

Soft tissue tumors occurring in the perinatal/infancy setting: 2nd part

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Abstract

In the second part, the following soft tissue tumors occurring in the perinatal period and/or in children and adolescents younger than 10 years, will be described: smooth muscle tumors, pericytic tumors, neurogenic tumors, vascular tumors and tumors of uncertain origin, including malignant extrarenal rhabdoid tumor and primitive myxoid mesenchymal tumor of infancy. For each entity, the following data are summarized: age of presentation, the most frequent localization, the typical macroscopic and microscopic findings, the immunohistochemical features and the molecular data which play a relevant role in their diagnosis. Each tumor entity is described with a practical approach, with the aim that this review will help perinatal and pediatric pathologists in the differential diagnosis of a group of tumors that are diagnostically challenging, due to their rarity and to the frequent lack of specific morphological and immunohistochemical markers.

Keywords

Soft tissue tumors, newborn, infant, diagnosis, pathology, immunohistochemistry.

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Smooth muscle tumors

Congenital smooth muscle hamartoma

Congenital smooth muscle hamartoma (CSMH) is a benign soft tissue tumor, typically presenting in newborns as a slightly elevated cutaneous

hyperpigmented plaque. The most frequent location of CSMH is the lumbosacral region. A rare location is the hard palate, where it may present as a polyp [1]. It may also present as an asymptomatic atrophic linear lesion in the skin, mimicking a reticular linear nevus [2]. Multiple CSMHs have been reported in

the back and arms in a seven-month-old girl [3]. The histological picture of CSMH is characterized, at low power, by the disorganized proliferation of smooth muscle cells, oriented in different directions, in the dermis (**Fig. 1A** and **Fig. 1B**). At higher power, proliferating smooth muscle cells appear arranged in

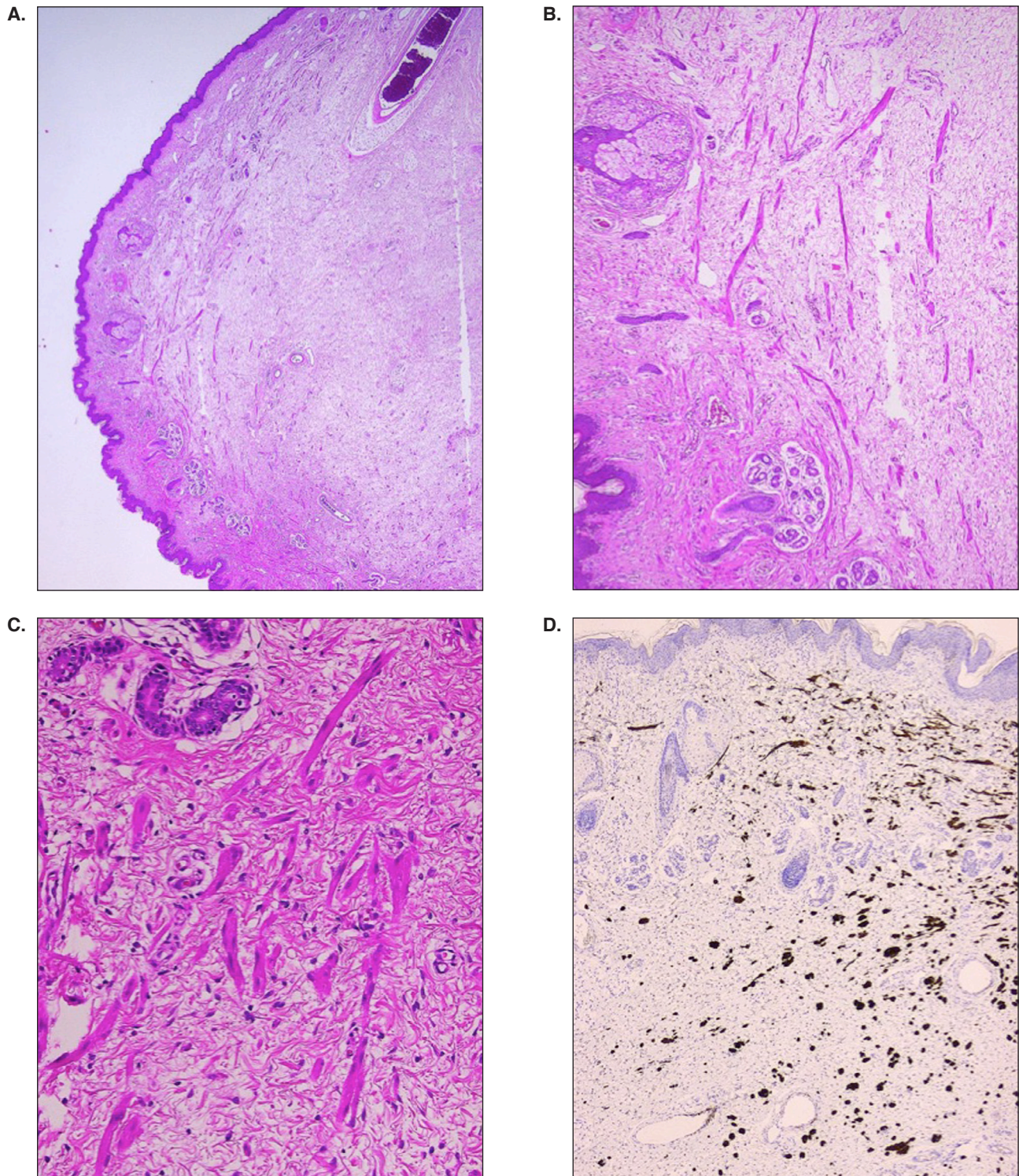


Figure 1. Smooth muscle hamartoma of the paranasal skin, in a 2-month-old boy. **A, B.** Disorganized proliferation of smooth muscle cells. **C.** At high power, proliferating muscle cells are oriented in different directions. **D.** Tumor cells show strong immunoreactivity for desmin.

short fascicles and show an eosinophilic cytoplasm (**Fig. 1C**). At immunohistochemistry, tumor cells show strong immunoreactivity for desmin (**Fig. 1D**). The proliferating smooth muscle cells often show a connection with hair follicles, suggesting the hypothesis of its origin from the arrectores pilorum muscles [4].

EBV-associated smooth muscle tumor

True leiomyosarcomas (LMSs) are rare, but may occasionally present in children, being often localized in the oral cavity. The last decades, smooth muscle tumors have been reported in immunosuppressed (congenital, post-transplant, AIDS) young patients [5]. Parenchymal organs and the soft tissues are often multifocally affected. EBV-associated smooth muscle tumors may present years after transplantation, and should be included in the differential diagnosis of all neoplasms occurring in pediatric patients following solid organ transplant [6]. On histology, at low power, the picture resembles a smooth muscle tumor, with bundles of spindle eosinophilic cells, with a usually bland cytology (**Fig. 2A**). Sometimes, a less differentiated aspect has been reported. At high power, spindled tumor cells show eosinophilic fibrillary cytoplasm and cigar-shaped nuclei, with frequent perinuclear vacuoles (**Fig. 2B** and **Fig. 2C**). Grading is not of any use. At immunohistochemistry, tumor cells show diffuse reactivity for smooth muscle actin, whereas desmin expression, when it is present, is mild (**Fig. 2D**). A strong immunostaining for H-caldesmon is a characteristic feature of this tumor entity (**Fig. 2E**). Interestingly, these tumors are associated with Epstein-Barr infection, which can be demonstrated by *in situ* hybridization for EBV-encoded small RNA (EBER) transcripts (**Fig. 2F**). EBV-associated smooth muscle tumors are usually much less aggressive than conventional LMSs, with 5 to 8% tumor-related mortality, which mainly relates to the degree of immunosuppression. Surgery and/or reduced immunosuppression show similar therapeutic results.

