Review

Soft tissue tumors occurring in the perinatal/infancy setting: 1st part

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Abstract

Soft tissue sarcomas represent an important chapter of pediatric oncology, accounting for about 10% of all malignancies in childhood. The aim of this work is to summarize the clinical, histological, immunohistochemical and genetic features of the most frequent soft tissue tumors presenting in infants and in young subjects before the age of 10. For each entity, the most relevant data regarding prognosis and treatment will be summarized, and the most important morphological and immunohistochemical features will be reported. The most frequent myofibroblastic tumors, fatty tumors and skeletal muscle tumors occurring in infancy and adolescence will be described in this first part. The aim of this work, mainly based on a practical approach, is to help perinatal and pediatric pathologists in the diagnosis of a group of tumors that are diagnostically challenging, due to their rarity, the contemporary expression of multiple immunohistochemical markers and frequent lack of known genetic abnormalities.

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Introduction

Soft tissue tumors occurring in newborns and infants include a wide range of benign, malignant and intermediately aggressive tumors. The latter are characterized by a tendency to local recurrence after excision and/or by a very

low, but present, metastatic potential. Pediatric soft tissue sarcomas account for approximately 10% of all malignancies in children, representing a very important chapter of pediatric oncology. With their so many 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, and can be intimidating for pathologists [1]. Here we'll review the most frequent soft tissue tumors occurring in the perinatal/infancy setting, highlighting those of them occurring with higher frequency. The tumor entities will be subdivided in groups, according to the putative cell of origin and/or the main line of differentiation of tumor cells, as reported in the recent update of the WHO classification of soft tissue tumors [2]. For each entity, we'll briefly summarize the clinical, histological, immunohistochemical and, when characteristic of the lesion, the genetic features. Moreover, the most relevant data regarding prognosis and treatment of the most aggressive soft tissue sarcomas occurring in newborns and infants will be presented, including the most recent data on the prognostic factors associated with response to chemotherapy of soft tissue sarcomas presenting in the perinatal/infancy setting [3]. The aim of this work is to give an overview of this complex field of infant and childhood pathology to neonatologists, pediatricians, oncologists and perinatal pathologists.

In the first part, the most frequent myofibroblastic tumors, fatty tumors and skeletal muscle tumors occurring in the perinatal/infancy setting will be described.

Myofibroblastic tumors

Myofibroblastic tumors represent a group of soft tissue tumors that are diagnostically challenging, due to their rarity, frequent lack of known genetic abnormalities, and, because of their expression of muscle markers, may be easily confused with neoplasms with myogenic differentiation.

Fibrous hamartoma of infancy

Fibrous hamartoma of infancy (FHI) is a benign superficial soft tissue tumor occurring predominantly in newborns and in infants aged less than two years. It appears as a rapidly growing nodule localized in the dermis and extending into the subcutaneous tissues, rarely appearing adherent to muscle or fascia. The axilla, shoulders and inguinal region represent the most frequent localizations of FHI, whereas this tumor has never been reported in hands and feet. The histological picture of FHI is characterized by a triphasic pattern: i) stellate immature mesenchymal cells, sometimes embedded in a myxoid matrix; ii) fascicles of bland fibroblasts and myofibroblasts in a fibrocollagenous matrix; iii) mature adipocytes (**Fig. 1**). Scattered lymphocytes are frequently observed, in the absence of significant cellular atypia and of mitoses. A recent study carried out on 145 patients affected by FHI, revealed a broader histologic spectrum than previously reported. In particular, one quarter of cases of FHI were found to closely resemble giant cell fibroblastoma (GCF) and, in rare cases, the presence of 'sarcomatous' areas was detected [4]. FHI is generally considered a benign non-aggressive tumor, and recurrences are rare. Surgery is the mainstay of treatment, but since EGFR exon 20 insertion/duplication mutations have very recently been described, tyrosine kinase inhibitors may in theory be of use [5].

Fibromatosis colli

Fibromatosis colli (FC), also known as sternomastoid tumor of infancy, is the most common cause of congenital torticollis. Newborns present with a solid tumor in the region of the sternocleidomastoid muscle, associated with torticollis and facial asymmetry. FC represents the most common neck mass occurring in the perinatal period, and it has to be differentiated from other congenital space-occupying lesions in the cervical region. The growing mass is well delineated from the surrounding structures and, at color-coded Doppler sonography, the tumor shows a peculiar increased diffuse or focal perfusion [6]. Males are more frequently affected, FC being prevalently observed in the right side. Occasionally, bilateral cases have been reported. The histological picture of FC is characterized by interlacing fascicles of fibroblast-like spindle cells, producing abundant collagen that surrounds skeletal muscle cells. At high power, spindle cells show oval nuclei and pale eosinophilic cytoplasm, in the absence of atypia. Mitoses, if present, are rare. Given that more than 90% of neonates affected by FC undergo complete spontaneous resolution, a wait-and-see policy is recommended, and surgery is only seldom necessary.

Infantile digital fibroma/inclusion body fibromatosis

Infantile digital fibroma is a rare benign lesion that usually occurs during the first 2 years of life,
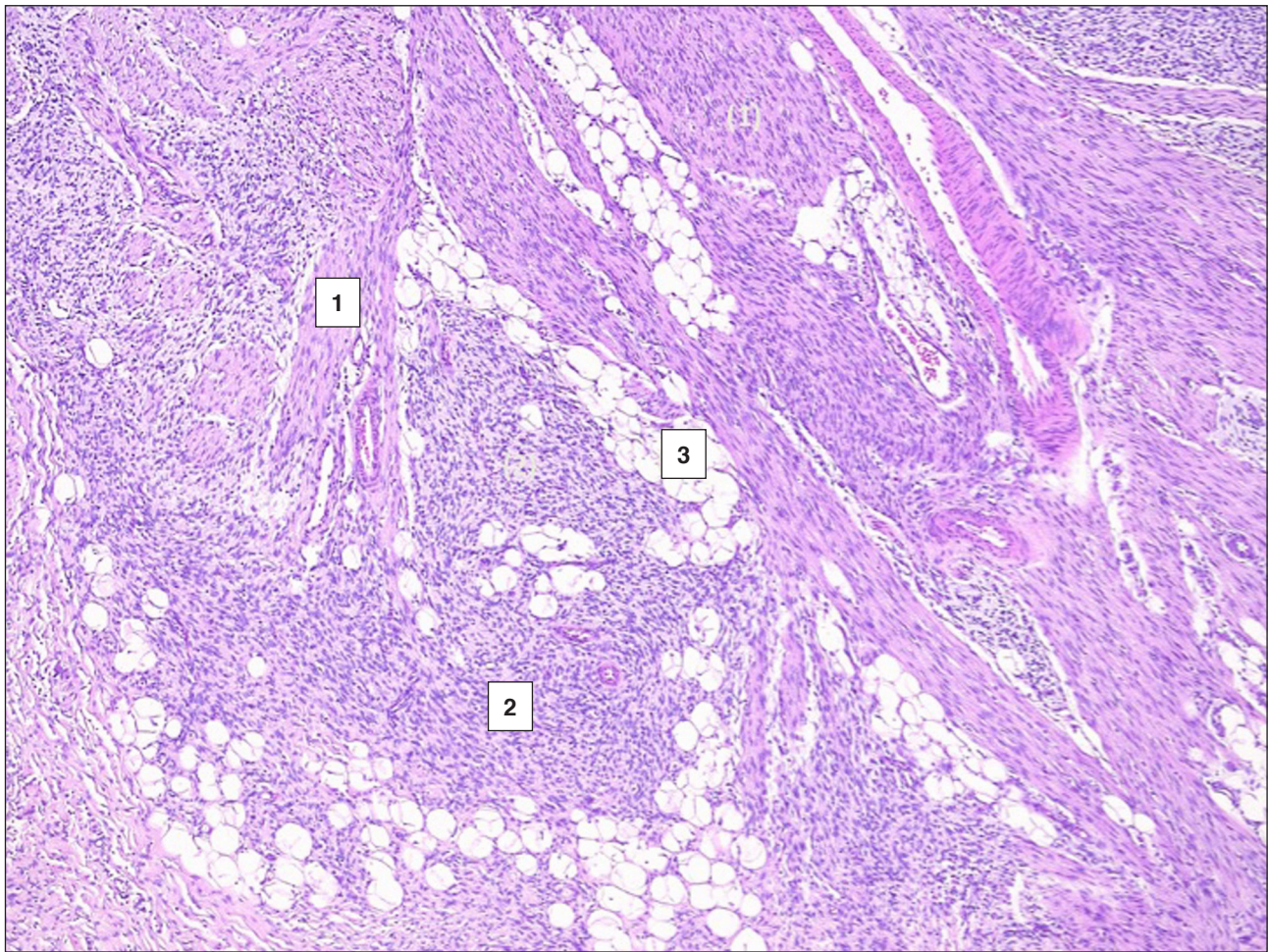
Figure 1. Fibrous hamartoma of infancy (FHI). Female, 8 months, subcutaneous tumor dorsal trunk. Low power view showing the (**1**) (myo)fibroblastic fascicles, (**2**) the immature mesenchymal cells, and (**3**) the mature fat.

