# Blood Vessels and Lymphatic Vessels

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## Introduction

The primary function of blood vessels (arteries and veins) is to distribute oxygen and nutrients to tissues throughout the body and to transmit carbon dioxide and metabolic waste material to excretory organs for removal. The lymphatic vessels are important for maintaining interstitial fluid balance and returning excess fluid to the venous system. The lymphatic vessels are also involved in presenting foreign material to the immune system via the lymph nodes.

Development of the vascular tree is essential for the formation of nearly every organ during embryonic and fetal life. In the fetus, there are some unique features of the vascular tree that facilitate the fetoplacental circulation in utero, such as the umbilical vein, umbilical arteries, ductus venosus, and ductus arteriosus. Understanding the morphologic features of these specialized vascular structures is important for the interpretation of pathologic changes that may occur. In addition, the fetal and neonatal vascular tree is free of the typical aging phenomena seen in the adult vasculature, so the histologic features of many fetal blood vessels fit those of classically described "normal" vessels without superimposed pathologic changes. However, pathologic changes of the vasculature and lymphatics can occur during the fetal and neonatal period, so understanding their normal structure is helpful.

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## Embryology

The cardiovascular system is the first functional organ system established in the developing embryo. Blood vessels begin to arise from mesoderm during gastrulation (week 3 of human development). The vascular system develops via two processes: *vasculogenesis*, which is the de novo establishment of blood vessels from blood islands with no prior existing blood vessels, and *angiogenesis*, which involves the budding, branching, or sprouting of new blood vessels from preexisting vessels [1, 2].

The first blood islands appear during the third week of development in mesoderm that will give rise to extraembryonic blood vessels, including near the umbilical vesicle (yolk sac), connecting stalk, allantois, and chorion. A few days later, blood islands form within the lateral plate mesoderm and other areas in the embryo that will give rise to intraembryonic blood vessels. Blood islands seem to arise from mesoderm adjacent to endoderm (splanchnopleuric mesoderm), not from mesoderm situated near ectoderm (somatopleuric mesoderm). Blood islands are derived from mesodermal cells that will differentiate into *hemangioblasts*. Hemangioblasts are partially differentiated precursor cells capable of giving rise to either hematopoietic cells or endothelial cells. Blood islands consist of an outer cell layer destined to differentiate into endothelial cells and a collection of inner cells that will give rise to hematopoietic cells, usually erythroid when associated with endothelial cells. The precursor cell committed to form an endothelial cell is referred to as an *angioblast*. Blood islands begin to coalesce to form lumens, thereby establishing a capillary network within the developing embryo. As the capillary network enlarges, angiogenesis (sprouting of new vessels) contributes to network expansion. There is also evidence that some endothelial cells retain their ability to give rise to hematopoietic cells; these are referred to as *hemogenic endothelium*. Blood vessel formation precedes hematopoiesis. Vasculogenesis is responsible for establishing the primary vascular beds,



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including the paired dorsal aortae, cardinal veins, and primary vascular plexus of the yolk sac, which join together to form a closed vascular loop. Once established, angiogenesis expands the vascular network by giving rise to additional vessels (mostly mediated via vascular endothelial growth factor (*VEGF*) signaling). Eventually, once the heart begins to beat at about day 21–22 and circulation is established, mechanical remodeling of the vascular beds occurs via the additional actions of mechanical shear forces acting on the vessels, with some vessels closing down and others being redirected, especially during the rotation of the heart [1–4].

The molecular regulation of early blood vessel formation is complex and involves multiple signaling pathways and molecules. Mesoderm formation is dependent on both fibroblast growth factor and transforming growth factor-beta signaling. A particular transcription factor, ETS translocation variant 2 (*ETV2*), a member of the ETS family of genes also known as *ER71*, has been identified as a transient obligatory factor regulating hemangioblast differentiation. *ETV2* expression in the hemangioblast is regulated by bone morphogenic protein (BMP), Notch, and Wnt protein signaling pathways in mesoderm cells. *ETV2* is only expressed transiently in the hemangioblast, but its expression is mandatory for hematopoietic and endothelial cell differentiation. *ETV2*, a DNA-binding transcription factor, appears to be a master regulator that initiates transcription of numerous other genes involved in endothelial differentiation, including other members of the ETS family of transcription factors and members of the VEGF signaling pathways, including both ligands and receptors. *VEGF* and its receptor *VEGFR2* then become the most important drivers of embryonic vessel formation from the hemangioblast. *VEGFR2* is expressed in the hemangioblast and endothelial cells but not in hematopoietic progeny. After the heart begins to beat and early blood flow is established, specification of arteries and veins begins. Lymphatic differentiation will not occur until later in embryonic development, at the end of the fifth week [4].

Arteries and veins are defined by the direction of blood flow, either away from the heart (arterial) or toward the heart (venous). Arterial and venous endothelial cells express specific molecular markers. Molecular markers of arterial endothelial differentiation include expression of ephrin-B2 (*EFNB2*), neuropilin-1 (*NRP1*), and members of the Notch pathway. Molecules expressed specifically in the venous system include arterial ephrin-B2 receptor and the neuropilin-2 receptor. Also in veins, Notch signaling is repressed by the expression of *COUP-TFII* (chicken ovalbumin upstream promoter transcription factor 2), which in humans is encoded by the nuclear receptor subfamily 2, group F, member 2 gene (*NR2F2*), which prevents activation of an "arterial" phenotype. The exact pathways specifying and maintaining the venous and arterial endothelial phenotypes still require further research. Data from certain model systems suggest that arterial and venous fates for endothelial cells may be predetermined from a very early developmental stage (angioblasts), but other data indicate some degree of plasticity such that artery and vein endothelium can interconvert, at least early in development. In the yolk sac blood vessels, the direction of blood flow seems to be a critical regulator of arterial-venous endothelial differentiation [2, 3].

In the early embryo, three major vascular networks—the vitelline, embryonic, and placental vasculature—join together. Each has its own arterial and venous component. The *vitelline vascular system* is composed of the vitelline arteries (which will fuse and give rise to the superior mesenteric artery in the adult), which arise from the dorsal aorta and pass through the vitellointestinal duct (yolk sac stalk). They empty into a capillary bed drained by the vitelline veins, which will contribute to the adult portal system and which pass back through the yolk sac stalk to enter the caudal end of the cardiac tube via the sinus venosus. The *embryonic vessels* will form the majority of the fetal and adult cardiovascular system. Its arterial components include the dorsal aorta, aortic arches, and umbilical arteries. The dorsal aorta is initially paired and later fuses from thoracic level 4 to lumbar level 4. The pharyngeal arch arteries connect the dorsal aorta to the ventral aorta. The caudal dorsal aorta gives rise to the umbilical arteries and laterally to intersegmental arteries. Three pairs of veins empty into the sinus venosus of the heart, including the vitelline veins, umbilical veins from the placenta (of which only the left will persist as the single umbilical vein in the fetus), and cardinal veins (anterior, common, and posterior). *Placental blood vessels* form initially in the connecting stalk (later to become the umbilical cord) and anastomose in the chorion. The paired umbilical arteries carry deoxygenated blood from the dorsal aorta and metabolic waste products to the placental villi, while the initially paired umbilical veins carry oxygenated blood and nutrients to the embryo via the sinus venosus. Although early establishment of the vascular network and specification of arteries and veins seem to be regulated by genetic programs and endothelial cell differentiation, later remodeling of the entire vascular network is highly dependent on blood flow patterns and hemodynamic signals, including pressure, perfusion, and flow dynamics. Blood flow patterns probably have direct mechanical effects on vessels, as well as altering genetic programs within endothelial cells. The end result of the remodeling process is the fetal vasculature, which is similar to the adult vasculature except for the presence of two vascular shunts, the ductus arteriosus and ductus venosus, and an intracardiac shunt, the foramen ovale. The umbilical vein and the two umbilical arteries are also unique to intrauterine life and regress quickly following birth and the cutting of the umbilical cord [1–4].