Pericytic tumors

Infantile myofibroma(tosis)

Infantile myofibroma(tosis) is a myofibroblastic proliferation in which a possible origin from perivascular progenitor cells has been hypothesized. The tumor can be sporadic or familial and is most commonly localized in the head, neck and trunk,

but rarely it has been described in the limbs [7]. Infantile myofibroma(tosis) may present in different clinicopathologic forms: 1) a solitary mass, better defined as myofibroma, localized in the skin, in soft tissues or in the oral mucosa [8]; 2) multiple nodules, localized in the skin, soft tissues or bones; 3) a generalized form, characterized by the presence of multiple myofibroblastic nodules in viscera, including the central nervous system, bones, skin and soft tissues. In all the three subtypes, the myofibroblastic nodules are more frequently detected at birth. There is a male predominance in solitary myofibroma and in the generalized form, whereas a female predominance has been reported in the subtype with multiple nodules. The cutaneous lesions appear as nodules, purple in color, or show a papular appearance. In cases with bone involvement, the clinical presentation is often related to pathological fractures. The histological picture of infantile myofibroma is characterized, at low power, by a roundish nodule with pushing margins, localized in the subcutaneous tissue (**Fig. 3A**). At higher power, tumor cells show oval vesicular nuclei and abundant ground-glass or eosinophilic cytoplasm. Nuclei are roundish or oval in shape, with clear chromatin and evident nucleoli. Thin-walled branching vessels, irregular in shape, are often prominent and characterize the histological picture (**Fig. 3B**). A typical feature of infantile myofibroma is the occurrence of vascular invasion, with protusion of tumor cells into the vascular lumen (**Fig. 3C**). This finding has no clinical significance and no prognostic value in myofibroma. Occasionally, spindle tumor cells are organized in short fascicles and dispersed in a myxoid or collagenous background. Small whorled nodules are frequently observed. Thin-walled branching vessels may be abundant and surrounded by myofibroblasts, giving rise to a solitary fibrous tumor-like picture. Mitoses are usually rare but can be numerous. This finding, together with the presence of vascular or perineural invasion, necrosis, infiltrative borders and hypercellularity should not be considered as signs of malignancy, but correspond to atypical/cellular myofibroma [9]. At immunohistochemistry, tumor cells show diffuse cytoplasmic immunoreactivity for smooth muscle actin. Recently, activating mutations in the platelet-derived growth factor receptor β (PDGFRB) have been reported in cases of familial and sporadic infantile myofibromatosis, suggesting imatinib as a promising therapeutic option for patients carrying these mutations [10, 11].

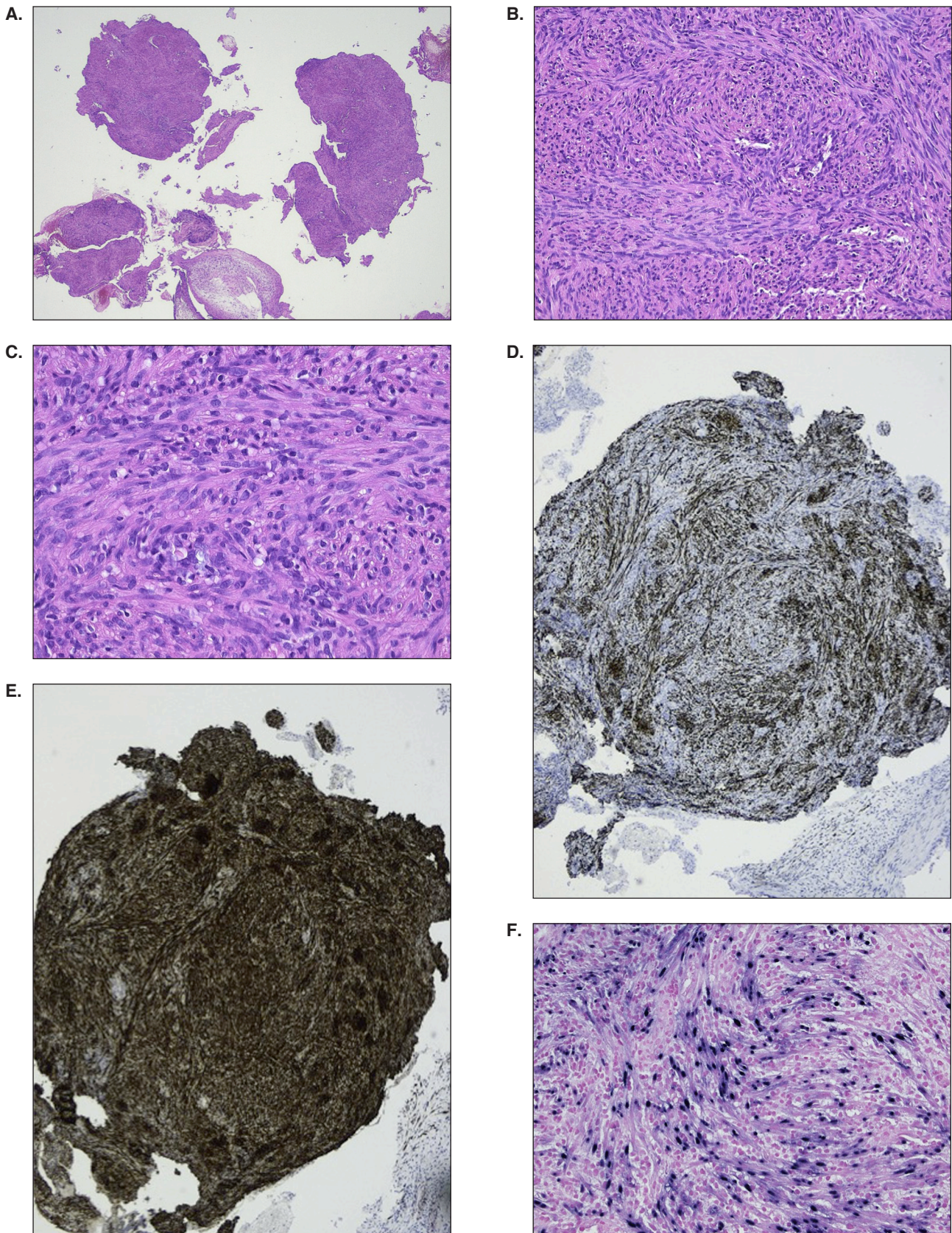


Figure 2. A. EBV-induced smooth muscle tumor of the lung. 8-year-old boy, affected by immunodeficiency, who underwent stem cell transplantation 10 months before. B. Spindled eosinophilic cells, characterized by a bland cytology, arranged in long fascicles. C. Proliferating smooth muscle cells are characterized by cigar-shaped nuclei, frequent perinuclear vacuoles and fibrillar cytoplasm. D. At immunohistochemistry, tumor cells show reactivity for desmin. E. Strong reactivity for h-caldesmon. F. *In situ* hybridization for EBV-encoded small RNA (EBER) transcripts is positive in the nuclei of the vast majority of proliferating smooth muscle cells.

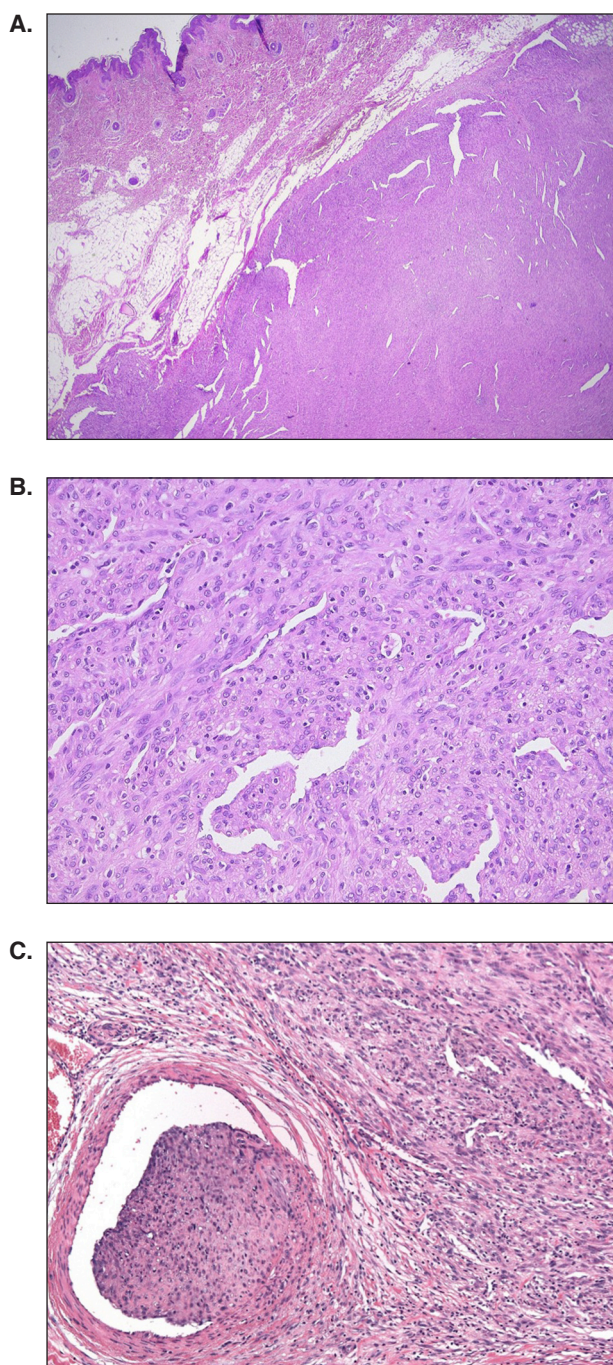


Figure 3. Myofibroma. 4-year-old boy, presenting with a nodule in the shoulder. **A.** At low power, myofibroma appears as a nodule characterized by pushing margins, localized in the subcutaneous tissue. **B.** At higher power, tumor cells show oval vesicular nuclei and abundant eosinophilic cytoplasm. Note the prominent thin-walled branching vessels. **C.** Vascular invasion with protusion of tumor cells into the vascular lumen. This finding has no clinical significance in myofibroma.

