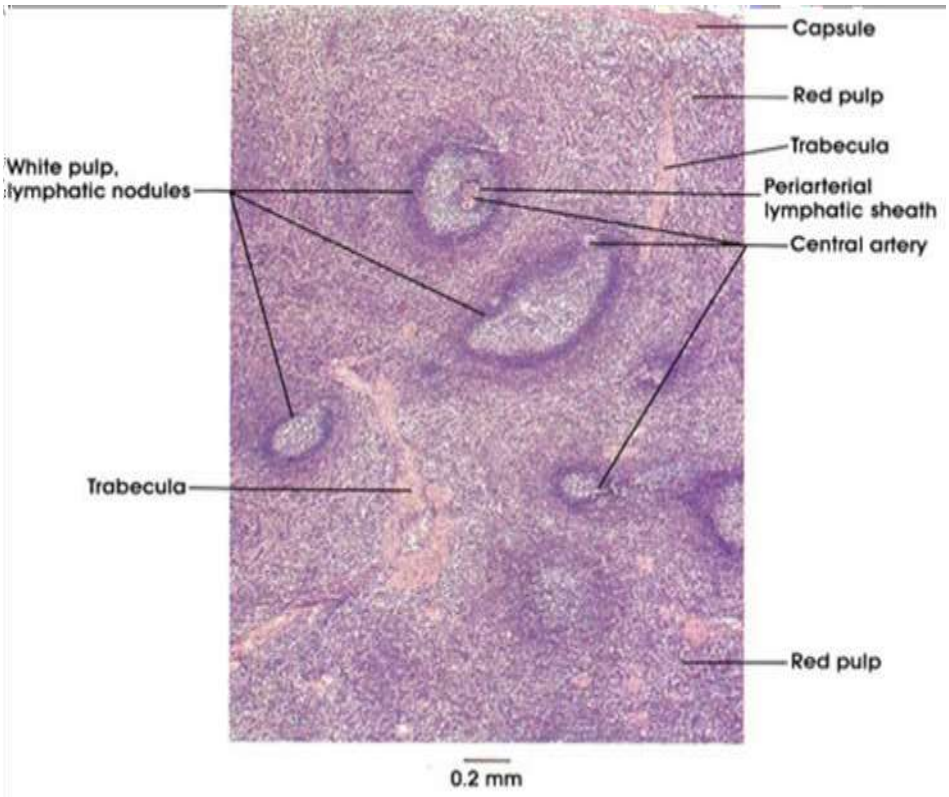
The microanatomy of the splenic white pulp differs between humans and rodents at which T-cells regions of human spleens may be interrupted by B-cells of the follicles. Therefore, there is no continuous periarteriolar lymphatic T-cell sheath around white pulp arterioles. An arteriole may be surrounded by T-cell lymphocytes at one level then runs across a follicle without any T cells around and finally re-enters the T-cell region. T and B-cell compartments are interdigitated in the human splenic white pulp [49].

Substantial numbers of dendritic cells (DCs) are found in the T-cell areas of peripheral lymphoid organs such as the spleen. These DCs (also called interdigitating cells) form a network through which T cells continually recirculate. DCs in the periphery can pick up antigens and migrate to the T-cell areas to initiate immunity. Dendritic cells serve a critical function in adaptive immune responses by capturing and displaying microbial antigens to T lymphocytes [50].

The red pulp is composed of a three-dimensional meshwork of splenic cords and venous sinuses. The splenic cords are composed of reticular fibers, reticular cells, and associated macrophages. The reticular cells are

considered to be myofibroblasts and may play a role in splenic contraction. The reticular fibers are composed of collagenous and elastic fibers, microfibers, reticular cells, basal lamina, and unmyelinated adrenergic nerve fibers. Within the spaces between the cords are blood cells, including erythrocytes, granulocytes, and circulating mononuclear cells. Also associated with the splenic cords, are lymphocytes and hematopoietic cells as well as plasma cells and plasma blasts that migrate from the follicles and the outer PALS after antigen-specific differentiation. The red pulp macrophages are phagocytic and remove old and damaged erythrocytes and blood-borne particulate matter [40].