presenting as a dome-shaped nodule on the finger/toe of infants. In about one third of cases, digital fibroma is congenital and is diagnosed at birth. It may also occur in non-digital sites: in that case, it is defined "inclusion body fibromatosis". It can be multiple, but it is usually a single nodule on the dorsal or lateral aspect of a finger. If it grows large enough, digital fibroma may extend to involve periosteum, causing joint deformities and rarely it may invade the underlying bone. The histological picture is characterized by a proliferation of bland fibroblast-like spindle cells organized in short interlacing fascicles embedded in a highly collagenized stroma. Spindle cells show oval nuclei and characteristic cytoplasmic eosinophilic inclusions (**Fig. 2**). These inclusions are better highlighted by a Masson stain, by which they appear as red globules. At immunohistochemistry, tumor cells are reactive for calponin and smooth muscle actin (SMA). Occasionally, immunoreactivity for h-Caldesmon, desmin and cytokeratin has been reported. The clinical evolution is characterized by complete resolution in 90% of patients. Given the

frequent spontaneous regression of the nodules, treatment for this entity is usually watchful waiting, but excision is recommended if the lesion becomes symptomatic [7]. Local recurrences after excision are frequent, being reported in 60 up to 90% of cases.

Desmoid fibromatosis of childhood

Desmoid fibromatosis (DF) is frequently diagnosed in the first two years of life, about 10% of cases presenting at birth and 24% being diagnosed within the first year after birth. Recently, DF of childhood has been included in the low-grade non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), a peculiar group of tumors typically occurring in children [8]. DF of childhood is generally considered an intermediate tumor, due to its tendency toward local recurrences after resection because of its infiltrative growth and frequent entrapment of vital structures. DF mainly occurs in the trunk, head and neck, followed by shoulder and extremities. The usual clinical presentation of DF of childhood
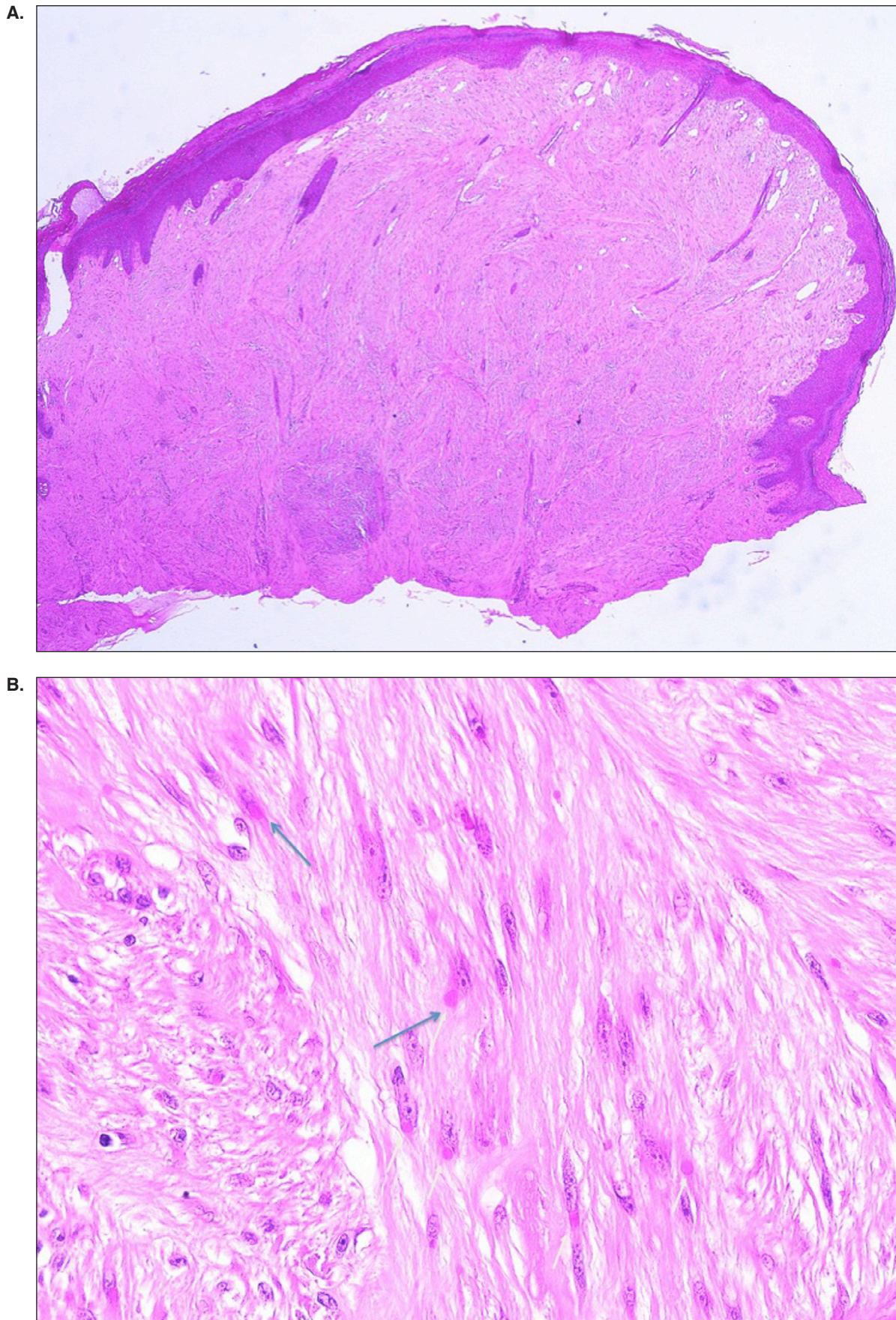
Figure 2. A. Infantile digital fibroma. Boy, 1-year-old, exophytic lesion on finger. Note the dome-shaped aspect and the fascicular proliferation. **B.** High power shows the bland myofibroblast type cells and the characteristic cytoplasmic eosinophilic globular inclusions (arrows).

is a slowly growing mass that may reach 15 cm in diameter and infiltrates adjacent muscles and bones. The histological picture is characterized by bland uniform spindle cells organized in fascicles, with abundant collagenous or myxoid matrix, and with thin elongated blood vessels (**Fig. 3A**). The prominent fascicular architecture, associated with the finding of a delicate vascular network at the edges of the fascicles, represents a peculiar histological clue of DF. Scattered mast cells and calcifications are often present. At immunohistochemistry, nuclear reactivity for beta-catenin has been reported in in about 70% of cases, and represents a typical marker of all DFs (**Fig. 3B**). Genetic changes in DF include trisomy of chromosomes 8 and 20, and mutations of the APC or Beta-catenin gene. The clinical course of DF of childhood is characterized by a favorable prognosis, with recurrences in one out of five patients. A small percentage of patients, less than 10%, show an aggressive clinical course, characterized by a high recurrence rate [9]. In more aggressive cases, radiotherapy has been proposed in recent years as a useful tool for the management of this tumor entity [10]. Negative prognostic signs are very young age at clinical presentation, nuclear reactivity of tumor cells for beta-catenin and p53 protein, mesenteric location, association with mutation of the APC gene and Gardner syndrome. Considering the variable clinical presentations, the multiple anatomic locations and the unpredictable biological behavior, an individualized treatment approach has been suggested by a recent European consensus of the Desmoid Working group [11].