Cellular myofibroma/myopericytoma with SRF-RELA fusion

Very recently, a new subtype within the myofibroma and myopericytoma spectrum, occurring

in childhood, has been identified. The histological picture is characterized by a cellular proliferation of oval to spindle cells with fibrillary eosinophilic cytoplasm, often arranged in intersecting fascicles or in nests, with a rich vascular network. Despite the dense cellularity and variable mitotic activity, no significant nuclear pleomorphism or necrosis is present. At immunohistochemistry, strong and diffuse expression for SMA and desmin characterize the vast majority of cases, while myogenin is consistently negative. Paired-end RNA sequencing for potential fusion gene discovery showed recurrent SRF gene rearrangements, including SRF-C3orf62 fusion and SRF-RELA fusion. No distant metastases were seen in the few cases with follow-up information. This lesion should not be confused with a myogenic sarcoma [12].

Neurogenic tumors

Neuromuscular choristoma

Neuromuscular choristoma (NMC), also known as neuromuscular hamartoma or Triton tumor, is a rare neurogenic soft tissue tumor, originating from the spinal and cranial nerves, characterized by the unique admixture of skeletal muscle cells and nerve cells. NMC most frequently presents in children below 3 years of age. It typically arises from the major proximal peripheral nerves, most commonly as a fusiform enlargement of the sciatic nerve [13]. The extension of NMC to the lumbosacral plexus may lead to abnormalities in proximal nerve, muscles and bones within the hemi-pelvis [14]. NMC may also present as an intracranial tumor [15] or may originate from the trigeminal nerve and present as an orbital tumor, simulating an aggressive neoplasm [16]. NMC is strongly associated with desmoid-type fibromatosis and, rarely, its clinical course may be complicated by aggressive fibromatosis [17]. The majority of NMCs associated with desmoid fibromatosis are characterized by the presence of CTNNB1 mutations, both in the NMC and the fibromatosis components, suggesting a common molecular pathogenesis [18]. At imaging, NMC shows infiltrative margins, invading the surrounding skeletal muscles and causing bone erosion [19]. The histological picture is characterized by a multinodular architecture and by the finding of skeletal muscle cells, fibrous tissue, and nerve cells in a disorganized arrangement characteristic of NMC. Regarding the therapeutic options for NMC, given the difficulties often encountered in the complete resection of this

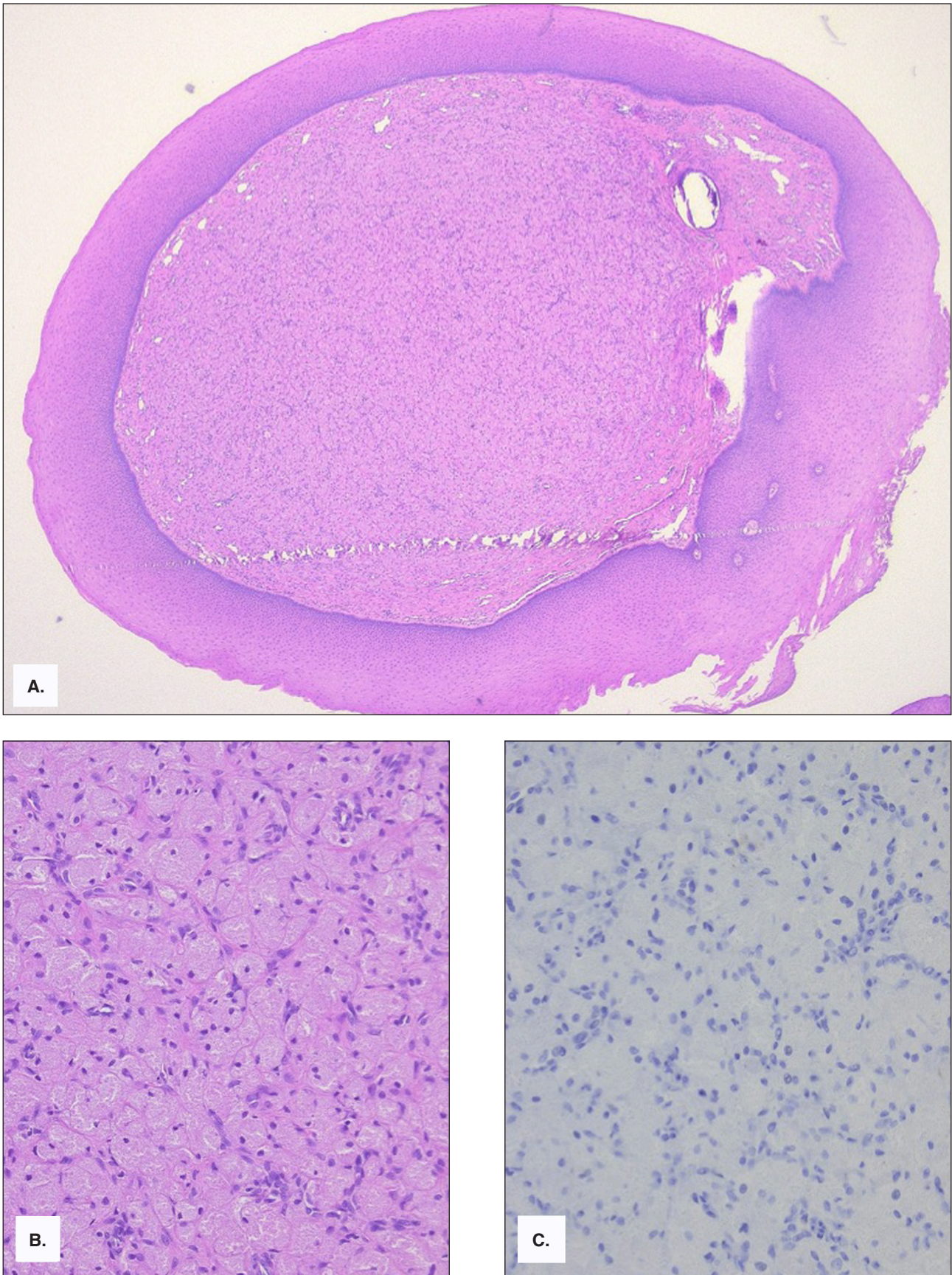


Figure 4. Congenital granular cell tumor (CGCT). Boy, 1-month-old, tumor of the gingiva at birth. **A.** At low power, CGCT appears as a eosinophilic nodule in strict contact with the gingival mucosa. **B.** At high power, tumor cells are characterized by ill-defined cell borders, and by a granular abundant pale eosinophilic cytoplasm. **C.** Absence of immunoreactivity for S100 protein.

tumor, corticosteroids have been recently proposed as an alternative treatment, aimed to modulate inflammation and sometimes leading to regression of the neoplasm.

Congenital granular cell tumor

Congenital granular cell tumor (CGCT), also known as Neuman tumor or congenital granular cell epulis, is a congenital benign tumor presenting at birth as a tumor mass of the oral mucosa, most frequently emerging from the gingiva. CGCT may also arise from the palate, tongue and vocal cords. [20]. Cutaneous involvement is less frequent, but rare cases have been described in soft tissues, particularly in arms. It mainly occurs in female newborns. The cell of origin of the lesion has not been clarified yet. CGCT is generally considered to be a different entity than the adult form of this lesion with different immunohistochemical features [21]. The histological picture is characterized, at low power, by a superficial submucosal localization, with pushing margins (**Fig. 4A**). At high power, tumor cells are large and often arranged in small nests, and are characterized by ill-defined cell borders and by a granular abundant pale eosinophilic cytoplasm (**Fig. 4B**). Dense collagenous septa may be detected. Nuclei are uniform, small, round, often eccentric, with homogenous fine chromatin, [22]. The immunohistochemical pattern of CGCT is characterized by the absence of significant immunostaining for S100 protein (**Fig. 4C**) and inhibin- α , which are positive in the granular cell tumors occurring in adulthood [23]. Granular cells of pediatric CGCT show positive cytoplasmic immunostaining for NSE and CD68 [24].

Melanotic neuroectodermal tumor of infancy

Melanotic neuroectodermal tumor of infancy (MNTI), also known as melanotic progonoma, is a very rare tumor that mainly presents during the first year of life. The mean age of affected patients is 4.3 months. The tumor mostly involves jaws (maxilla, mandible) and only rarely the skull. The neoplasm shows an intermediate biological behavior, being locally aggressive and characterized by the ability to cause bone erosion. Only rarely, MNTI may exhibit malignant behavior with local lymph node metastases and bone invasion [25]. The histopathological picture of MNTI is characterized, at low power, by its location near and under the teeth root (**Fig. 5A**) and by the presence of abundant pigment. A

typical feature is the finding of infiltrating margins. At higher power, MNTI shows a biphasic pattern, with nests of large epithelioid cells containing melanin and small neuroblastic cells with a scant cytoplasm.