Lymphatic vessels begin to appear in the developing human around the end of the fifth week of embryonic

development. There are two possible models for lymphatic formation. The favored model is direct budding of lymphatic endothelium from veins. The second model is the formation of multiple clefts in the mesenchyme lined by endothelial cells with a lymphatic phenotype, which coalesce to form the lymphatic complex and then join the venous vascular complex by endothelial cell sprouting and/or migration. During weeks 6–9 of development, six lymphatic sacs form, including two jugular lymph sacs near the junction of the subclavian veins with the anterior cardinal veins (the future internal jugular vein), two iliac lymph sacs near the junction of the iliac veins with the posterior cardinal veins, one retroperitoneal lymph sac in the root of the mesentery on the posterior abdominal wall, and one *cisterna chyli* dorsal to the retroperitoneal lymph sac, at the level of the adrenal glands. The lymphatic vessels grow along the major veins, and the jugular lymph sacs connect to the cisterna chyli via the right and left thoracic ducts. These two ducts will partially fuse in the middle portions, and the final thoracic duct is composed of a portion of the right thoracic duct caudally, the anastomosed portion of the ducts in the middle, and the cranial portion of the left thoracic duct. The final right thoracic duct represents the remaining cranial portion of the original right duct. The final main (left) thoracic duct, which is established by early fetal life, will join the venous system at the angle of the joining of the left internal jugular vein and the left subclavian vein. Molecularly, the earliest marker for the developing lymphatic endothelial cell is prospero-related homeobox protein 1 (*PROX1*). Absence of *PROX1* results in a complete absence of lymphatic formation. Therefore, *PROX1* is essential for lymphatic development and has been shown to be important for the maintenance of the lymphatic endothelial phenotype in adulthood. Other genes are also important in establishing the final lymphatic endothelial phenotype [5–7].

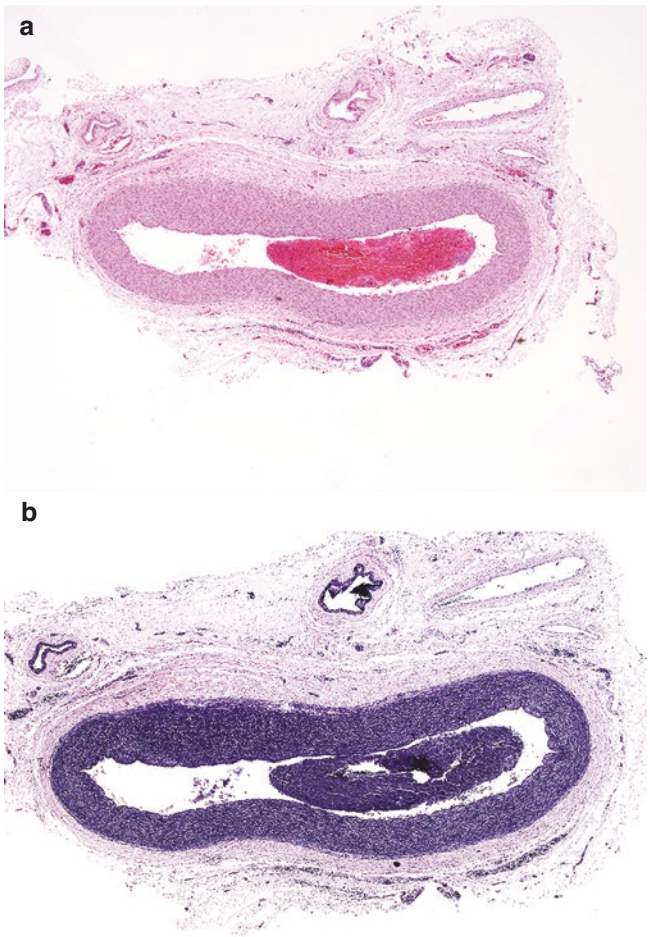


**Fig. 2.1** Fetal aorta at 23 weeks gestation. In this low-power view, note the bulky tunica media and the abundant elastic fibers within the tunica media (**a** H&E, 4×; **b** Verhoeff-van Gieson, 4×)

## Histology

### *Aorta*

The aorta of fetuses and newborns has the same anatomical structure and mural features that are present in adulthood. The innermost layer, the tunica intima, is composed of a simple squamous layer of endothelial cells with very little additional supporting intimal fibrous tissue. The presence of fibrointimal thickening or foamy macrophages within the intima is considered abnormal in the fetal or newborn period. The tunica media comprises the bulk of the aortic wall and is composed of densely packed circumferential layers of elastic tissue with intervening collagen (Figs. 2.1 and 2.2). The nuclei present in the media consist predominantly of smooth

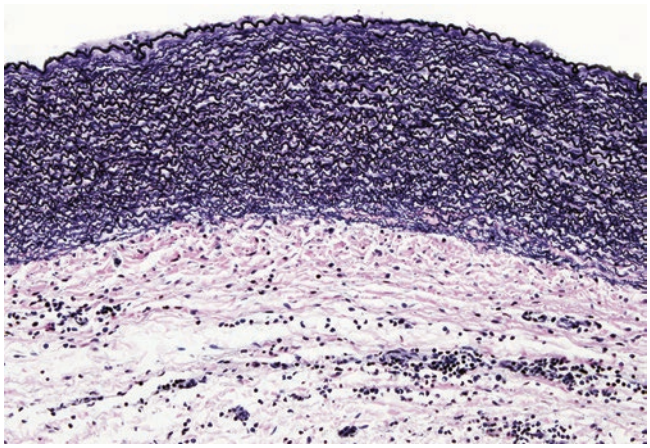

**Fig. 2.2** Fetal aorta at 23 weeks gestation. This higher-power view highlights the darkly stained elastic fibers within the tunica media (Verhoeff-van Gieson, 20×)

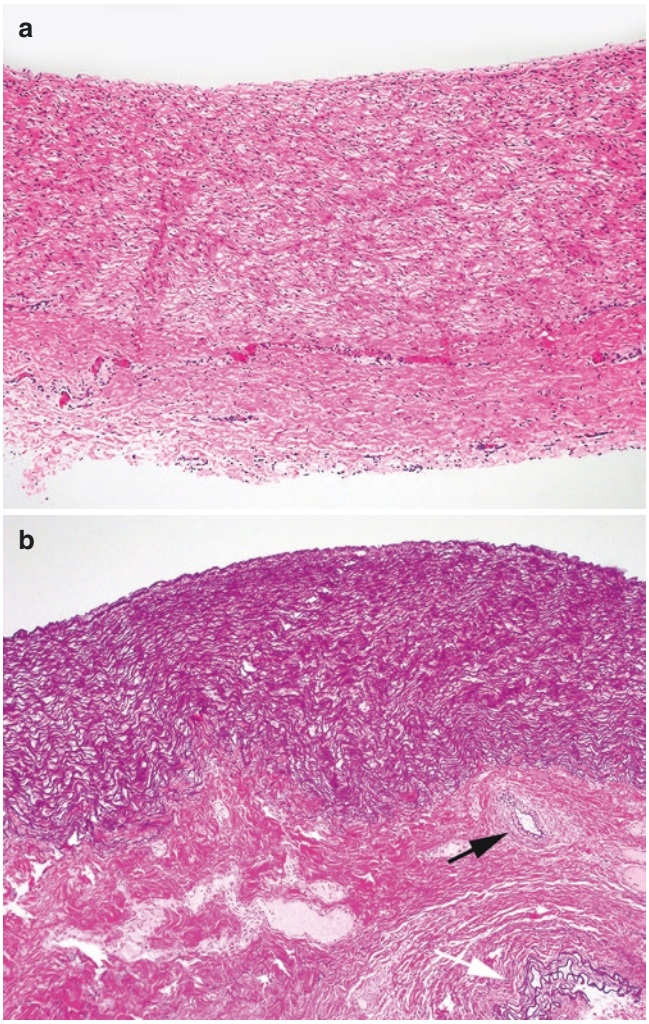


**Fig. 2.3** Fetal aorta at term. (**a**) A medium-power view of the fetal aorta at 38 weeks gestation is shown, with the thick tunica media containing abundant elastic fibers. Note the thicker and more compact tunica adventitia at this gestational age, containing vasa vasorum (H&E, 10×). (**b**) Elastic stain of fetal aorta at 38 weeks gestation is shown. Note the thick tunica media with abundant elastic fibers. The thick and compact tunica adventitia at this gestational age contains vasa vasorum (*black arrow*) and a large branch artery (*white arrow*) (Verhoeff-van Gieson, 20×)