In rats, the red pulp consists of venous sinuses filled with blood, which give this compartment its typical deep red color, and the splenic cords. The venous sinuses are recognizable by their content, mainly red blood cells surrounded by endothelial cells. The splenic cords are conspicuous, consisting predominantly of nucleated cells between the sinuses. Among macrophages, lymphocytes, and occasionally megakaryocytes, all types of blood cells can be found in the reticular meshwork of the splenic cords. This meshwork of reticular cells is supported by fine reticular fibers [50].



Fig(2): Photomicrograph shows the histological structure of the spleen [23].

Simina and Janse [50] revealed that the splenic white pulp consists of three major compartments, which are recognizable in routine stained sections of rats: periarteriolar lymphatic sheath, follicles, and the marginal zone.

The periarteriolar lymphoid sheath surrounds the central artery and consists of predominantly small lymphocytes and therefore appears somewhat darker than the two other compartments of the white pulp in a routine stained section. The PALS can be subdivided into an inner and outer PALS, each differing in the cellular structure. The inner PALS contains almost all small lymphocytes. In the outer PLAS, small and medium-sized lymphocytes are present, and especially after antigenic stimulation, many plasma cells are also present [50].

The follicles are globular structures attached to the PLAS, consisting of a mantle zone or corona, with densely packed small and medium-sized lymphocytes, and a follicular center with large lymphocytes. The follicular center appears in routine stained sections paler than the surrounding compartment due to its relatively low number of nucleated cells. After antigen stimulation, the follicular center contains many blast cells, large cells

with a pyroninophilic cytoplasm. Apart from the lymphoid cells, the follicular centers contain large macrophages, filled with condensed nuclear material with a high affinity for dyes, the so-called tingible body macrophages. Other non-lymphoid cells are not recognizable at the light microscope. The marginal zone of the rat spleen is very prominent in comparison with other species and consists of several layers of medium-sized, slightly pyroninophilic lymphocytes. It surrounds both the PALS and the follicle and is separated from the follicle by the marginal sinus [44].

The cells of the spleen are B cells, T cells, macrophages, dendritic cells, natural killer cells, and red blood cells. The spleen contains about 25% of the exchangeable T-lymphocytes and about 15% of the exchangeable B-lymphocytes. B cells are lymphocytes that develop in the bone marrow in mammals. They rearrange their immunoglobulin genes and express a unique receptor for antigen on their cell surface [45].

B cells are lymphocytes that develop in the bone marrow in mammals. They rearrange their immunoglobulin genes and express a unique receptor for antigen on their cell surface. At this point, they migrate to a secondary lymphoid organ e.g., spleen, and may be activated by an encounter with antigen to become antibody-secreting plasma cells [50].

B cells form about 30% of the recirculating pool of small lymphocytes and their lifespan is short i.e., days or weeks. They are found in the germinal center of the lymph nodes, in the white pulp of the spleen, and in gut-associated lymphoid tissue, waiting for the arrival of specific antigens. B cells are important antigen-presenting cells. Mature B cells differentiate on antigen stimulation to plasma cells that synthesize and secrete antibodies. Stimulation of B cells usually requires the cooperation of T cells [50].

In addition to their important role in humoral immunity, B cells also regulate many other functions essential for immune homeostasis. Of major importance, B cells are required for the initiation of T-cell immune responses [41].

T cells are lymphocytes that require maturation in the thymus and form several subclasses with specific functions. They are the source of the cell-mediated immunity [30].

Natural killer cells constitute a minor subset of normal lymphocytes that initiate innate immune responses toward tumor and virus-infected cells. They can mediate spontaneous cytotoxicity toward these abnormal cells and rapidly secrete numerous cytokines and chemokines to promote subsequent adaptive immune responses [61]. Macrophages are derived from myeloid stem cells in the bone marrow. They exist as free cells in the blood and fixed cells in the tissues. Macrophages are an important link between the innate and acquired immune response. Their main functions are phagocytosis, opsonization, killing antibody-coated infected cells or tumor cells through the release of lytic enzymes, and they secrete prostaglandins and synthesize complement components [49].

Most of the blood flow to the spleen passes through the marginal zone and directly along the white pulp leads to efficient monitoring of the blood by the immune system. In the spleen, both innate and adaptive immune responses can be efficiently mounted, making it an important organ for immune homeostasis. Whereas the white pulp is restricted to being involved in both innate and adaptive immunity, through its specific macrophage populations and marginal zone B cells [50].

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