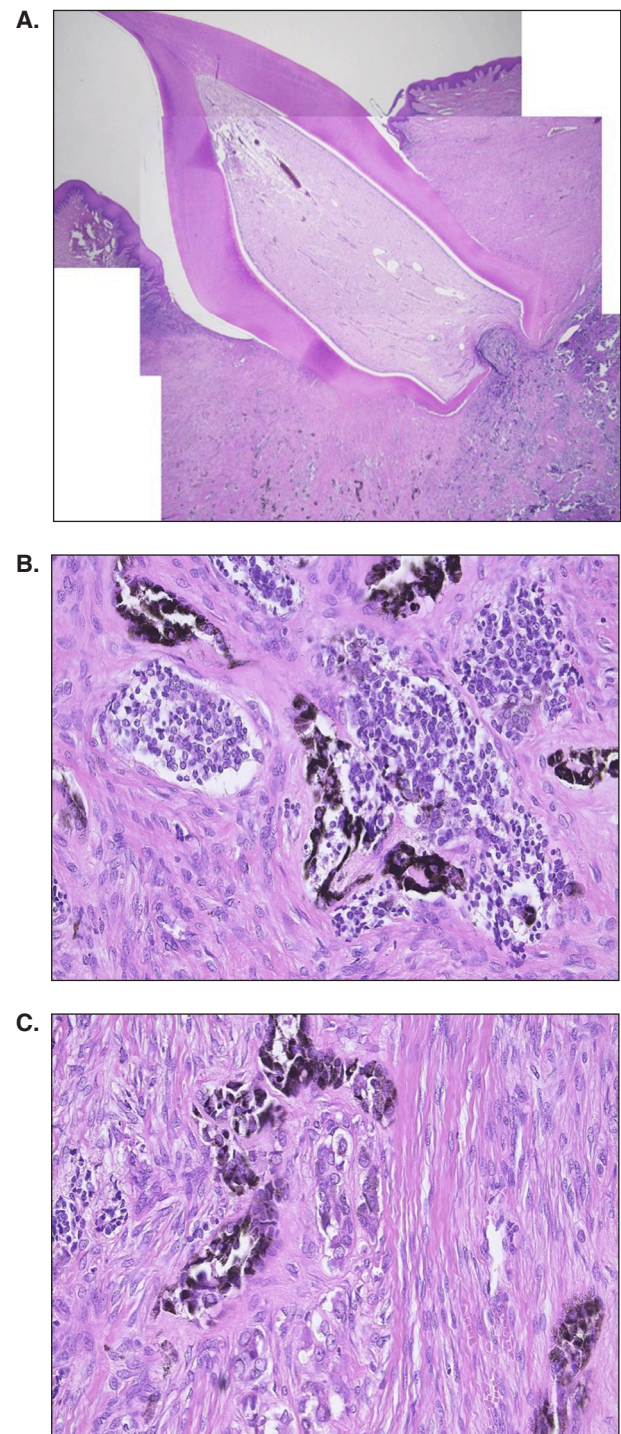


Figure 5. Melanotic neuroectodermal tumor of infancy (MNTI) localized in the maxilla of a 7-month-old female. **A.** At low power, the tumor is located near and under the teeth root and characterized by the presence of abundant pigment and by infiltrating margins. **B.** At high power, MNTI shows a biphasic pattern, with nests of large epithelioid cells containing melanin and small neuroblastic cells with a scant cytoplasm. **C.** Melanin-rich epithelioid tumor cells are arranged in nests separated by a dense fibrous stroma.

melanin mixed with small neuroblastic cells, surrounded by spindle cells embedded in abundant collagenous stroma (**Fig. 5B**). A subset of the large epithelioid tumor cells contain large granules of melanin, which show the typical black color at H&E (**Fig. 5C**). At immunohistochemistry, the biphasic pattern is confirmed: the large epithelioid cells are immunoreactive for cytokeratins, EMA and HMB-45, whereas neuroblastic cells are stained by synaptophysin, GFAP and NSE [26]. Although MNTI is a rapidly growing tumor and it is locally highly invasive, radical surgery is associated with a favorable outcome, even in cases with extensive intracranial extension [27].

Tumors of uncertain differentiation

Malignant extrarenal rhabdoid tumor

Malignant extrarenal rhabdoid tumor (MERT) is an aggressive soft tissue tumor that typically presents in children younger than 10 year [28].

MERT develops most frequently in the limbs and along the vertebral axis including perineum, pelvis, retroperitoneum and neck. At histology, MERT is characterized by the finding of rhabdoid cells, i.e. large epithelioid cells with eccentric eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli (**Fig. 6**). A high mitotic index and foci of intratumoral necrosis are frequently detected. In some cases, rhabdoid cells are observed only in limited areas, whereas the majority of tumor cells are undifferentiated small progenitor cells, with scant clear cytoplasm. At immunohistochemistry, MERT is characterized by the co-expression of cytokeratin, EMA and desmin. CD99, synaptophysin, CD57 and neuron-specific enolase immunostaining are detected in the majority of cases. Nearly all MERTS are characterized by the loss of the nuclear expression of INI1 protein, that may help in the differential diagnosis between MERT and other non-rhabdoid soft tissue sarcomas of infancy. Molecular genetics reveal bi-allelic inactivation of the SMARCB1/hSNF5/INI1 tumor suppressor gene, which plays a

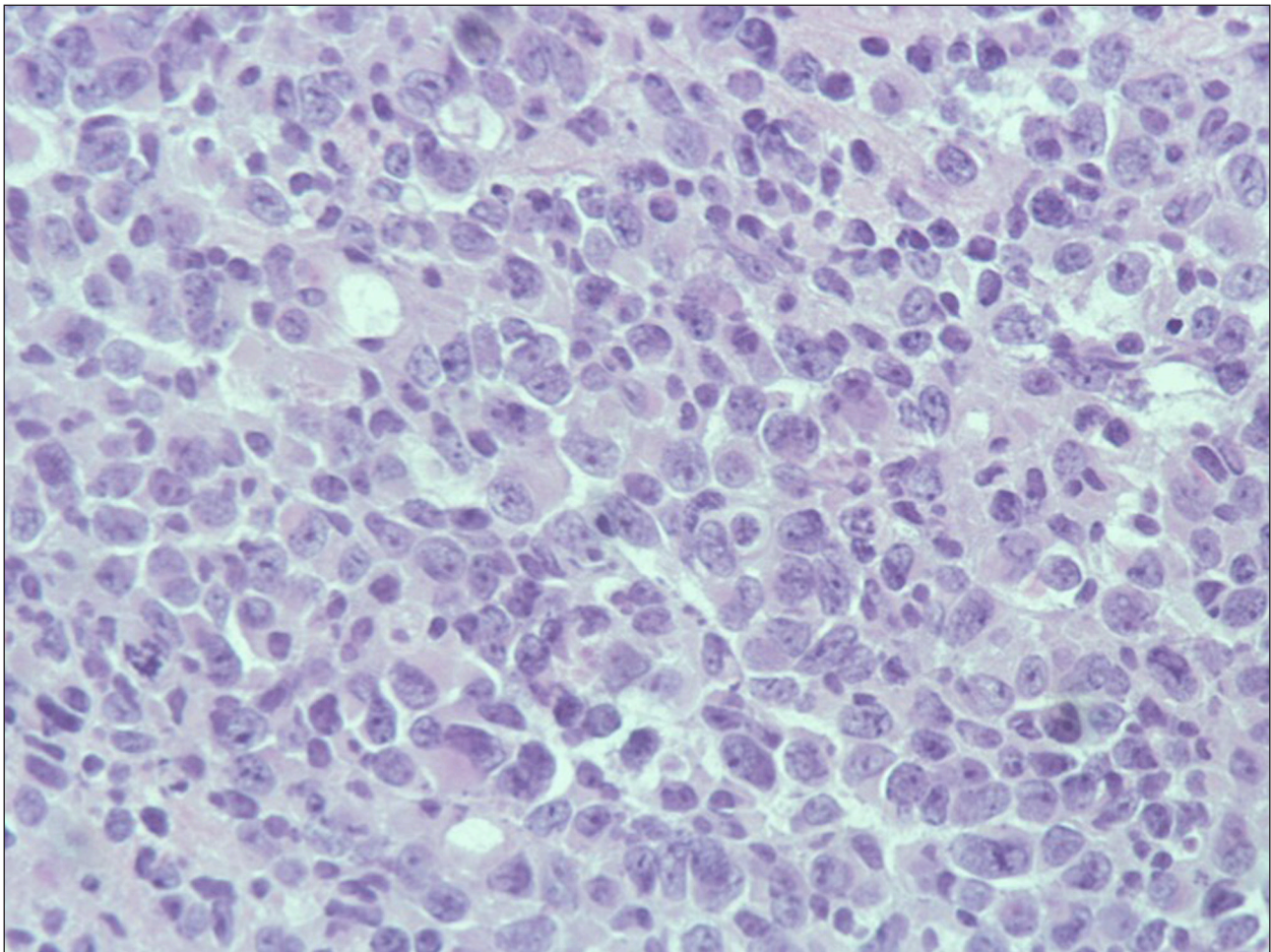


Figure 6. Atypical teratoid rhabdoid tumor (ATRT) of the brain, showing rhabdoid cells (the same are present in malignant extrarenal rhabdoid tumor [MERT]).

major role in chromatin remodeling and cell cycle regulation. The prognosis of MERT is unfavorable, being characterized by a very poor clinical outcome [29]. Local recurrence occurs frequently, and metastatic rate is 50% to 80%: lungs, lymph nodes, liver and bone are the most frequent metastatic sites.