Gardner fibroma

Gardner fibroma is a benign hypocellular fibrous tumor, which may be sporadic but is associated with Gardner syndrome/familial adenomatous polyposis (FAP) in 80% of cases [12]. The triad of extra-abdominal soft tissue fibroma(s), osteomas, and dental abnormalities in patients with familial adenomatous polyposis has been named Gardner syndrome. 30% of patients present in the first year of life and, rarely, Gardner fibroma may be diagnosed at birth [13]. It appears as a poorly demarcated fibrous tumor, mainly occurring in the paraspinal region, abdominal wall, trunk, head and neck, and extremities. At histology, Gardner fibroma is characterized by sheets of dense collagen fibers separated by clear clefts, with embedded scattered bland spindle cells and mast cells. Islands of mature adipocytes are often observed entrapped within the collagen bundles (**Fig. 4**). At immunohistochemistry, spindle cells show diffuse reactivity for CD34, whereas nuclear reactivity for beta-catenin is found in 70% of cases. About half of these lesions recur as desmoid tumors and the diagnosis of Gardner fibroma should be considered a possible sentinel lesion of previously unrecognized FAP families.

Juvenile hyaline fibromatosis

Juvenile hyaline fibromatosis (JHF) is an extremely rare recessive disorder with the formation of pseudotumoral masses in skin, gingiva, joints and bones, usually in infants. JFH may present within the first year of age, with a characteristic stiffness of the knees and elbows associated with papules on the paranasal folds, periauricular and perianal regions [14]. JHF is caused by inactivating mutations in the ANTXR2 gene, leading to dysregulation of basement membrane homeostasis. On histology, the lesions consist of plump fibroblasts embedded in a prominent eosinophilic hyaline material (**Fig. 5**). Recurrences and de novo lesions are frequent and can lead to deformity and dysfunctions. The disease has a relentlessly progressive course, with most patients surviving only up to the 4th decade, and, at the best of our knowledge, there is no specific treatment for this disorder. Recently, JHF has been included in the spectrum of the hyaline fibromatosis syndrome (HFS), with infantile systemic hyalinosis (ISH) being the severe form and JHF representing the milder form [15].

Fibrous umbilical polyp

Fibrous umbilical polyp is a distinctive lesion of early childhood with an uncertain pathogenesis. In the majority of patients, it is diagnosed in the first year of age, ranging from 3 up to 18 months. A male predominance, over 90%, has been reported. At clinical examination, the fibrous umbilical polyp appears as a well-circumscribed dome-shaped or pedunculated nodule. At histology, it is characterized by a dermal proliferation of moderately cellular fibrous tissue without significant inflammation (**Fig. 6A**). Fibroblastic cells are plump to elongate with abundant pale eosinophilic cytoplasm (**Fig. 6B**). In a subset of lesions, some cells show mild atypia or ganglion cell-like morphology. Vascularity is sparse and the lesions are non-encapsulated. Hyperkeratosis is commonly observed in the overlying epidermis. At immunohistochemistry, focal staining for muscle-specific actin and desmin is observed in a subset
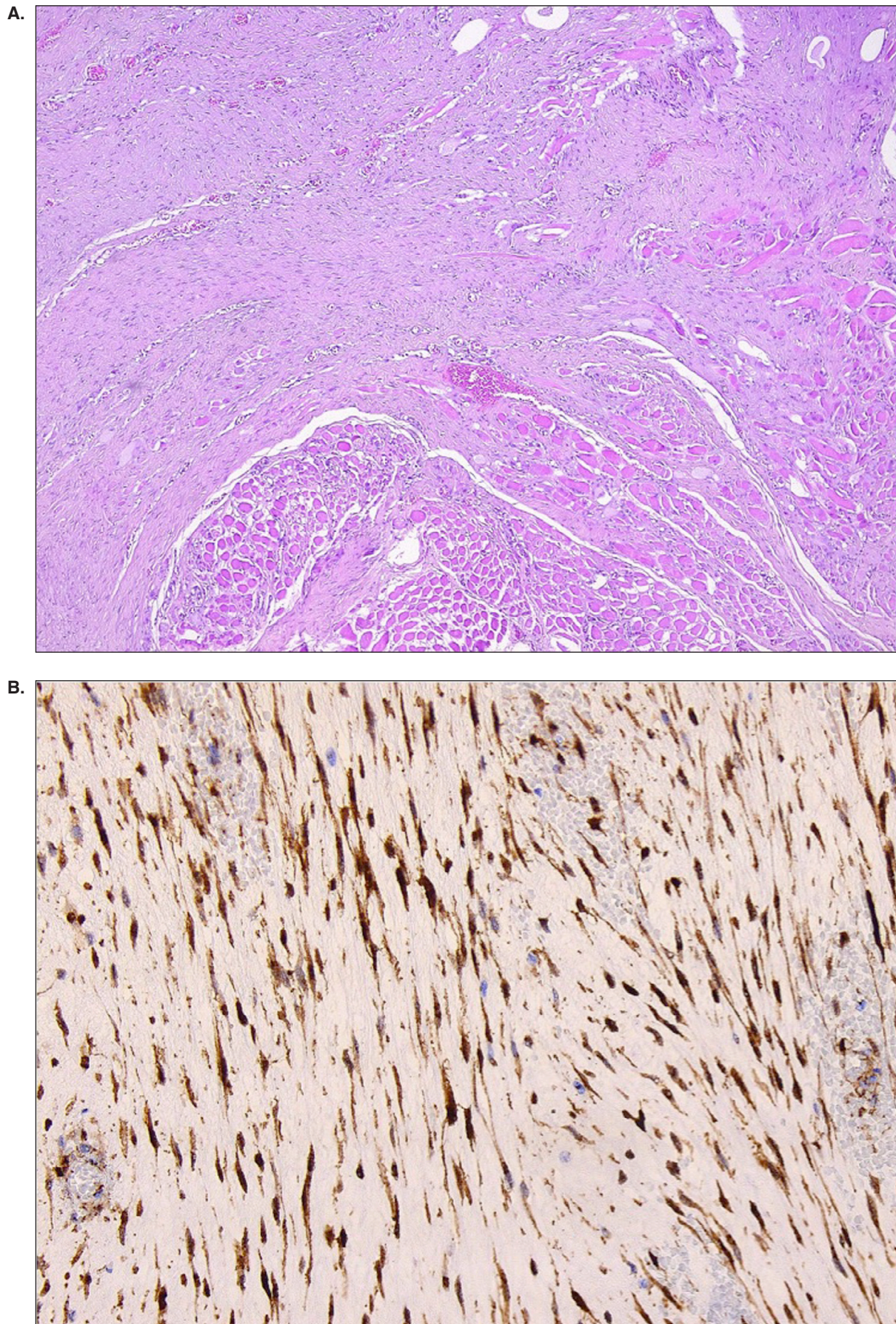
Figure 3. A. Male, 3 years, tumor leg. Note the moderately cellular fascicular tumor, infiltrating into the skeletal muscle, typical for desmoid tumor. **B.** Nuclear and cytoplasmic beta-catenin staining in desmoid tumor.
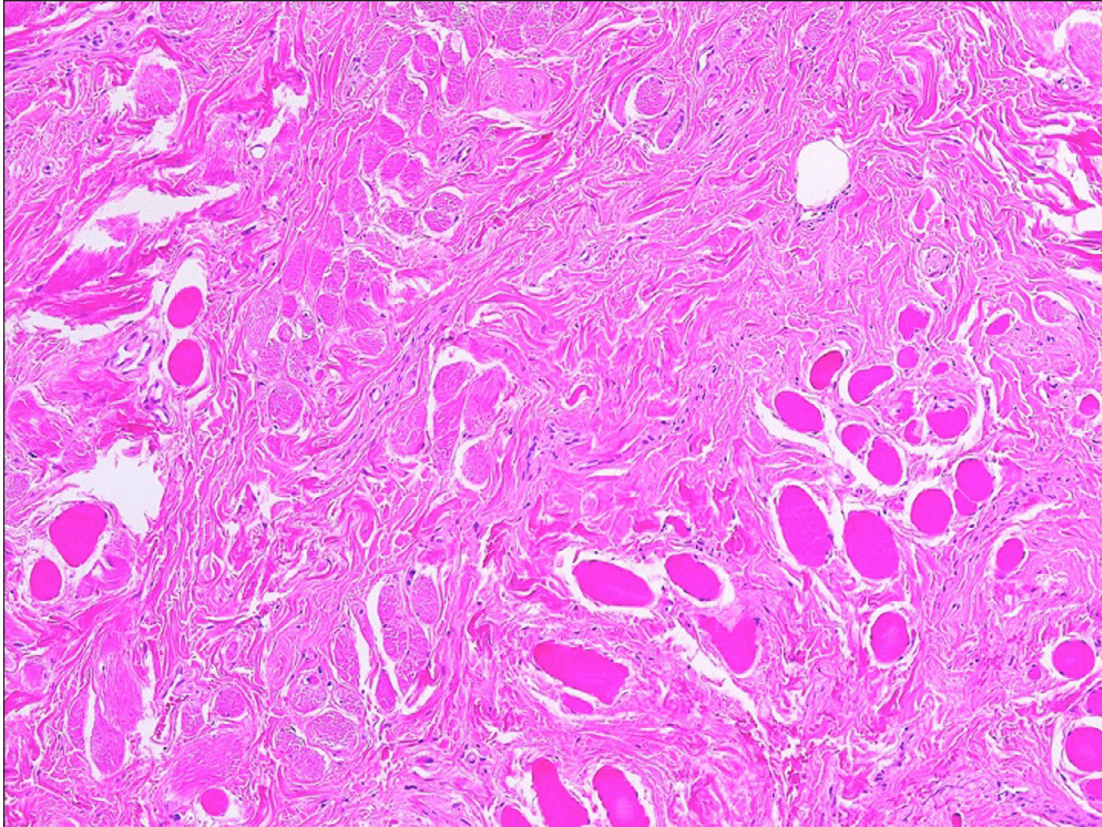
Figure 4. Female, 11 years, axillary lesion. This Gardner fibroma shows a hypocellular, collagen-rich aspect with infiltration into the muscle.
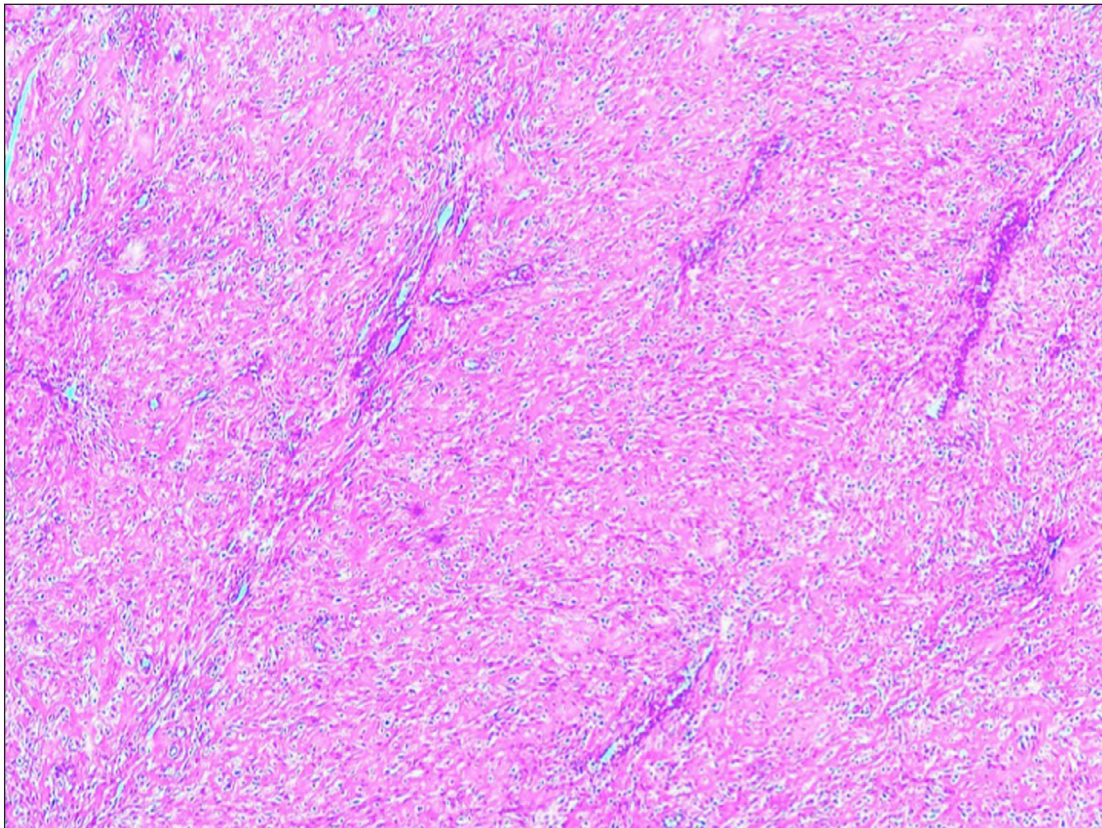