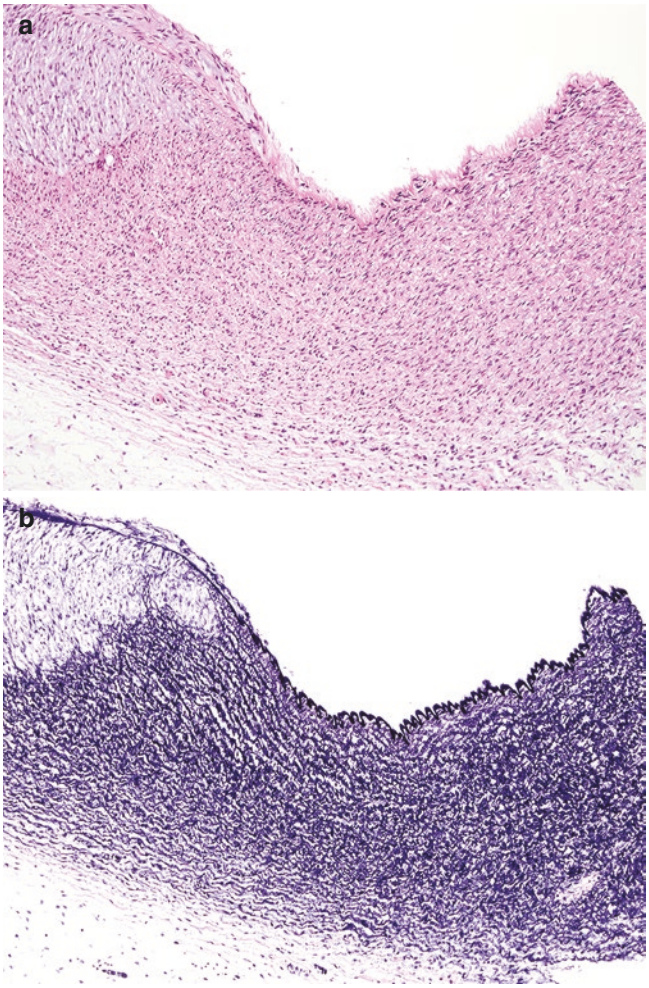


**Fig. 2.4** Ductus arteriosus in the midtrimester, at 21 weeks gestation. Note the features of a muscular artery, including intima, internal elastic lamina, media, and adventitia. Even at this gestational age, focal intimal thickening is present (**a** H&E, 10×; **b** Verhoeff-van Gieson, 10×)

muscle cells and fibroblasts. The wall is free of inflammatory cells in the normal state. The outermost layer is the tunica adventitia, which consists of loose fibrous connective tissue containing vessels of the vasa vasorum (Fig. 2.3).

## Ductus Arteriosus

The ductus arteriosus is the vascular structure in fetal life that shunts the relatively oxygenated blood from the right ventricle/pulmonary artery to the descending aorta, thus providing oxygenated blood to the systemic circulation and bypassing the pulmonary circuit. The ductus arteriosus is a muscular artery with an intima, media, and adventitia. The media of the ductus arteriosus lacks the tightly packed elastic fibers of the aorta, but it does have some elastic fibers, with a prominent internal elastic lamina (Fig. 2.4). The intima of the ductus arteriosus may show slight thickening during fetal life, and it has been shown that the histological changes characteristic of closure of the ductus arteriosus begin before birth [8] (Fig. 2.5). Following birth, the ductus arteriosus functionally closes within 1–2 days, but it does not structurally close for several weeks. The morphological changes seen with the closure of the ductus arteriosus (Fig. 2.6) include (1) increased thickness of the intima, with formation of intimal cushions; (2) increased thickness of the media; (3) thickening and fragmentation of the internal elastic lamina; (4) increased ground substance and connective tissue in the intima and media; and (5) the appearance of spaces in the inner part of the media [8].

## Umbilical Vein

Though not usually seen in the examination of the adult abdomen, the umbilical vein is easily identified in the internal pathologic examination of all fetuses as the vascular structure extending from the umbilicus to the liver. In the midtrimester, the vein is a thin-walled, easily collapsible structure; it appears thicker in fetuses near term and in neonates. The vein has an inner intimal layer, a fairly thick media composed of haphazardly arranged smooth muscle fibers, and a relatively thick adventitia (Figs. 2.7 and 2.8) [9].

The umbilical vein is frequently catheterized to gain vascular access, especially in premature neonates, so it is subject to pathologic conditions such as endothelial injury, thrombosis, or even rupture. The umbilical vein involutes after birth, with obliteration of the lumen and formation of a fibrous cord which becomes the round ligament or ligamentum teres of the liver.

## Umbilical Arteries

The two umbilical arteries arise from the internal iliac arteries and can be identified in the fetus as they course along each side of the urinary bladder toward the umbilicus, where they enter the Wharton's jelly of the umbilical cord. The umbilical arteries, therefore, transmit systemic, relatively deoxygenated blood from the fetus to the placenta. Within the fetal body, the two umbilical arteries are typically the same size and increase mildly in size over gestation. When only a single umbilical artery is present within the umbilical cord, there is usually only one umbilical artery noted during

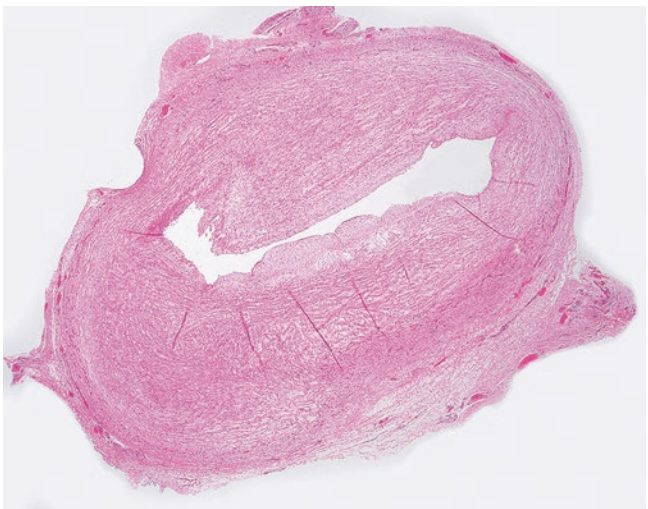

**Fig. 2.5** Ductus arteriosus at term. A low-power view of a complete cross section of the ductus arteriosus in a term fetus. Note the thick media, smaller lumen, and areas of focal intimal thickening. Compare with Figs. 2.4 and 2.6 (H&E, 2×)

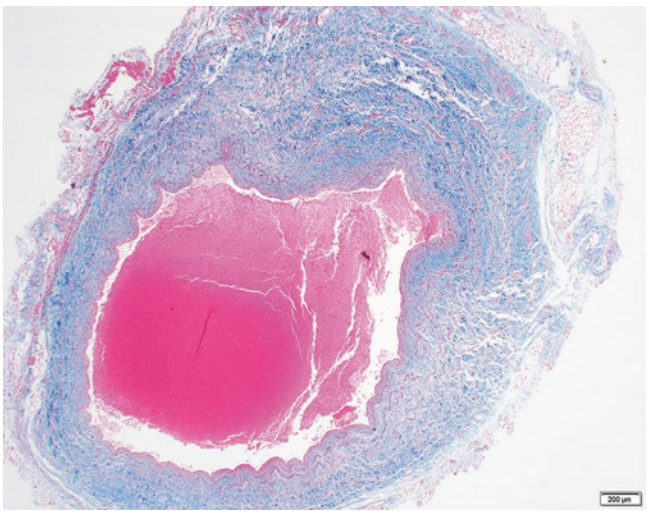

**Fig. 2.7** Umbilical vein. Low-power view of the umbilical vein from a 35-week stillborn fetus. The endothelial lining has sloughed, but note the thick media composed of collagen fibers with haphazardly arranged smooth muscle (Masson trichrome, 2×)