Primitive myxoid mesenchymal tumor of infancy

Primitive myxoid mesenchymal tumor of infancy is a very rare soft tissue tumor of infancy and early childhood [30]. It occurs primarily in the trunk, head and neck and in the extremities as a multinodular plexiform tumor. At histology, this tumor entity shows an abundant myxoid background, in which polygonal spindle and round cells are dispersed (**Fig. 7A**). Tumor cells are typically arranged in cords separated by myxoid matrix, resulting in a typical lace-like pattern (**Fig. 7B**). Nuclei are round or oval, with clear chromatin and frequent grooves. Tumor cells may show the tendency to a perivascular condensation and to a vaguely nodular arrangement. A delicate vascular network characterizes the morphological pattern. At immunohistochemistry, tumor cells are reactive for CD99, in the absence of reactivity for muscular markers. Recently (BCL6)-interacting co-repressor (BCOR) tandem duplications have been described, leading to diffuse BCOR nuclear expression at immunohistochemistry (**Fig. 7C**) [31]. The clinical behavior is characterized by frequent local recurrence, whereas distant metastases are rare, indicating it as a tumor of intermediate biological potential.

Vascular tumors

The vascular paradox is represented by the discrepancy between the high incidence of benign vascular tumors in infancy and the rarity of malignant vascular lesions. In fact, malignant vascular tumors are very uncommon in children, but their early diagnosis is very important, given the impact of an early and proper diagnosis on the prognosis of these patients [32].

Congenital hemangioma

Congenital hemangioma (CH) is typically diagnosed at birth, affecting both girls and boys with equal frequency. It presents as a plaque or as an exophytic mass located on the skin of head, neck, or limbs. Rarely, CH has been reported in

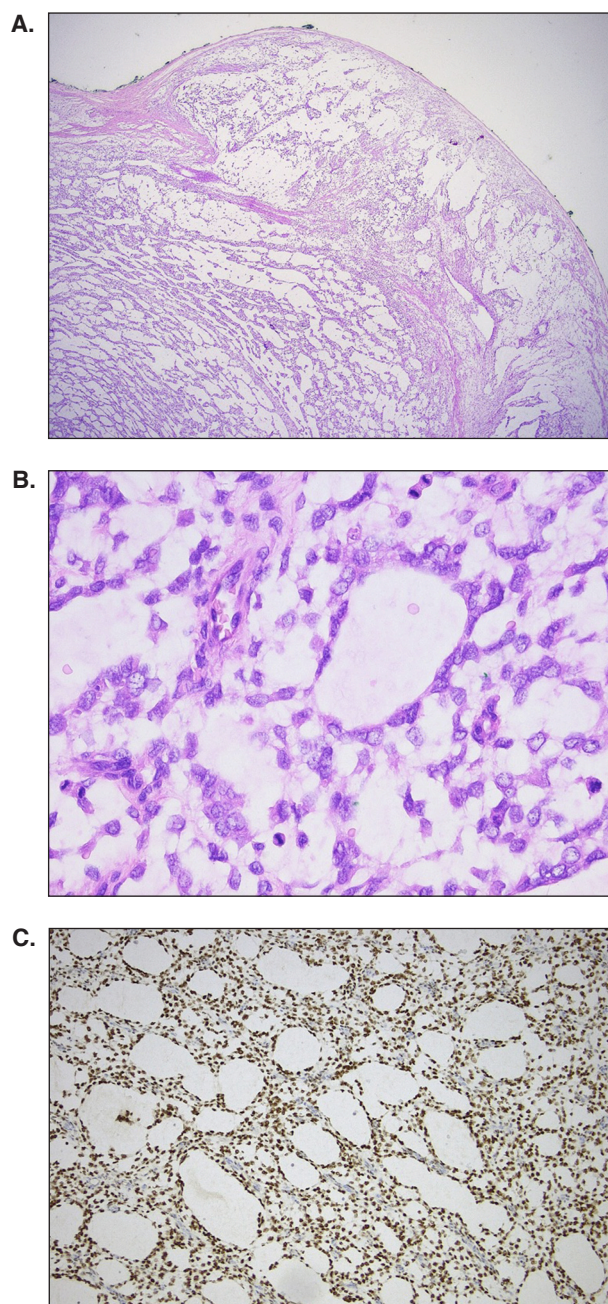


Figure 7. Primitive myxoid mesenchymal tumor of infancy. 1-year-old female with recurring tumor in left arm (courtesy of Louis Libbrecht, Université Catholique de Louvain). **A.** At low power, the tumor is characterized by an abundant myxoid background, in which polygonal spindle and round cells are dispersed. **B.** Tumor cells, with round or elongated nuclei, are arranged in cords separated by myxoid matrix, resulting in a typical lace-like pattern. **C.** Diffuse (BCL6)-interacting co-repressor (BCOR) nuclear expression can aid in the diagnosis of primitive myxoid mesenchymal tumor of infancy.

hands [33]. Based upon their clinical evolution, three major subtypes of CHs have been identified: rapidly involuting congenital hemangioma (RICH), non-involuting congenital hemangioma (NICH) and partially involuting congenital hemangioma (PICH).

In most cases, RICH involutes completely within the first year of age, whereas NICH never regresses, and it may require eventual excision. PICH, the intermediate subtype, involutes but not completely, showing overlapping features of RICH and NICH [34]. When compared with infantile hemangiomas, both NICH and RICH show distinctive features on ultrasound, including visible vessels and calcifications, whose presence has been suggested as a useful tool for the distinction of congenital from

infantile hemangioma [35]. The histological picture of RICH is characterized, at low power, by a solid nodular pattern in which branching thin-walled vessels are prominent (**Fig. 8A**). At higher power, the proliferation of highly-packed poorly-canalized capillaries is more evident (**Fig. 8B**). Proliferating vessels are surrounded by abundant pericytes, with abundant eosinophilic cytoplasm. Mitoses are frequent and mast cells are easily detected. At immunohistochemistry, a typical feature of RICH