Figure 5. 2-year-old male with cheeck and gingival hypertrophy. Plump fibroblasts in a uniform non-fibrillar eosinophilic hyaline background characterize juvenile hyaline fibromatosis (JHF).
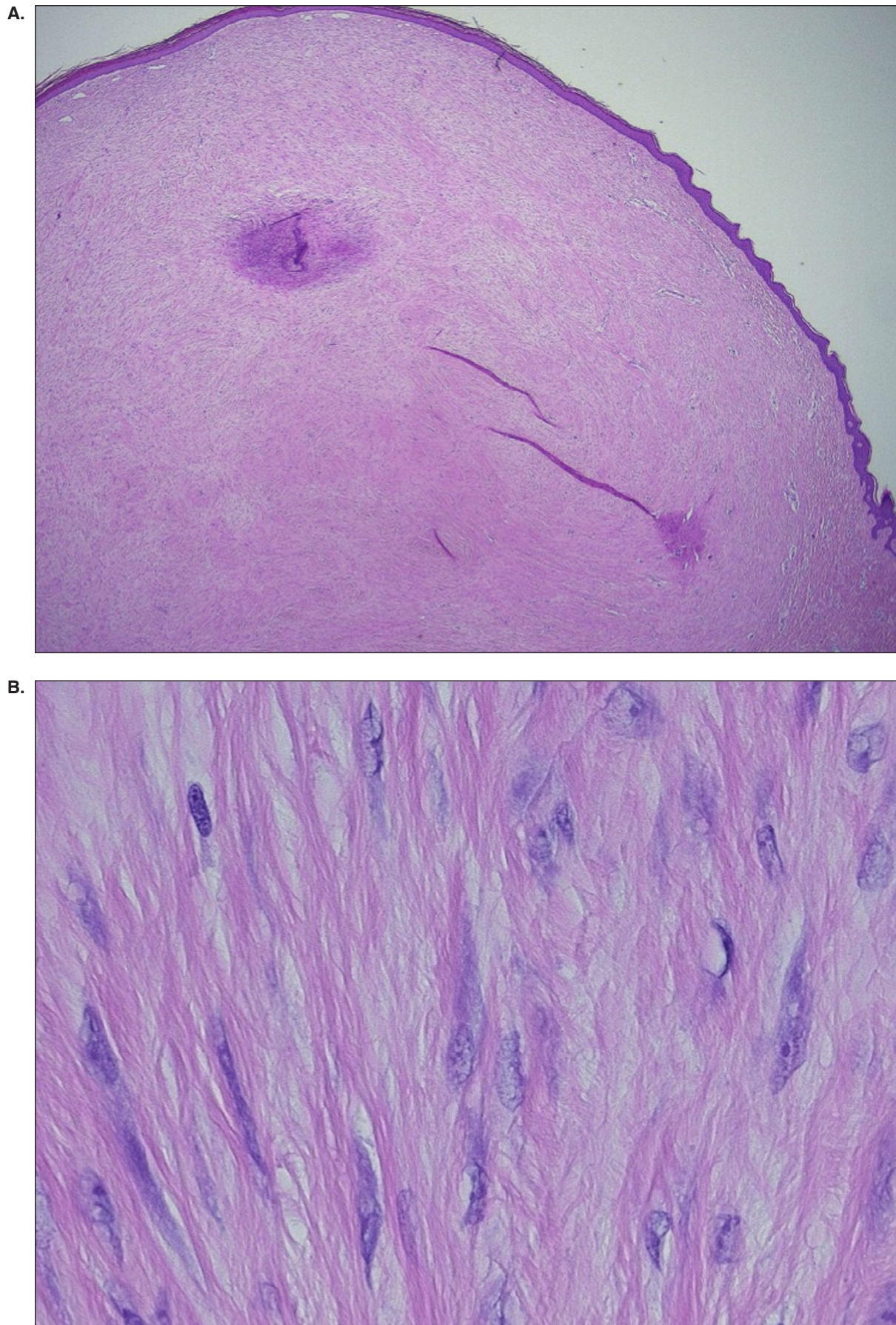
Figure 6. A. Female, 1-year-old, polypoid lesion of umbilicus. Fibrous umbilical polyp, presenting as a moderately cellular dome-shaped lesion. **B.** At higher power, non-atypical myofibroblast-type cells are seen.

of cases. The lesion has a benign course, and no recurrence has been reported after excision [16].