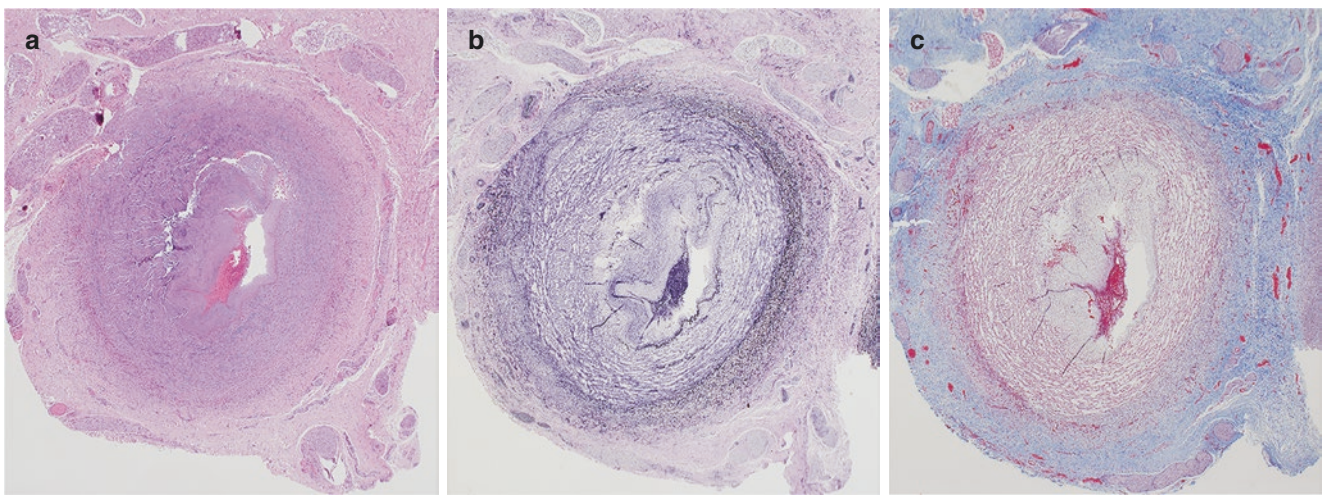


**Fig. 2.6** Ductus arteriosus after birth. The ductus arteriosus of a term infant who lived for 6 days is shown. Note the features of closure of the ductus arteriosus, including increased thickness of the intima with formation of intimal cushions (**a**); fragmentation of the internal elastic lamina (**b**); and increased connective tissue in the intima (**c**). (**a** H&E, 2×; **b** Verhoeff-van Gieson, 2×; **c** Masson trichrome, 2×)

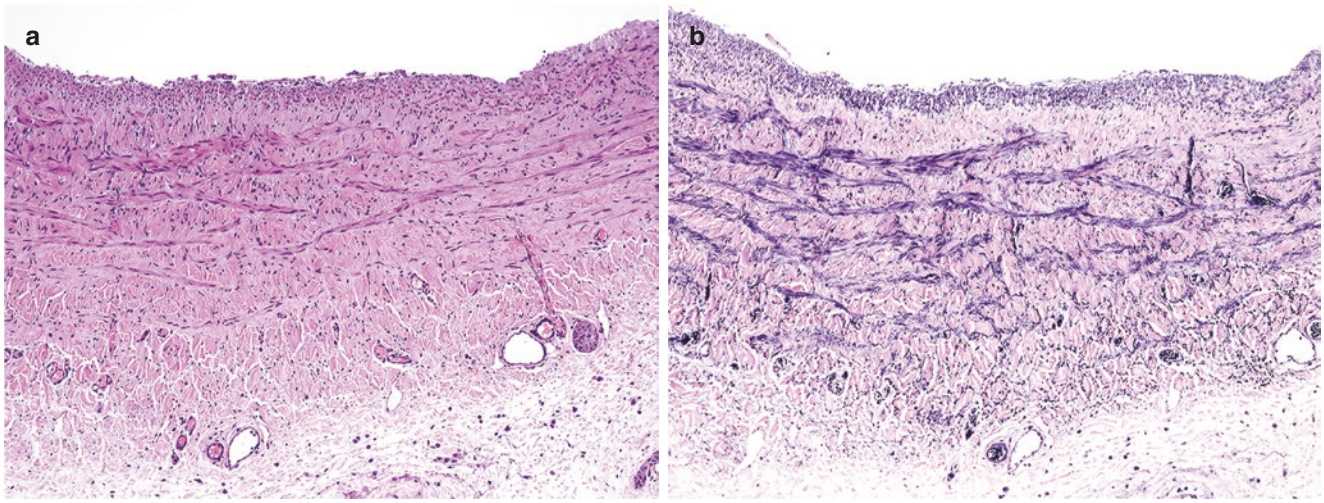


**Fig. 2.8** Umbilical vein at term. Note the features of the umbilical vein at term, including a lining endothelium, an inner intimal layer, and a fairly thick media composed of haphazardly arranged smooth muscle. No internal elastic lamina is seen (**a** H&E, 10×; **b** Verhoeff-van Gieson, 10×)

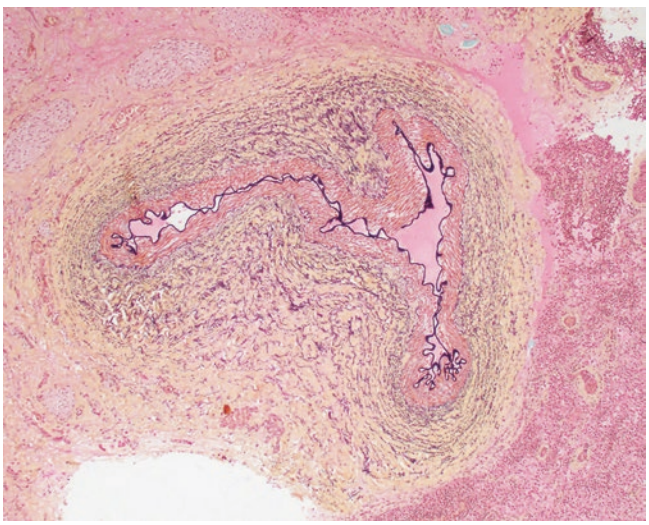

**Fig. 2.9** Umbilical artery within the fetal body at term (stillbirth at 37 weeks gestation). The umbilical artery in this section contains a prominent internal elastic lamina and two distinct muscular layers in the media (pentachrome stain, 4×)

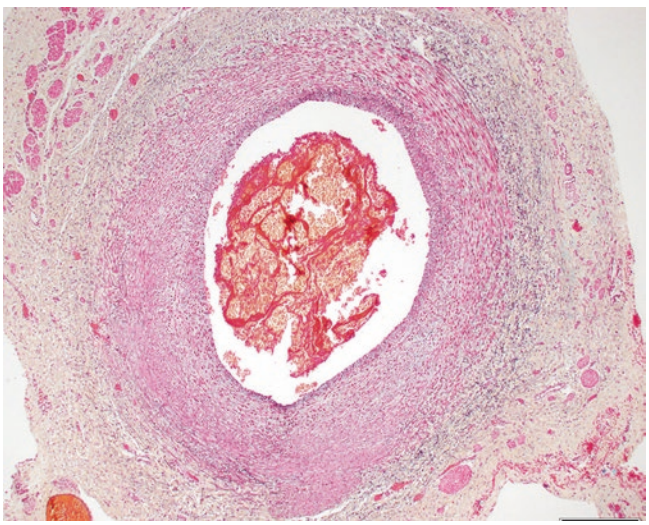

**Fig. 2.10** Umbilical artery within the fetal body at 5 days of life (born at 32 weeks gestation). The media lacks an internal elastic lamina, but degenerating elastic fibers are seen in the media. Intraluminal fibrin is present (pentachrome stain, 4×)

the fetal examination as well. The umbilical artery may be absent on either the left or the right side, and this is easily recognized when examining the umbilical artery course along the side of the urinary bladder. Aberrant umbilical artery origin from the abdominal aorta has also been described [10].