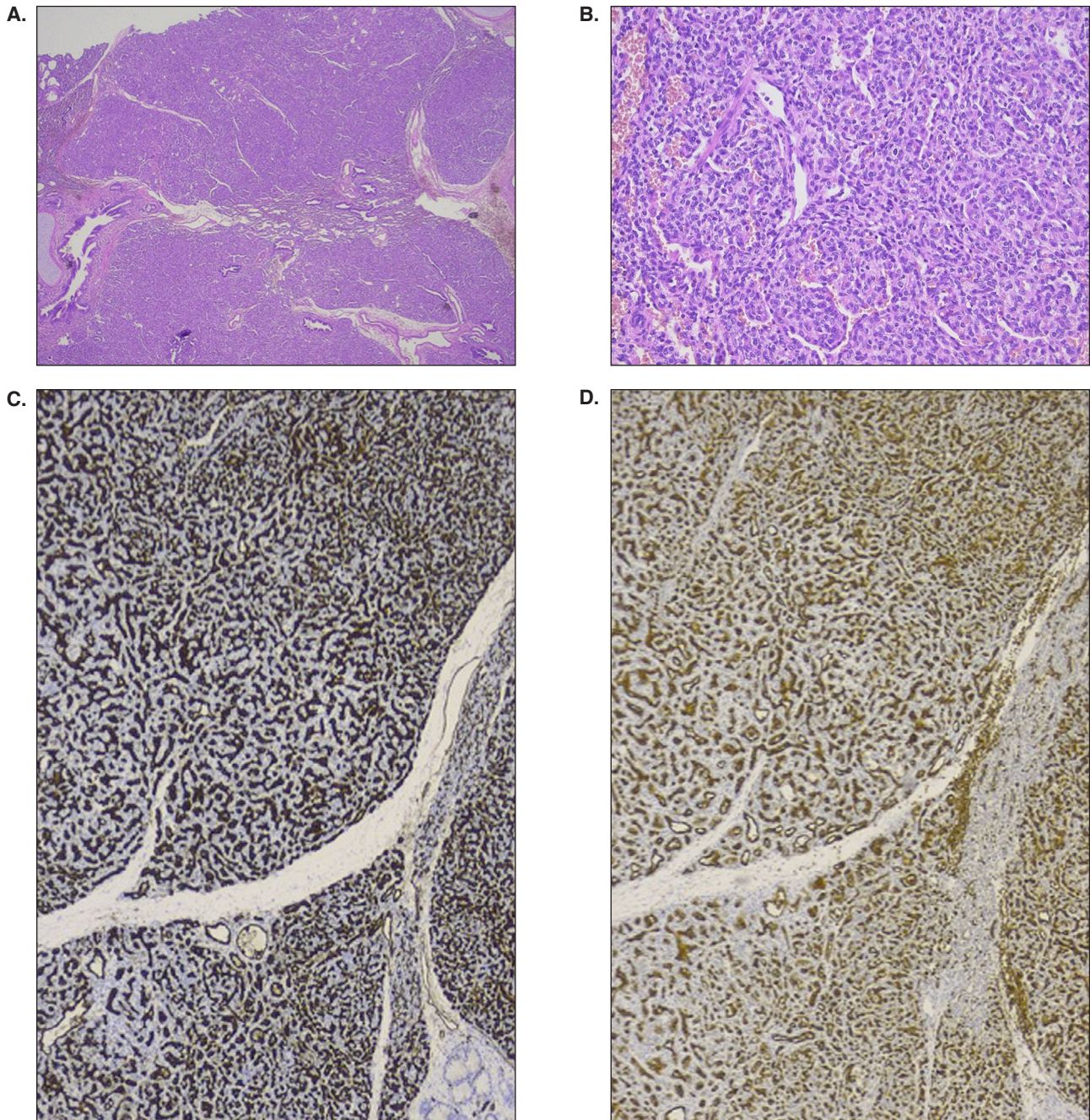


Figure 8. Rapidly involuting congenital hemangioma (RICH) of the lung in a newborn female. **A.** At low power, RICH is characterized by the proliferation of highly packed poorly canalized capillaries. **B.** At higher power, proliferating thin vessels with plump endothelial cells are surrounded by abundant pericytes. **C, D.** At immunohistochemistry, tumor cells are strongly reactive for CD31 (**C**) and GLUT1 (**D**).

tumor cells is their strong reactivity for CD31 and GLUT1 (**Fig. 8C** and **Fig. 8D**).

The histological picture of NICH is often characterized by a different pattern. At low power, NICH appears less cellular than RICH. A diffuse proliferation of variably-sized blood vessels characterize the picture of NICH, with dysplastic veins or arteries intermingled between solid nodules (**Fig. 9A**). At higher power, dysplastic vessels show thick wall and irregular borders, and are surrounded by a densely sclerotic fibrous stroma. Cellular lobules of highly-packed capillaries are also present

(**Fig. 9B**). At immunohistochemistry, proliferating endothelial cells show diffuse immunostaining for CD31, while GLUT1 only stains the red blood cells, not the endothelial cells (**Fig. 9C** and **Fig. 9D**).

The major distinctive feature that allows the differential diagnosis between RICH and NICH is the absence of a significant expression of GLUT1 in NICH [36]. The clinical course of cutaneous CH is always favorable and, after excision or laser therapy, recurrences are not reported even in the non-involting forms. The exception to this rule is represented by the rare hepatic RICH, which may be

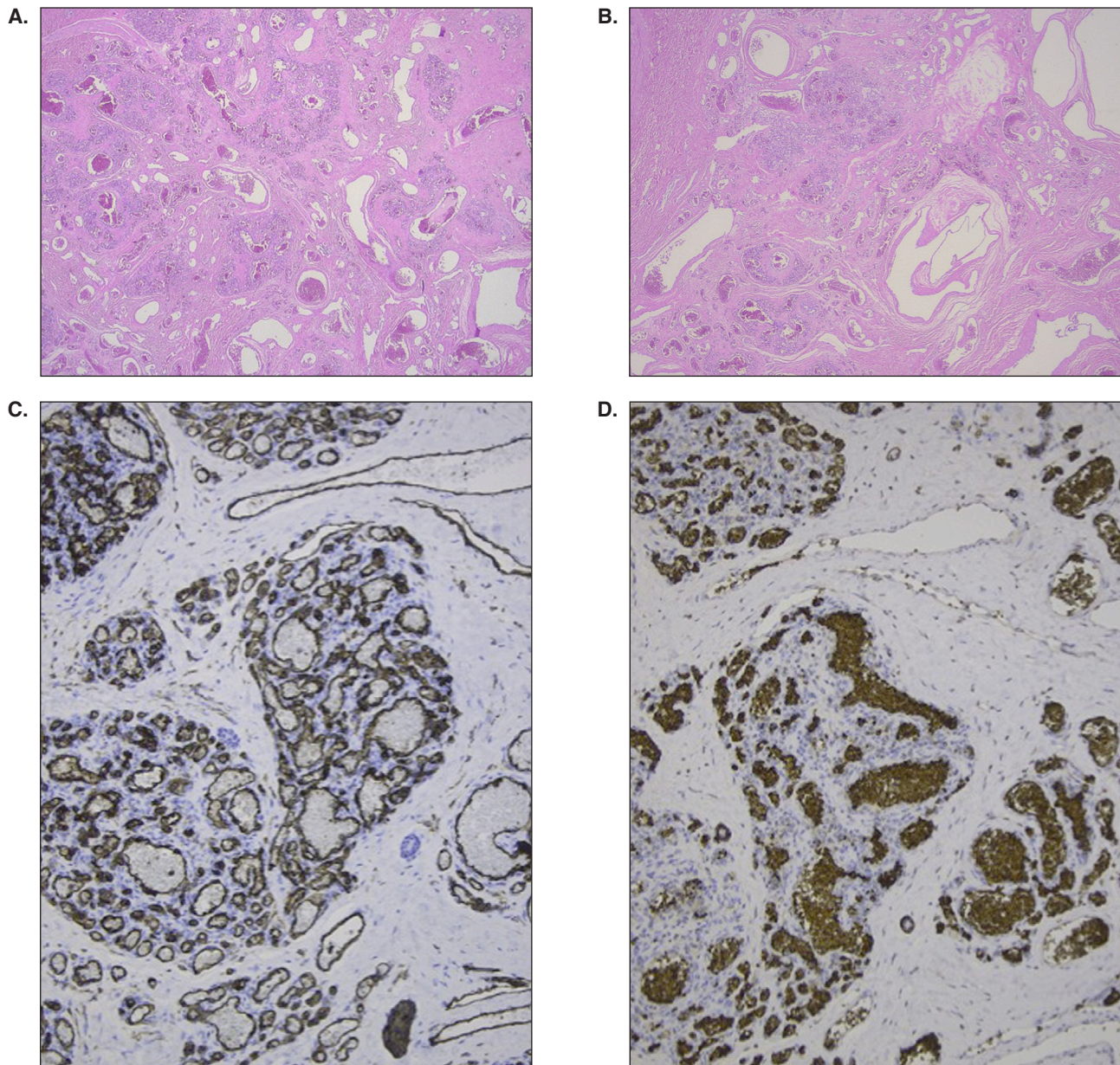


Figure 9. Cutaneous non involuting congenital hemangioma (NICH) presenting as a subcutaneous lesion around the knee in a 5-year-old male. No clinical improvement after Inderal therapy. **A.** At low power, the tumor shows a plexiform pattern. **B.** At higher power, the admixture of large vessels and capillaries characterize the histological pattern. **C, D.** At immunohistochemistry, endothelial cells show diffuse immunostaining for CD31 (**C**), while GLUT1 only stains the red blood cells, not the endothelial cells (**D**).

complicated by cardiac failure due to arteriovenous or porto-venous shunting [37].

Juvenile capillary hemangioma (infantile hemangioma)

Juvenile capillary hemangioma (JCH) is a frequent soft tissue tumor in childhood and infancy, affecting about 4% of children [38]. Young girls are more affected. JCH may present in the perinatal period, preterm babies being more affected than at term infants [39]. Head and neck represent the most frequent locations of JCH, accounting for about 50% of cases. JCH is superficial, being mainly localized in the dermis or in the subcutaneous tissue. The histological picture of JCH, at low power, is characterized by the finding of multiple lobules of tightly-packed poorly-canalized capillaries that result in a solid appearance that obscures the vascular nature of the tumor (**Fig. 10A**). At higher power, proliferating endothelial cells show a plump appearance, with abundant eosinophilic cytoplasm and oval nuclei with scattered vascular lumens. Mitoses are frequently found (**Fig. 10B**). Solid areas are also present, characterized by inconspicuous lumina and by the prominence of pericytes. Large capillaries are, generally, more abundant at the periphery of the neoplasm. In a minority of cases, a perineural and/or endoneural invasion may be detected. At immunohistochemistry, tumor cells show a diffuse and strong immunoreactivity for GLUT1. Small JCHs are simply maintained under periodic follow up, whereas larger tumors undergo surgical excision or laser therapy.

Papillary intralymphatic angioendothelioma (Dabska tumor)

Papillary intralymphatic angioendothelioma (PILA) is a locally aggressive and rarely metastasizing vascular tumor, characterized by the proliferation of large lymphatic channels with intraluminal papillary endothelial proliferations [40]. It is generally considered a tumor of infancy and childhood, even though it may arise even in adults. PILA generally arises in the dermis or in the subcutaneous adipose tissue, but in rare cases a deep intraosseous location has been reported [41]. The histological picture is characterized by the presence of dilated lymphatic channels containing peculiar intraluminal papillary proliferations. Pseudopapillary structures are formed by an acellular hyaline core surrounded by small dark

cells with a hobnail appearance. Occasionally, lymphatic vessels with a single papillary structure may acquire a glomeruloid appearance. The immunohistochemical pattern is characterized by reactivity of tumor cells for CD31 and D2-40. Recently, a rare variant of acquired hemangioma with “dabskoid” features has been described, expanding the histological spectrum of common acquired hemangiomas [42]. The clinical course of PILA is characterized by rare local recurrences, due to incomplete excision, and extremely rare distant metastases, with excellent prognosis after complete surgical excision.