Lipofibromatosis

Lipofibromatosis (LPF) is a poorly circumscribed slow-growing fibro-fatty neoplasm, prevalently occurring in the hands, where it is occasionally associated with macrodactyly, in limbs and feet. LPF may be congenital and present soon after birth with diffuse lower extremity enlargement associated with significant tibial deformities [17]. LPF may also occur later in life, before 12 years of age. The histological picture is characterized by lobules of adipocytes surrounded by fibrous fascicles in which spindled fibroblasts and myofibroblasts are observed (**Fig. 7**). Cytological atypia and mitoses are absent in the majority of cases. At immunohistochemistry, spindle cells may show focal reactivity for alpha-SMA, CD34, CD99 and bcl-2, whereas desmin immunostaining is absent. The clinical course of classical LPF is characterized by frequent recurrences, occurring in more than 60% of cases. The high rate of recurrences is associated with early diagnosis, incomplete excision and high number of mitoses in the spindle cells of the fibrous fascicles. Recently, a novel soft tissue tumors resembling LPF, but displaying cytologic atypia and a neural immunophenotype, has been defined lipofibromatosis-like neural tumor (LPF-NT). The new entity is characterized by a superficial location, occurrence in children and young adults, by a notably infiltrative growth pattern reminiscent of LPF and a distinct immunoprofile of S100 protein and CD34 reactivity, suggestive of neural differentiation. The vast majority of LPF-like neural tumors were characterized by TPR-NTRK1 and TPM3-NTRK1 gene fusions, which were further validated by fluorescence *in situ* hybridization (FISH), that identified recurrent NTRK1 gene rearrangements in more than 70% of cases, leading to NTRK1 oncogenic activation [18].

Giant cell fibroblastoma

GCF is a superficial dermal tumor typical of young boys younger than 10 years. It may occur in multiple sites, but GCF shows a preferential location in trunk and limbs. The tumor is included in the group of soft tissue tumors of intermediate malignancy, due to the high rate of recurrences (50%) after surgical excision, in the absence of distant metastases. The histological picture is characterized by the proliferation of pleomorphic spindle cells, with hyperchromatic nuclei, embedded in a myxoid or fibro-myxoid stroma. Cellularity may change from a field to the next, showing hypercellular zones adjacent to hypocellular, characterized by a more abundant hyalinized fibrous stroma. A typical histological finding in GCF is the presence of irregular-shaped pseudovascular structures lined by giant or mononuclear cells. Margins are typically infiltrative and tumor cells often invade the subcutaneous tissue, encircling and dividing adipocytes. (**Fig. 8**). The immunohistochemical panel useful for the diagnosis of GCF is restricted to CD34, highly expressed by the vast majority of tumor cells, whereas other endothelial markers and S100 protein are negative. t(17;22), involving the COL1A1 and PDGFB genes, represents the typical cytogenetic marker of GCF. As such it is related to dermatofibrosarcoma protuberans (DFSP), and hybrid cases or recurrences looking like DFSP have been described. Recently, GCF has been reported in a young patient affected by Kabuki syndrome, a genetic condition characterized by distinctive facial phenotype, mental retardation, and internal organ malformations.

Cranial fasciitis

Cranial fasciitis (CF) is a rare variant of nodular fasciitis that occurs mostly in children below 6 years [19]. The average age of onset is 2 years. CF mainly occurs in males, with a M/F ratio 2:1. The lesion is preferentially observed in the cranial region. Clinically, CF usually presents as a rapidly growing solitary and painless nodule. The etiology of CF is still unknown, but it is thought to be a reactive proliferative process. CF has been reported to arise from the deep fascia, periosteum or from the fibrous layers that cover fontanelles and cranial sutures. At CT scan, the lesion appears osteolytic involving both the inner and outer tables of bone with a soft tissue component. The histological picture of CF is very similar to nodular fasciitis in adults. It is characterized by the proliferation of spindled to ovoid cells arranged in short fascicles giving rise to a storiform or a nodular pattern. The cellular areas are mixed with loose areas, characterized by a myxoid background in which stellate and spindle cells are embedded, as well as erythrocytes and lymphocytes, resulting is a tissue culture-like appearance. Mitotic figures are often frequent but not atypical. At immunohistochemistry, the proliferating myofibroblastic cells show reactivity for SMA, in the absence of any significant immunostaining for desmin, S-100 protein, CD34 and epithelial membrane antigen (EMA). Regarding the therapeutic approach to CF, a "watch and wait"
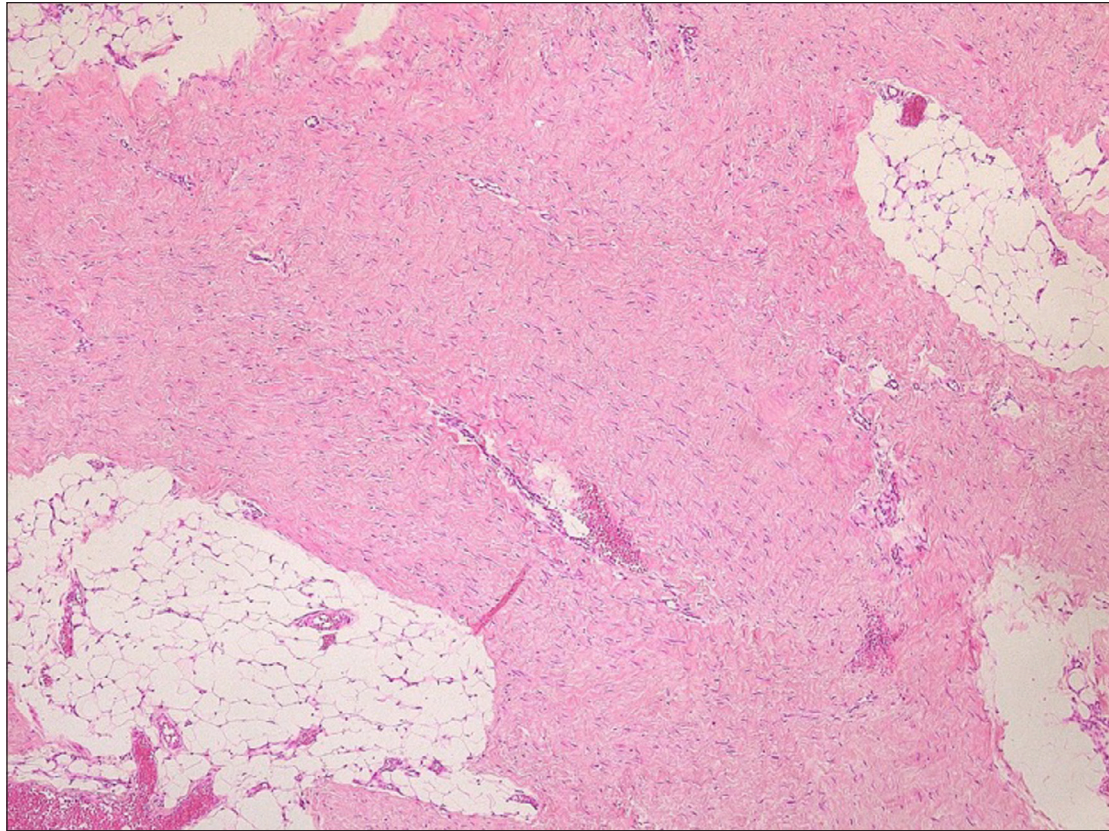
Figure 7. 2-year-old boy, tumor of the abdominal wall. Lipofibromatosis (LPF), consisting of mature fat and desmoid-like fascicles of spindle cells.
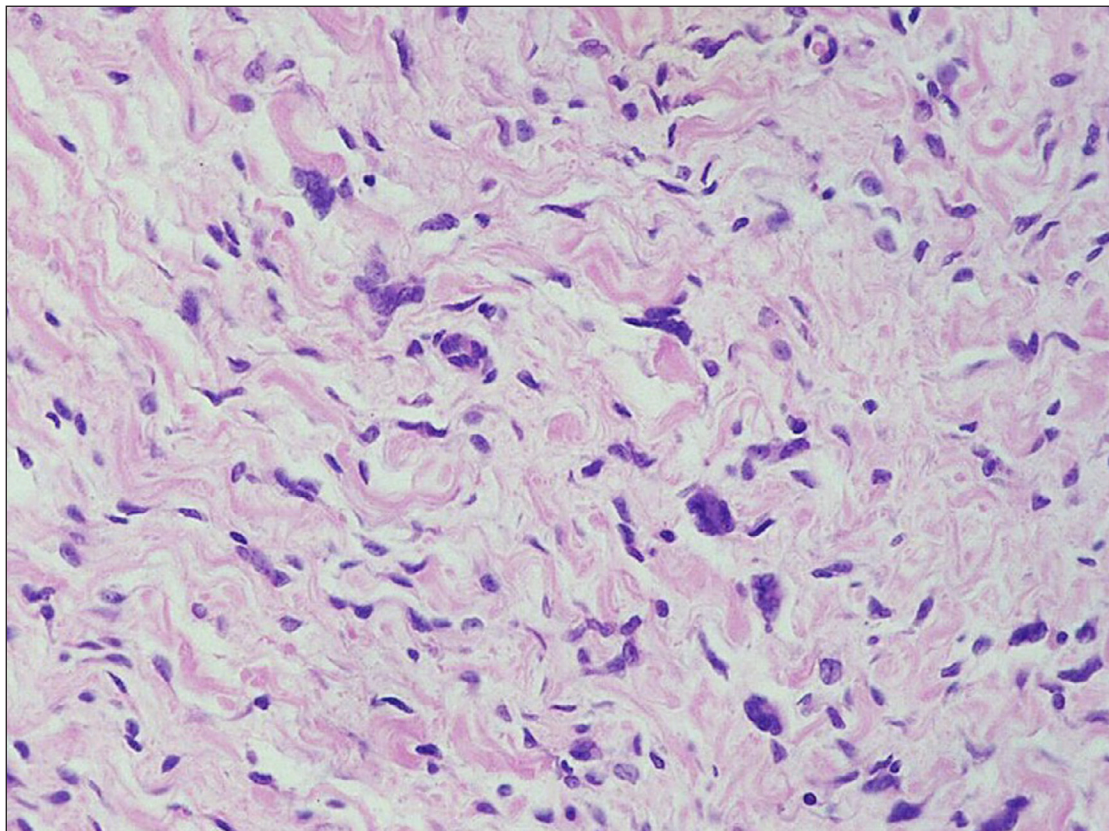