The histology of the umbilical arteries within the fetal body (i.e., between the internal iliac arteries and the umbilical cord) is not well described, but the umbilical artery within the umbilical cord is typically devoid of an internal elastic lamina. From personal observations, we have noted that some umbilical arteries within the fetal body have a well-developed internal elastic lamina and some do not (Figs. 2.9 and 2.10). This difference may be related to how close the sections are taken to the systemic arteries versus the umbilical cord, or it may be related to autolysis, but there are no definitive studies examining the morphologic transition from systemic arteries to umbilical arteries. Within the umbilical cord proper, the umbilical arteries are characterized by two distinct muscular layers, an outer circular layer and an inner spiral longitudinal layer; they lack a well-defined internal elastic lamina (see Fig. 36.20).

Like the umbilical vein, the umbilical arteries are frequently catheterized, especially to gain vascular access in premature neonates, so they are subject to pathologic conditions such as endothelial injury, thrombosis, or even rupture. The umbilical arteries involute after birth (Fig. 2.11), and their proximal portions become the hypogastric arteries. The distal portions become fibrous ligaments known as the lateral umbilical ligaments [9].

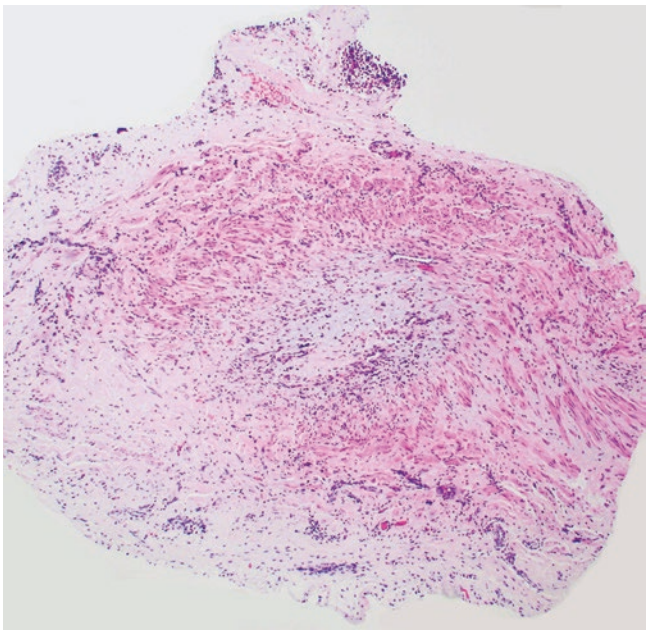

**Fig. 2.11** Umbilical artery at 3 weeks of life (born at 26 weeks gestation). The lumen of the artery (*center*) is closing down, and there is a discontinuous, smooth muscle layer surrounding the lumen (H&E, 4×)

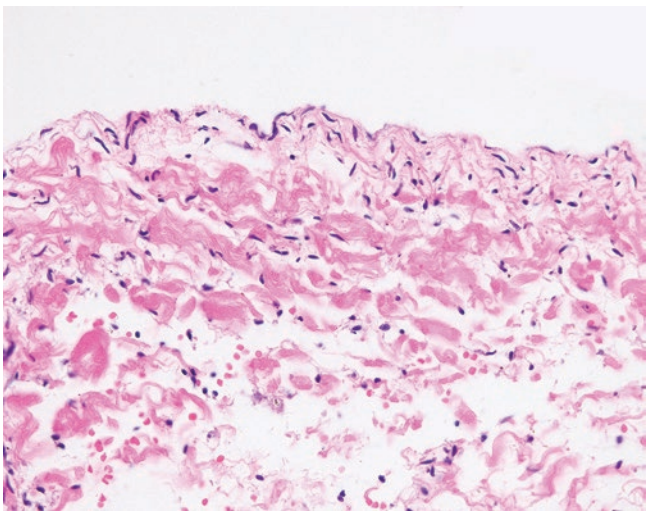

**Fig. 2.13** Ductus venosus at 36 weeks gestation. Higher-power view of the ductus venosus at near term. The wall is thicker and more well-defined than in Fig. 2.12. The wall is composed of thicker collagen bands. Occasional smooth muscle can be present, but none is seen in this image (H&E, 40×)

## Ductus Venosus

The ductus venosus is the vascular shunt present in fetal life within the liver that allows oxygenated blood from the umbilical vein to enter the inferior vena cava and then proceed to the right side of the heart. It can be identified grossly by opening the umbilical vein into the sinus intermedius of the liver (see Fig. 5.2). The ductus venosus arises from the rostral wall of the sinus intermedius and typically has a smaller diameter than the umbilical vein. The inner lining of the ductus venosus is usually smooth gray-white, and it has a very thin wall. The histology is characterized by an endothelial lining, occasional smooth muscle cells, and a thin, fibrous wall [11] (Figs. 2.12 and 2.13). The inlet of the ductus venosus commonly has a grossly visible lip or rim, sometimes referred to as a sphincter. One group argued that it is not a true sphincter because in their analysis it lacked smooth muscle, but they did demonstrate a condensation of elastic fibers forming a shelf-like structure. They postulated that the elastic tissue at the inlet of the ductus venosus may accelerate blood flow from the sinus intermedius into the ductus venosus and that the shelf may also reduce back flow [11].

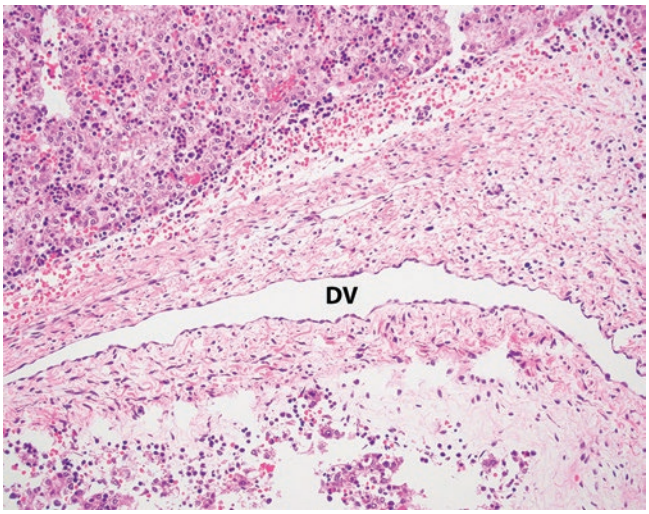


**Fig. 2.12** Ductus venosus at 18 weeks gestation. The ductus venosus (DV) as shown here is extremely thin-walled at this gestational age. The wall is composed of loosely arranged collagen fibers, which in places merge imperceptibly with the surrounding connective tissue. Smooth muscle is not appreciated as a component of the wall in this image. The ductus venosus has a flattened endothelial lining. Note the hepatic parenchyma in the upper left (H&E, 20×)

The ductus venosus functionally closes within a few minutes of birth and the cutting of the umbilical cord because the umbilical vein blood flow ceases, but the ductus venosus structurally closes at approximately 4–6 days after birth. It generally closes at the low end of this range in term neonates and at the higher end of the range in premature infants [12]. Agenesis of the ductus venosus can have deleterious effects on fetal blood flow and is associated with hydrops fetalis [13].