Kaposiform hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor of infancy and childhood, which often presents in the first months of life (50% of cases) [43]. KHE is characterized by the contemporary presence of histological features common to Kaposi sarcoma (KS) and capillary hemangioma. It often presents as a solitary lesion, which may be superficial, localized in the dermis. Rarely, KHE may be deeply located, mainly insurging in the retroperitoneum. The most frequent locations of KHE are the extremities, head and neck. Occasionally it may present as multifocal lesions [44]. The cutaneous lesions present as slightly raised blue-red lesions. The histological picture is characterized, at low power, by the finding of multiple nodules resembling a capillary hemangioma, associated with large dilated vessels irregular in shape (**Fig. 11A**). At higher power, spindle tumor cells appear arranged in short fascicles, with slit-like spaces often containing erythrocytes, mimicking KS (**Fig. 11B**). Small and large lymphatic channels are typically seen at the periphery of the main tumor mass. At immunohistochemistry, tumor endothelial cells are CD31, CD34, and FLI1-positive but typically negative for GLUT1. The absence of reactivity for GLUT1 may help in the differential diagnosis with JCH. The majority of tumor cells are immunoreactive for D2-40, consistent with a lymphatic origin. The clinical picture of KHE occurring in infancy can be complicated with lymphangiomatosis (\pm 20% of patients). The clinical course of large, deep-seated KHE is frequently associated with consumptive coagulopathy and life-threatening hemorrhage, giving rise to the Kasabach-Merritt syndrome (about 50% of patients), which may

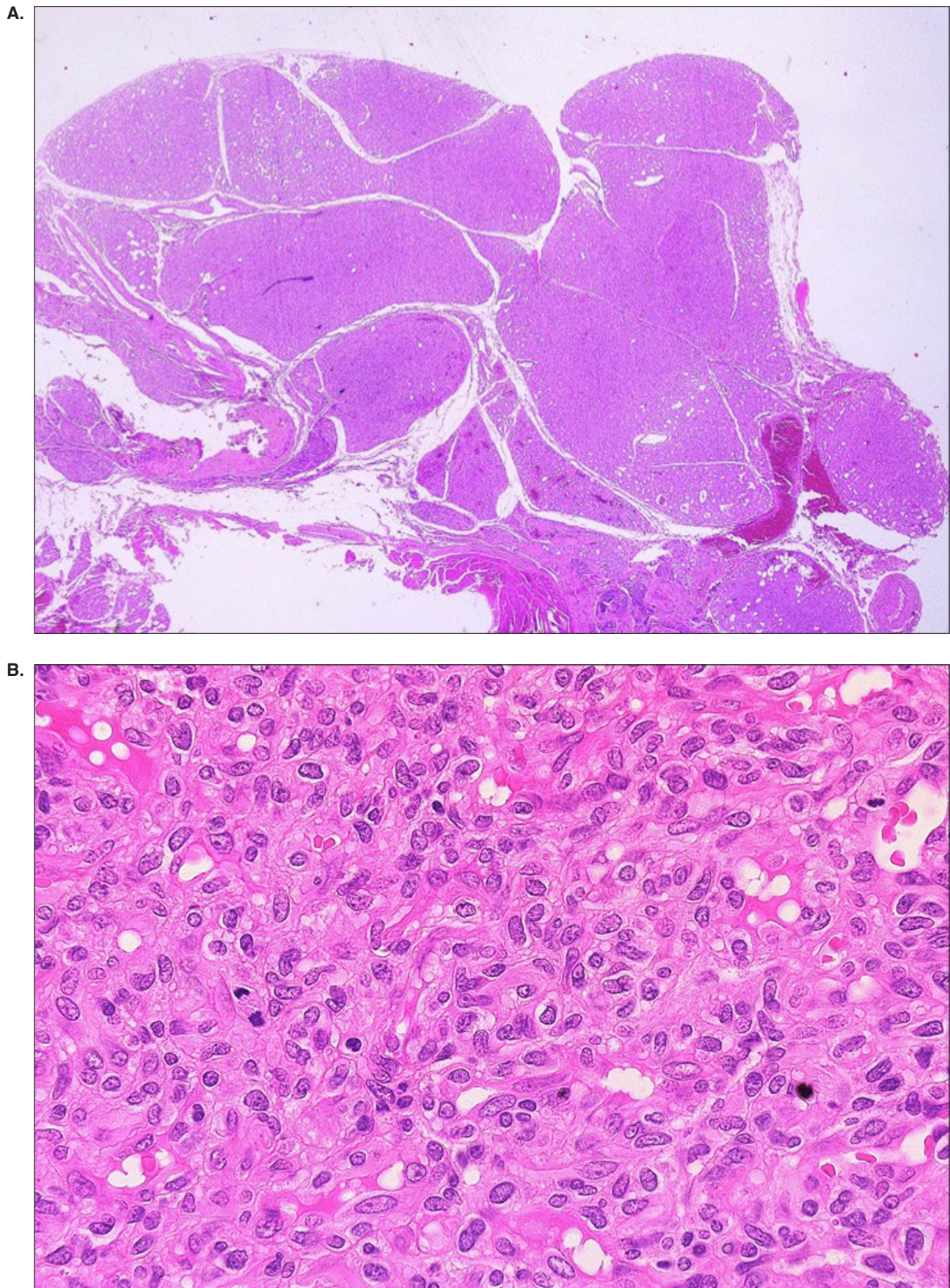


Figure 10. Cutaneous infantile hemangioma (IH) in the neck of a 1-year-old female. **A.** At panoramic view, IH shows a multinodular pattern. **B.** At higher power, endothelial cells show a plump appearance, with scattered vascular lumens. Mitoses are frequently found.

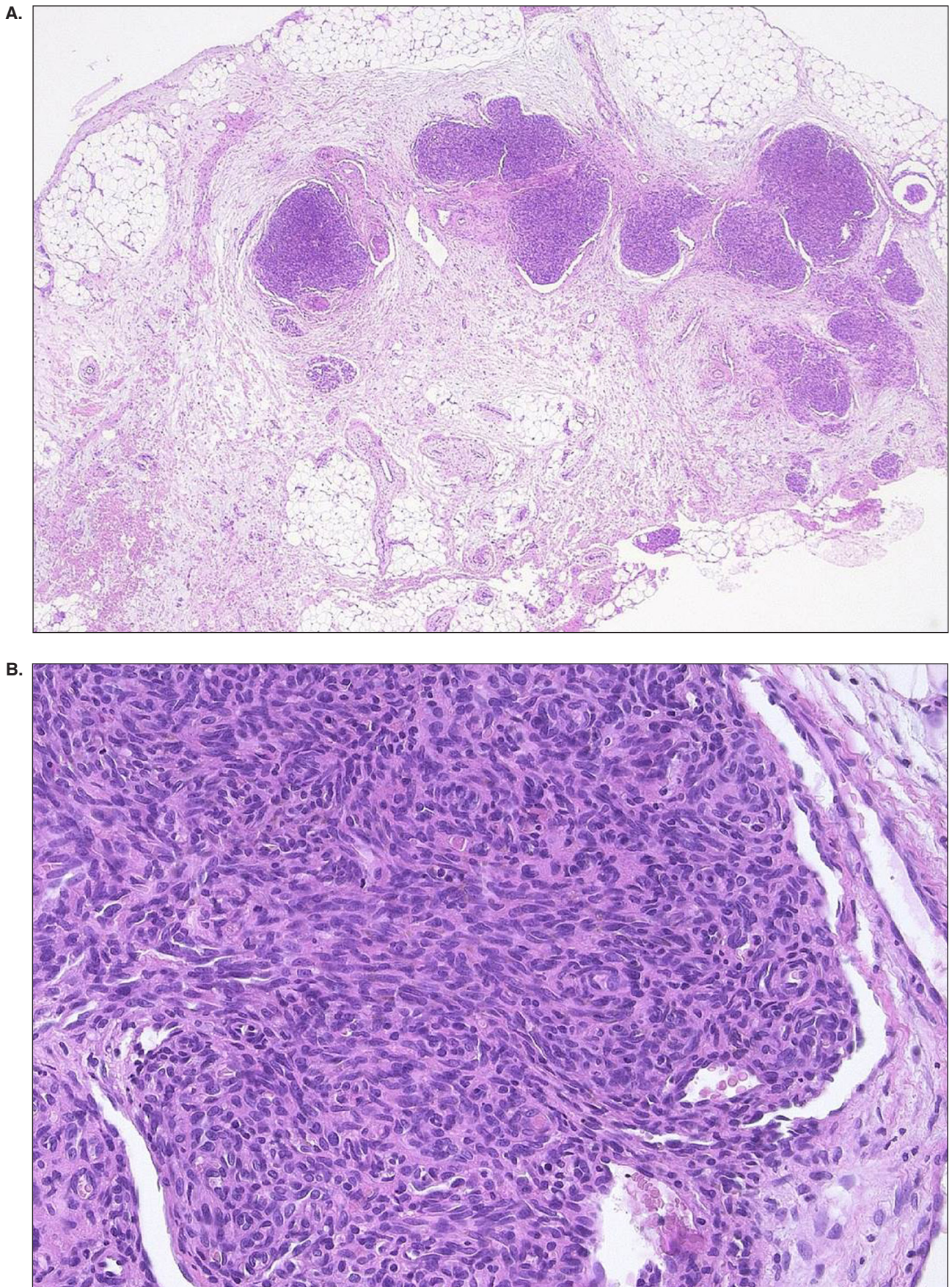


Figure 11. Kaposiform hemangioendothelioma (KHE) of the skin in a 4-month-old boy. **A.** At low power, a nodular pattern is evident, with dilated vessels surrounding more solid areas. **B.** At higher power, the solid areas are kaposiform with fascicles of spindle cells.