Figure 8. Boy, 7-year-old, trunk. Detail of a giant cell fibroblastoma (GCF), showing the typical pseudovascular clefts delineated by multinucleated giant cells.

approach might be appropriate and recommended, given that spontaneous regression may occur. If not, surgical resection can be performed. Recurrences are very rare. In recent years, intralesional injection of corticosteroids has been demonstrated to cause rapid and complete resolution of CF.

Congenital/infantile fibrosarcoma

Infantile fibrosarcoma (IF) is a soft tissue tumor occurring in the first year of life, 50% of cases being congenital and diagnosed at birth [20]. IF is a member of pediatric NRSTS, a heterogeneous group encompassing more than 50 different histological diagnoses arising from primitive mesenchymal tissue [21]. Clinically, IF presents as a rapidly growing mass, mainly localized in the distal extremities, head and neck, and trunk. On initial clinical presentation, IF can mimic an infantile hemangioma [22]. The neoplasm may reach a large size and, when localized in the head, its appearance may be alarming. At histology, IF is characterized by the proliferation of spindle cells organized in interlacing fascicles, giving rise to the typical herringbone pattern (**Fig. 9**). Tumor cells may also show a round cell pattern, associated with branching vessels, originating a hemangiopericytoma-like pattern. The myxoid variant of IF is characterized by immature stellate, spindle or round cells surrounded by a myxoid matrix. Foci of intratumoral coagulative necrosis are frequently found. On immunohistochemistry, some SMA expression can be found. The most frequent cytogenetic abnormalities observed in IF is t(12;15), resulting in the ETV6-NTRK3 fusion gene, and ETV6 rearrangement. The recent report at ASCO 2017 by Hyman DM (oral presentation) suggesting the activity of larotrectinib, a selective tropomyosin receptor kinase inhibitor targeting tumor cells with NTRK3 fusions, might represent an intriguing novel potential therapeutic options in children affected by IF. After excision, IF appears as a neoplasm of intermediate biological potential: the recurrence rate
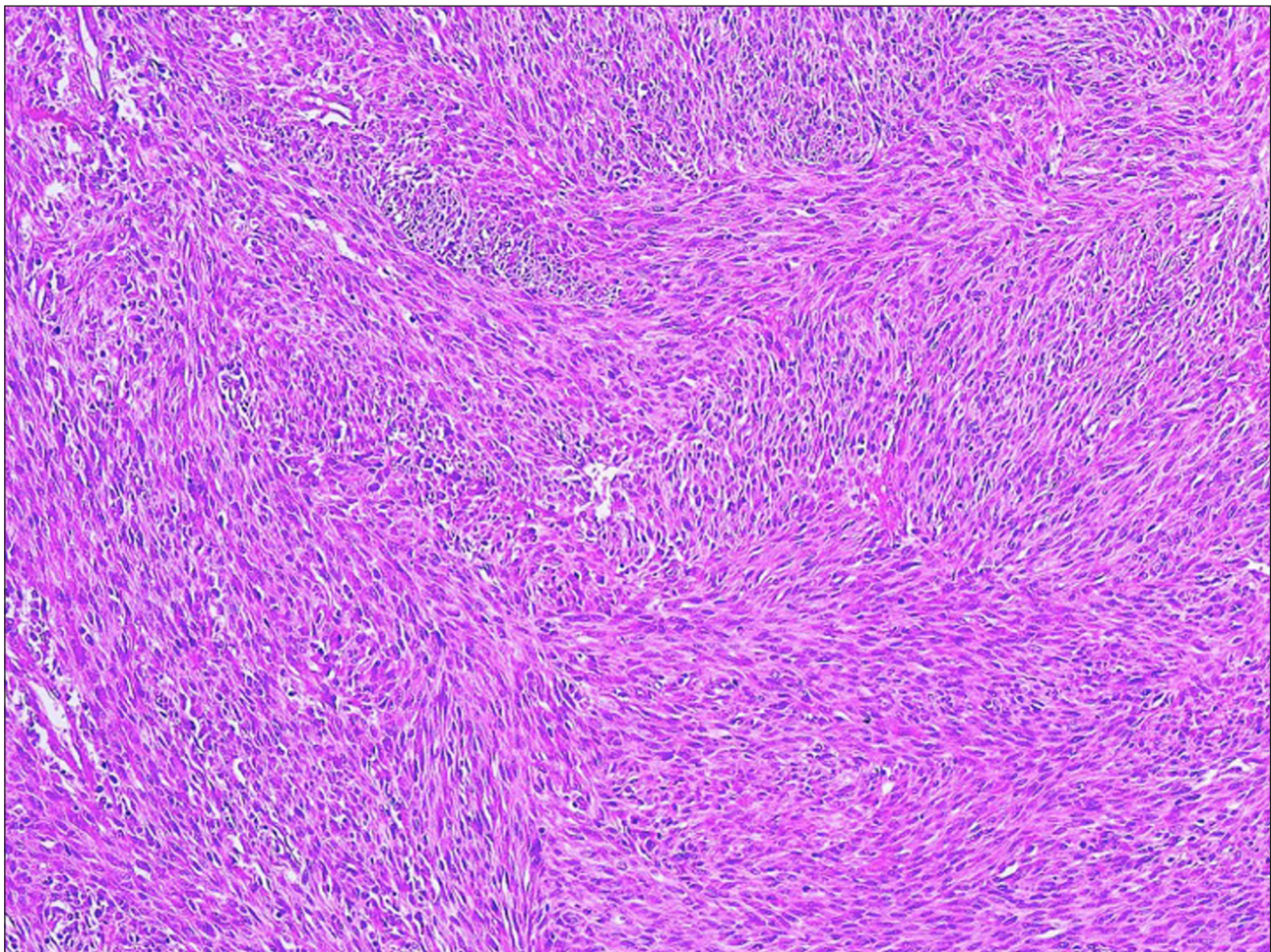