## Other Fetal Veins and Arteries

The general organization of most nonspecialized fetal arteries and veins is similar to that seen in the same vascular structures in adults [9]. Muscular arteries, such as the renal arteries or other arterial branches arising from the aorta (Fig. 2.14), are characterized by a very thin intimal layer consisting almost exclusively of the endothelial cell layer. Immunohistochemical studies have shown that endothelial cells mark with CD31, CD34, von Willebrand factor, and Fli-1, but expression may vary by organ

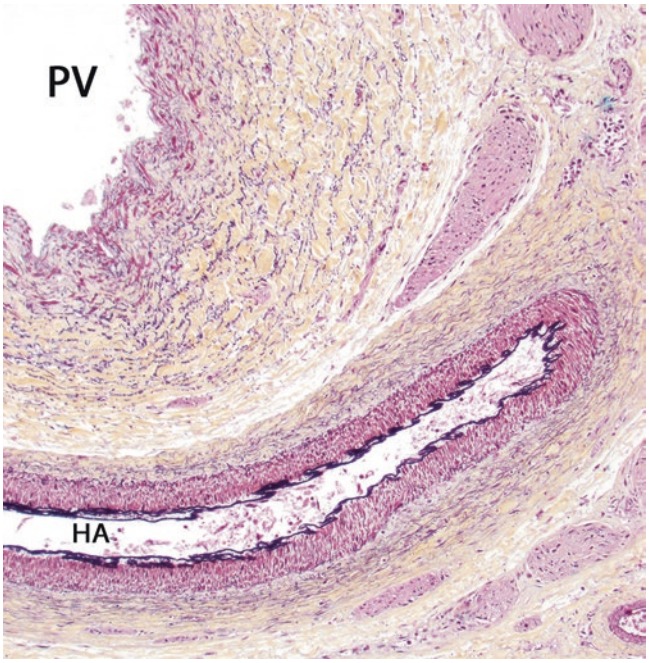


**Fig. 2.14** Portal vein and hepatic artery at 35 weeks gestation. Fetal veins and arteries have histologic features similar to their adult counterparts. These are sections of medium- to large-sized fetal vessels, the portal vein (PV) and the hepatic artery (HA). The PV is one of the larger veins of the body and thus has recognizable smooth muscle media composed of somewhat haphazardly arranged smooth muscle, elastic fibers, and collagen. An internal elastic lamina is not present in the PV. However, the internal elastic lamina can be seen in the HA as an undulating dark layer highlighted by the elastic stain. The media of the HA is a well-organized smooth muscle layer. The adventitial collagen is yellow in this stain (pentachrome stain, 10×)

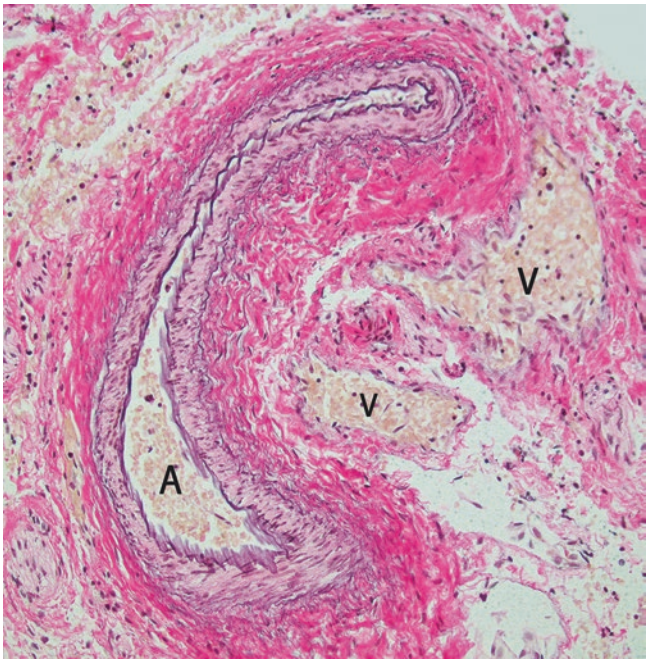


**Fig. 2.15** Small artery and vein at term. This image shows an example of a smaller artery (A) and associated veins (V). The artery demonstrates well-defined internal and external elastic laminae by the elastic stain. The media of the artery, between the two elastic laminae, is a well-organized smooth muscle layer. The adventitial collagen (*pink*) is fairly thick in this image. The adjacent thin-walled veins do not have recognizable smooth muscle in the media, which is composed of elastic fibers and collagen. An internal elastic lamina is not present in the veins (elastic stain, 4×)

and even by organ compartment [14]. The media is the middle layer composed of the often undulating-appearing internal elastic lamina just beneath the endothelium and the muscular coat composed of smooth muscle cells. The vascular smooth muscle runs in spiral or circumferential patterns and is intermixed with collagen fibrils and elastin fibers [15]. A variable external elastic lamina may be present (Fig. 2.15). The tunica adventitia of fetal muscular arteries is typically fibrous in nature [9]. Larger arteries branch and become smaller arterioles, which ultimately terminate as capillaries. Capillaries consist of a single layer of endothelium resting on a basement membrane and lack a muscular media or elastic fibers [15]. Although capillaries have no fibrous support or adventitia, pericytes are present in and among the basement membrane [15]. Pericytes provide structural support for the capillary and can be highlighted by an immunostain for smooth muscle actin. Because they have contractile properties, they may also be involved in the regulation of blood flow [15]. In some sites, such as the liver (see Fig. 5.11) and fetal adrenal cortex (see Fig. 20.13), the equivalent of capillaries is known as *sinusoids*. Sinusoids are generally more dilated than capillaries, their endothelium may have prominent gaps or fenestrations, and in some organs, there is no associated basement membrane [15].

The venous structures of the fetus—even large veins such as the inferior vena cava and renal veins—are very thin-

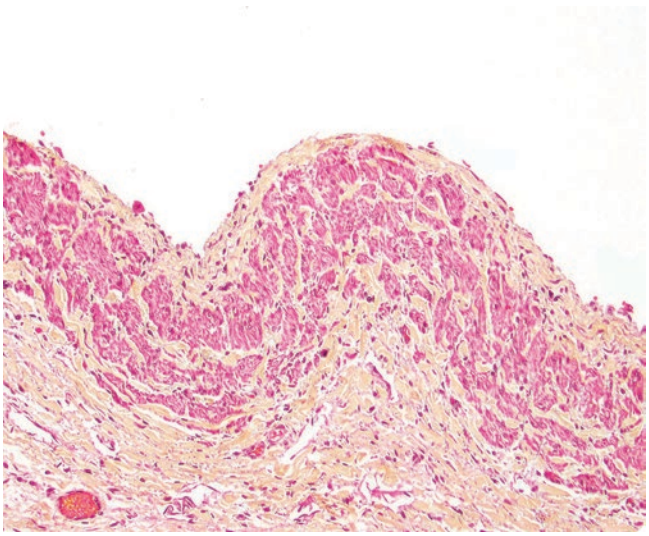

**Fig. 2.16** Inferior vena cava at 32 weeks gestation. This is the largest vein of the fetal body and thus has recognizable smooth muscle media, which is composed of somewhat loosely arranged smooth muscle fibers and collagen. An internal elastic lamina is not present (pentachrome stain, 10×)

walled structures that may be easily overlooked grossly, especially in the midtrimester. Similar to arteries, veins have three distinct layers, but the media typically lacks an internal or external elastic lamina, is thinner, and has fewer, more haphazardly arranged muscle fibers (Fig. 2.16). In some cases,

very little muscle tissue is seen in the media, and the wall is composed mostly of fibrous tissue (see Fig. 2.15) [15].

### Lymphatic Vessels

Lymphatic vessels are present in most fetal tissues and typically present as thin-walled vascular structures with a flattened, endothelium-like lining that can be highlighted by immunohistochemistry for D2-40, PROX1, or LYVE-1. Small lymphatic channels closely resemble capillaries with no significant muscular media. Larger lymphatic channels have a thin, muscular media with no distinction into circular or longitudinally oriented layers. The thoracic duct and right lymphatic duct have a longitudinal muscular layer [15] (Fig. 2.17). In stillbirths, the lymphatic endothelium is often sloughed, thereby making immunohistochemistry of limited value. Lymphatic channels may contain clusters of small lymphocytes, which can sometimes be helpful in distinguishing them from capillaries.