be successfully treated with sirolimus [45]. The prognosis of KHE is related to the site of origin of the tumor. When located in the retroperitoneum, the mortality rate is very high, due to the extensive infiltration of retroperitoneal soft tissues that contraindicates surgical excision. Regional lymph node metastases are frequent, whereas distant metastases have not been reported.

Lymphangioma

Lymphangioma is generally considered a lymphatic malformation that may be diagnosed at birth. Cervical lymphangioma, characterized by the accumulation of lymph in the jugular lymphatics of the nuchal region, may be diagnosed in the fetus before birth, being frequently associated with other congenital anomalies, including Down syndrome [46]. Another peculiar presentation of lymphangioma in neonates is represented by the occurrence of multiple vesicles in the oral cavity, most commonly on the tongue [47]. Most patients present before the age of two years. Lymphangioma may be subdivided into two clinical-pathological entities: i) a superficial one,

lymphangioma circumscriptum, also known as the microcystic type; ii) a deeper lesion, also known as cavernous lymphangioma. Lymphangioma circumscriptum is more frequently diagnosed at birth. It presents as multiple vesicles, translucent or pink-red in color due to small bleedings, localized on limbs, in proximal location. Sometimes, the hyperplastic papillomatous hyperplasia of the overlying epidermis gives rise to a verrucous lesion. The histological picture of lymphangioma is characterized by the presence of dilated lymphatic vessels in the superficial dermis, immediately beneath the epidermis. A focal lymphocytic infiltrate may be detected in the fibrous septa separating the vascular lumens (**Fig. 12**). In verrucous lesions, the thin-walled dilated lymphatic vessels are separated by hyperplastic epidermal septa. In rare cases, lymphangioma is multiple and deep-seated, and it is localized in the stomach, in the intestinal tract and in the liver, leading to liver transplant [48]. Treatment is mainly based on sclerotherapy, surgery, laser therapy, or on a combination of these therapeutic modalities [49]. The clinical course of lymphangioma after excision is often complicated by recurrences.

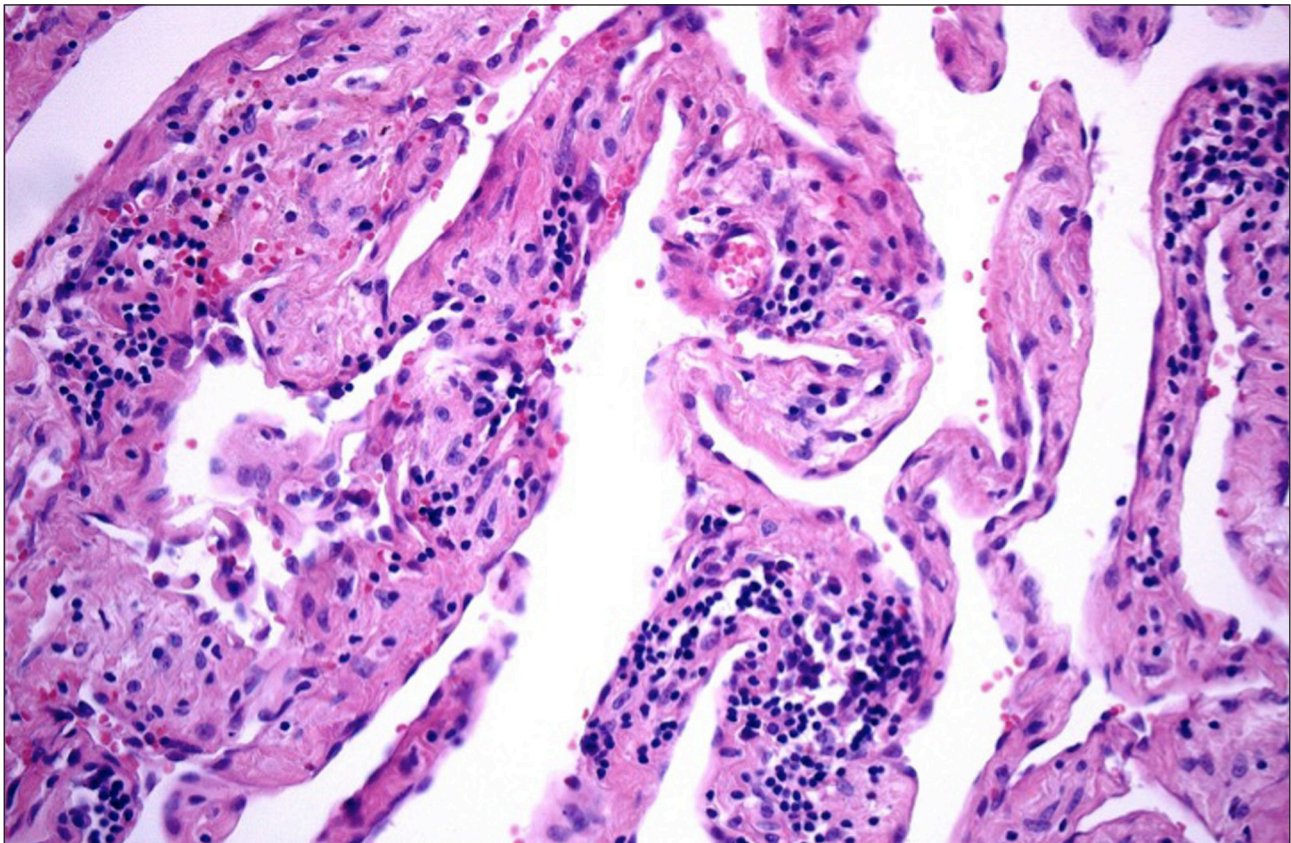


Figure 12. Retroperitoneal lymphangioma, in a 1-year-old male. Dilated lymphatic vessels with a very flat endothelium, separated by fibrous septa with lymphocytic aggregates.

Endemic Kaposi sarcoma (children, Equatorial Africa)

KS is a vascular cell proliferation strictly associated with human HHV-8 infection, generally classified as a vascular tumor of intermediate biological behavior. KS that presents in childhood, mainly in African areas in which HHV-8 is endemic, is characterized by a more aggressive behavior, and sometimes it is lethal. KS may present in early childhood, the majority of cases being diagnosed between 1 and 10 years of age [50]. Its clinical evolution is characterized by three clinical stages: the patch stage, with cutaneous blue-red macules; the plaque stage, characterized by the elevation of macular lesions, and the nodular stage. Juvenile KS is often localized in the oral cavity, larynx, pleura, in the inguinal soft tissues, lymph nodes, and in the gastrointestinal tract. The histological picture of endemic KS is characterized, in all stages, by the occurrence of thin vessels with bland endothelial cells, surrounded by spindle cells. Extravasated red blood cells, scattered lymphocytes and PAS-positive diastase-resistant hyaline globules complete the histological picture of endemic KS. In the nodular stage, spindle cells arranged in fascicles predominate, with slit-like vascular spaces containing red blood cells intermingled with spindle cells. At immunohistochemistry, the spindled tumor cells show strong and diffuse nuclear reactivity for HHV8 in a granular pattern. They also show immunostaining for CD31, CD34 and D2-40, a finding suggestive for the lymphatic origin or differentiation of KS. The clinical course of infantile KS is often characterized by an aggressive behavior, chemotherapy being required for achieving its remission. A minority of young patients are affected by overwhelming disseminated disease that may be lethal [51].

Conclusions

With their varied histological appearances, associated with the difficulties in defining the line of differentiation exhibited by tumor cells in a large percentage of neoplasms, soft tissue tumors represent one of the most complex fields of human pathology. In this review, we focused on the pathological and clinical features of soft tissue tumors presenting at birth and in early infancy. A lot of the discussed entities are rare and thus challenging. Hopefully, this overview might contribute to their appropriate diagnosis and management.

Declaration of interest

The Authors declare that there is no conflict of interest.

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