Figure 9. 9-month-old boy, tumor on scalp. Note the typical herringbone pattern as seen in congenital/infantile fibrosarcoma (IF).
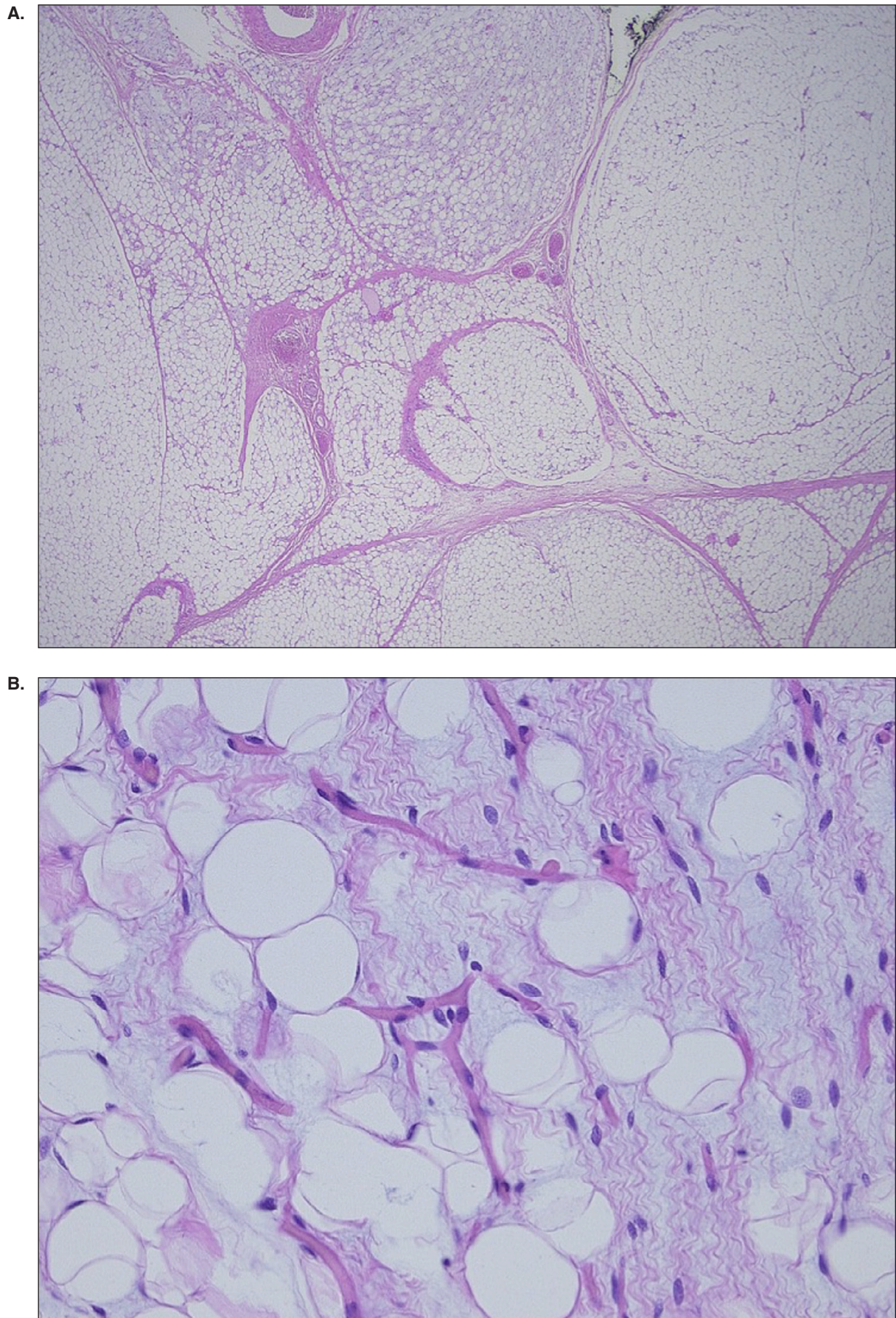
Figure 10. A. 3-year-old boy, tumor in neck. Lipoblastoma is characterized by a lobular growth pattern. **B.** At high power, a "crow's feet" like branching vascular pattern and a myxoid background can be seen as in myxoid liposarcoma.

is about 30%, metastases are rare and the overall survival at 5 years is about 90%.

Fatty tumors

Lipoblastoma

Lipoblastoma is an adipocytic benign nepoplasm, mainly occurring in the first three years of life, presenting as a well demarcated slowly growing tumor most frequently localized in the trunk and extremities [23]. Rarely, lipoblastoma may arise in the mesentery, presenting as a small intestinal volvulum with non-biliary vomiting [24]. The histological picture of lipoblastoma is characterized by a lobular pattern, with nodules of adipocytes surrounded by fibrous septa (**Fig. 10A**). Lipoblasts, immature spindle adipocyte precursors and mature adipocytes characterize the cytological picture. A myxoid stroma and a plexiform vascular pattern may be present, thus mimicking myxoid liposarcoma (**Fig. 10B**). The immunohistochemical pattern is characterized by diffuse reactivity for S100 protein. Typical genetic changes detected in lipoblastoma are rearrangements of the long arm of chromosome 8, the 8q11-13 region, resulting in two fusion genes, HAS2/PLAG1 and COL1A2/PLAG1. When the tumor occurs as a diffuse proliferation, the lesion is defined lipoblastomatosis, that differs from lipoblastoma for its infiltrative growth pattern, and for recurrences occurring in about 15% of cases.

Skeletal muscle tumors

Fetal rhabdomyoma

Fetal rhabdomyoma (FRM) is a soft tissue tumor that typically arises in children and young adults (median age 4 years) with a peculiar prevalent localization: the postauricular region. Less frequently, FRM may be localized in the trunk, hands, feet, larynx and in the anal region. Rarely, FRM may originate from the tonsils, presenting with a polyp-like appearance [25]. The histological picture is characterized by the finding of multiple cell types, including stem/progenitors, which represent the different stages of development of skeletal muscle cells. Immature spindle muscle cell precursors (**Fig. 11A**), often showing an eosinophilic eccentric cytoplasm and cross-striations, appear often embedded in an abundant myxoid matrix (**Fig. 11B**). Myotubes are often detected. Nuclei are bland, in the absence of significant atypia, and mitoses are very rare. At immunohistochemistry, tumor cells show strong and
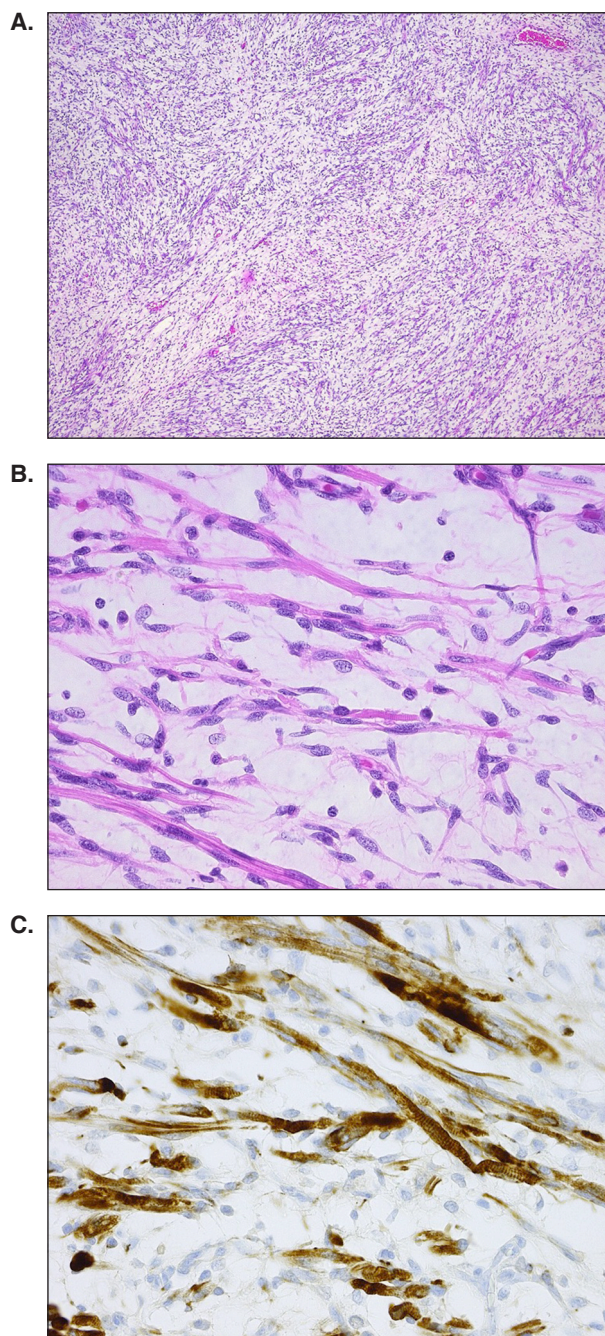
Figure 11. A. Male, newborn, 9 cm subcutaneous mass in neck. Low power view of fetal rhabdomyoma (FRM) showing the myxoid and spindle cell appearance. **B.** At high power, clear-cut skeletal muscle differentiation can be seen, including cross striations. **C.** FRM. Desmin expression highlights the cross striations.
Courtesy of Louis Libbrecht, Université Catholique de Louvain, Belgium.