## Special Considerations

### Hyrtl's Anastomosis

Hyrtl's anastomosis, defined as a connection between the two umbilical arteries, is very common in normal pregnancies [16, 17]. The types of connections include a true vessel between the two arteries, a fenestration between the two arteries, or a fusion of segments of the arteries. These anastomoses may occur within the umbilical cord at a median distance of 7–16 mm from the cord insertion, at the cord insertion itself, or on the placental surface [17]. Hemodynamic studies have shown that Hyrtl's anastomoses function as either a safety valve or a pressure equalizer between the two umbilical arteries [16].

### Cystic Hygroma and Other Lymphatic Malformations

*Cystic hygroma* is a clinical term used to describe a cystic neck mass in the posterior cervical space. By ultrasound, a cystic hygroma is a large, fluid-filled structure with septations in the posterior neck; it can be a sign of aneuploidy in a second-trimester ultrasound [18, 19]. The aneuploidy most commonly associated with cystic hygroma is monosomy X (Turner syndrome), but other aneuploid conditions can also present with a cystic hygroma [19]. Cystic hygroma may be present with other signs of fetal hydrops, such as subcutaneous edema and effusions.

Pathologically, what is called cystic hygroma clinically arises as a result of obstruction of lymphatic flow secondary to lymphatic malformations such as hypoplasia or failure of fusion between lymphatic primordia and the jugular vein [20]. Most fetuses with cystic hygroma seen on ultrasound have a large posterior nuchal fluid-filled sac that has ill-defined borders and is not easily separated from the overlying (often edematous) skin. This lesion is composed of multiple irregular spaces with abundant, paucicellular intervening connective tissue (Fig. 2.18). The spaces may or may not have a lining, but some lymphatic channels can be seen

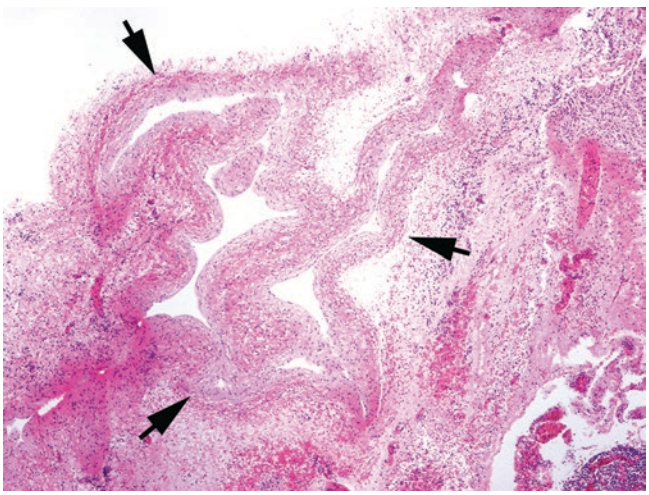

**Fig. 2.17** Thoracic duct at 26 weeks gestation. The thoracic duct is the collapsed structure seen between the three arrows. Note that it has a thin, longitudinal muscular layer and a lymphatic endothelial lining that is nearly imperceptible at this power (H&E, 10×)

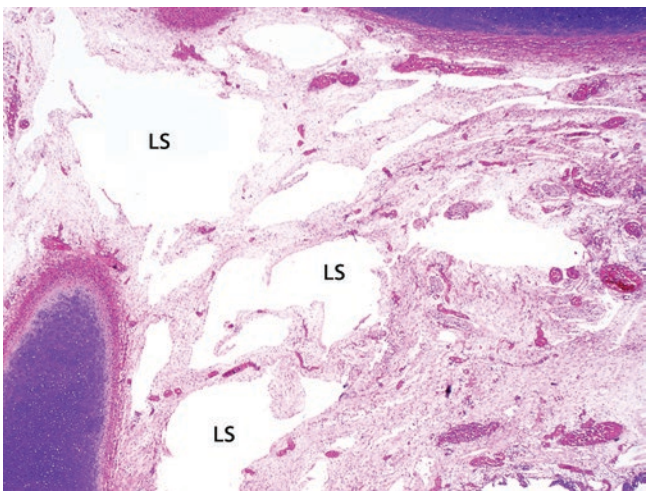


**Fig. 2.18** Cystic hygroma. This is a section from a cystic hygroma in a 26-week fetus with hydrops fetalis. Note the numerous dilated lymphatic spaces (LS), three of which are indicated in this photomicrograph. Loose, fibrous connective tissue is noted between the spaces, and no obvious smooth muscle is seen. The cells lining the spaces are mostly sloughed to imperceptible at this power. Cartilaginous tissue of the neck is seen in the lower left and upper right corners (H&E, 10×)

using D2-40 or PROX1 immunohistochemistry. Because most of the fluid is in the connective tissue and not in dilated lymphatic channels, this lesion has also been referred to as *postnuchal fluid accumulation* [20]. Recently, the more general term *lymphatic malformation* has been applied to a variety of lesions with a lymphatic component. These lesions are further subdivided descriptively as localized, macrocystic, microcystic, or combined. Lymphatic malformations contain multiple variably sized lymphovascular channels with flattened endothelium. Intervening connective tissue is fairly scanty and may contain smooth muscle and adipose tissue. The spaces may contain lymphocytes [20, 21].

## Periaortic/Retroperitoneal Soft Tissues

In routine sections of the aorta, or even of the kidney and adrenal glands, retroperitoneal soft tissue is often present. This tissue can contain specialized structures such as lymph nodes, paraganglia, and sympathetic ganglia (Fig. 2.19). Because these tissues can be especially prominent in fetuses, it is important to be aware of their histologic appearance, so as not to confuse them with a pathologic abnormality. Paraganglia are seen very frequently in the fetal retroperitoneum near the sympathetic trunk and close to sympathetic ganglia. They can sometimes attain large size and be encapsulated, especially in the periaortic region, which has led to the term *para-aortic bodies*. In the early 1900s, Zuckerkandl described masses of extra-adrenal chromaffin cells in close association with the inferior mesenteric artery (organs of Zuckerkandl), but similar tissue has been described at multiple sites along the aorta [22]. Studies have shown that abdominal para-aortic bodies increase in size up to 3 years of life and then undergo degenerative changes marked by increasing stroma. The process appears to be complete by 14 years of age [23].

Paraganglia are composed of neuroendocrine cells of neural crest origin and are also known as *extra-adrenal chromaffin cells*. On routine H&E sections, paraganglia can be recognized as encapsulated or nonencapsulated collections of fairly uniform polygonal cells with granular cytoplasm and small, oval nuclei without nucleoli, arranged in nests and cords with prominent intervening vasculature. The chromaffin cells of paraganglia can be highlighted by typical neuroendocrine stains such as chromogranin and synaptophysin (Figs. 2.20 and 2.21). Paraganglia are often associated with sympathetic

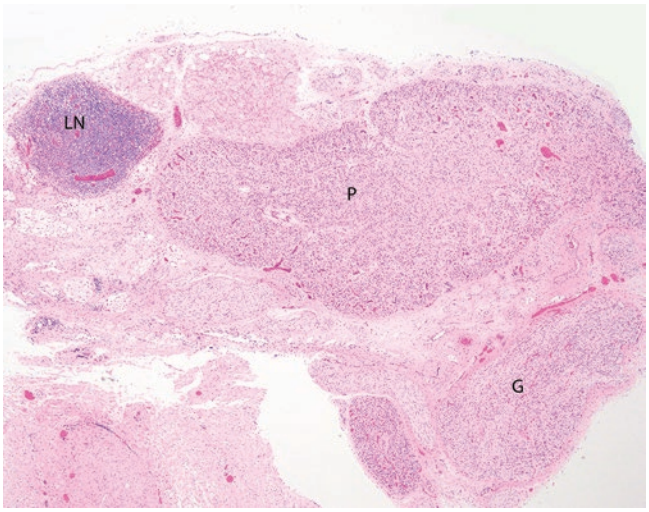


**Fig. 2.19** Periaortic soft tissues in a term fetus. This low-power image shows some of the specialized structures present in periaortic soft tissue, including lymph node (LN), encapsulated paraganglion (P), and sympathetic ganglion (G) (H&E, 4×)

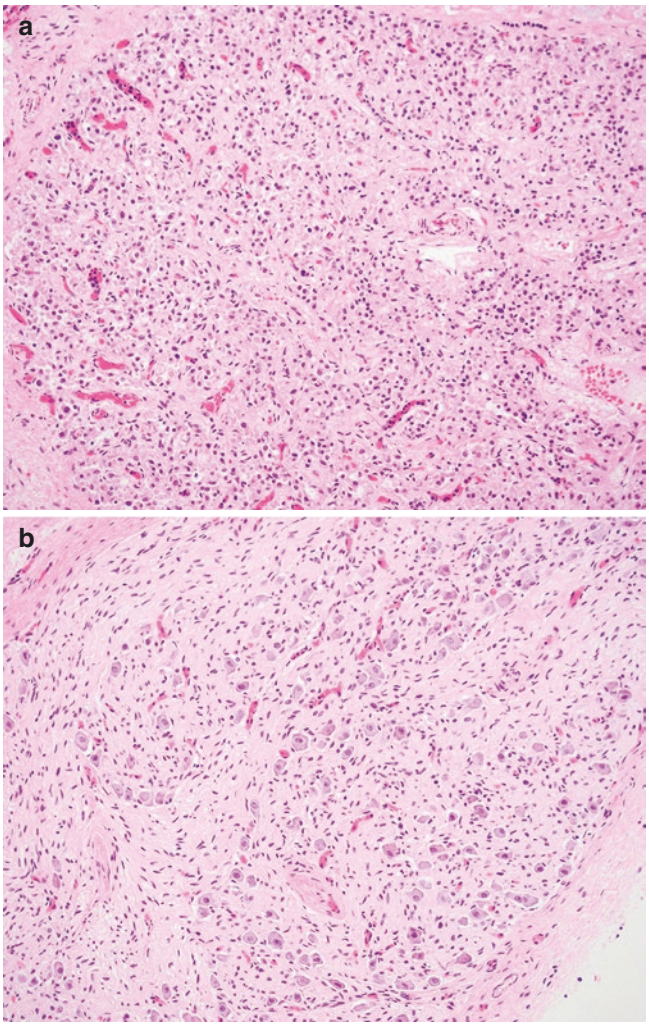


**Fig. 2.20** Comparison of paraganglion and ganglion. (**a**) *Paraganglion:* Note the uniform, polygonal neuroendocrine cells with abundant cytoplasm and small oval nuclei without nucleoli arranged in nests and cords with prominent intervening vasculature. (**b**) *Sympathetic ganglion:* Note the more heterogeneous appearance, with numerous ganglion cells characterized by abundant eosinophilic cytoplasm and eccentrically placed large nuclei, many with nucleoli. The lightly eosinophilic background of ganglia is composed of wavy nerve fibers (H&E, 20×)

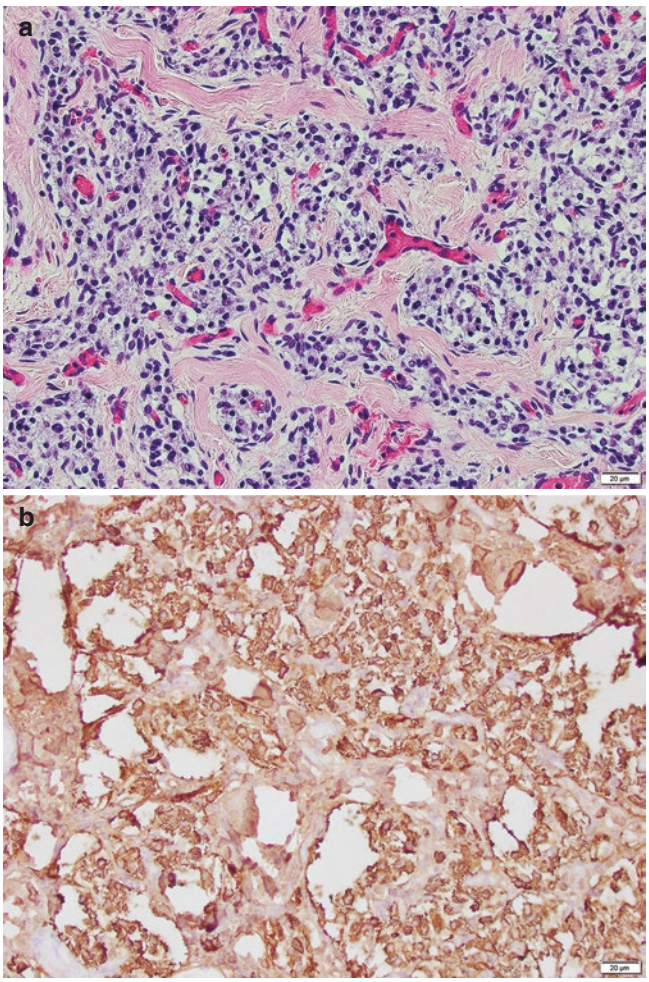


**Fig. 2.21** Paraganglion in the retroperitoneal tissues at 29 weeks gestation. (**a**) This paraganglion is slightly better preserved than the term example in Fig. 2.20. Note the uniform, polygonal neuroendocrine cells with slightly granular cytoplasm and small oval nuclei without nucleoli, arranged in nests and cords with prominent intervening vasculature. Intervening fibrous tissue is noted (H&E, 20×). (**b**) Chromogranin immunostain confirms the neuroendocrine origin of these cells (chromogranin immunohistochemistry, 20×)

ganglia, which provide a stark histologic contrast. Sympathetic ganglia appear more heterogeneous than paraganglia at low power and are punctuated by numerous ganglion cells with abundant eosinophilic cytoplasm and eccentrically placed large nuclei, many with nucleoli. The lightly eosinophilic background of ganglia is composed of wavy nerve fibers (see Fig. 2.20). In first- and second-trimester fetuses, sympathetic ganglia can appear immature and should not be confused with a neuroblastic tumor (Fig. 2.22).

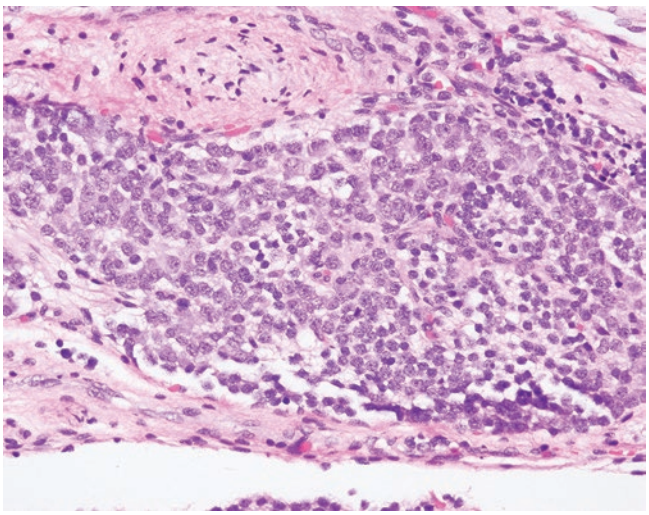

**Fig. 2.22** Sympathetic ganglion in the retroperitoneal tissues at 16 weeks gestation. The ganglion is composed of closely packed, immature-appearing ganglion cells at this gestational age. At this high power, the development of the eccentric eosinophilic cytoplasm and even nucleoli can be seen. The wavy stroma seen in the more mature ganglion (as in Fig. 2.20) is not as prominent (H&E, 40×)

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