diffuse reactivity for desmin (**Fig. 11C**) and muscle-specific actin. Focal immunostaining for myogenin is often detected in differentiated rhabdomyoblasts. The clinical course is benign, in spite of uncommon local recurrences. Mutations in the Hedgehog pathway have been reported in FRM, suggesting a role for Hedgehog signaling activation in the origin of this rare

striated muscle-type soft tissue tumor of childhood [26]. Recently, using a monoclonal antibody specific for the cardiac isoform of alpha-actin (alpha-CA), extracardiac rhabdomyomas showed a focal mild reactivity, contrasting with the abundant expression of alpha-CA in cardiac rhabdomyomas. This finding suggested the hypothesis of a different cell of origin for soft tissue and cardiac rhabdomyomas [27].

Embryonal rhabdomyosarcoma

Rhabdomyosarcoma (RMS), a tumor of striated muscle, is the most common sarcoma of soft tissues diagnosed in children aged 0 to 14 years, accounting for 50% of tumors in this age group. Embryonal RMS is more frequent in early childhood, the typical presentation ranging from 3 to 12 years, whereas alveolar RMS usually arises between 10 and 25 years. Head and neck, genitourinary tract, liver, retroperitoneum, nasopharynx, orbit, oral cavity and ear are generally considered the most frequent sites of insurgence of embryonal RMS. Typicallly, it presents as a polyp originating beneath the mucosa in the nose, upper respiratory tract, bladder or vagina. Rarely, embryonal RMS may arise in the liver in children, showing a cystic appearance that may lead to a wrong diagnosis of hydatic cyst [28]. At histology, the conventional variant of embryonal RMS appears as a round/spindle cell sarcoma, characterized by an abundant myxoid matrix. Tumor cells show the tendency to condensate around vascular structures. Occasionally, spindle tumor cells with abundant eosinophilic fibrillary cytoplasm and cross-striations are detected. Large atypical cells, with polymorphic large atypical nuclei, may be observed in embryonal RMS (**Fig. 12A**). The botryoid variant is characterized by a cambium layer underneath the mucosal surface (**Fig. 12B**). In the anaplastic variant, many very atypical cells and mitotic figures are present, and heterologous chondroid differentiation can be seen (**Fig. 12C**). At immunohistochemistry, tumor cells are reactive to desmin, muscle-specific actin and myogenin (Myf4), a nuclear transcription factor highly specific for skeletal muscle cells (**Fig. 12D**). Nuclear expression of
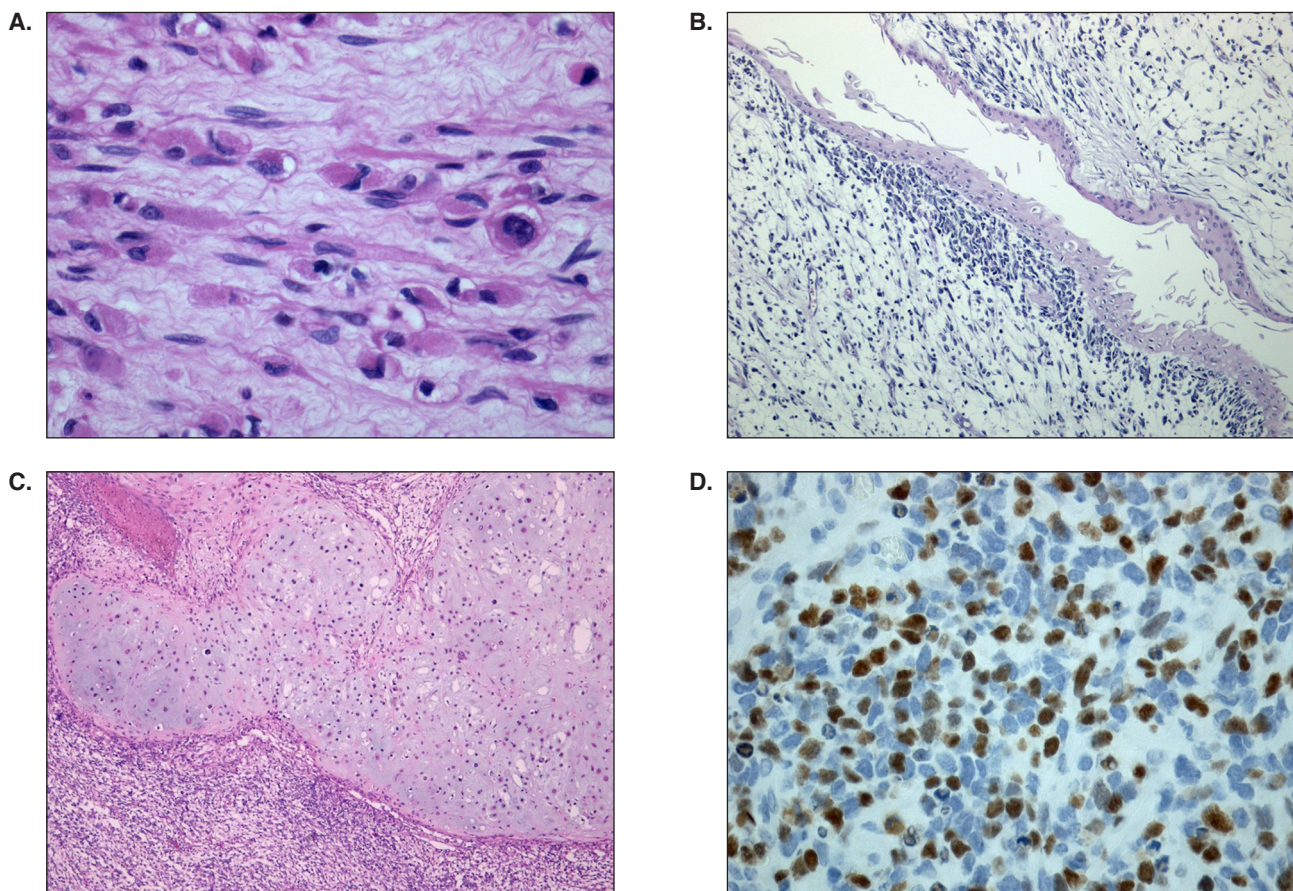
Figure 12. A. 10-year-old boy, bladder tumor. Detail of an embryonal rhabdomyosarcoma (RMS), showing rhabdomyoblasts with atypical nuclei. **B.** 6-year-old girl, tumor in pharynx. Note the cambium layer in this botryoid variant of embryonal RMS. **C.** 10-year-old boy, tumor in retroperitoneum. Anaplastic embryonal RMS with heterologous cartilage differentiation. **D.** Nuclear myogenin expression in embryonal RMS.
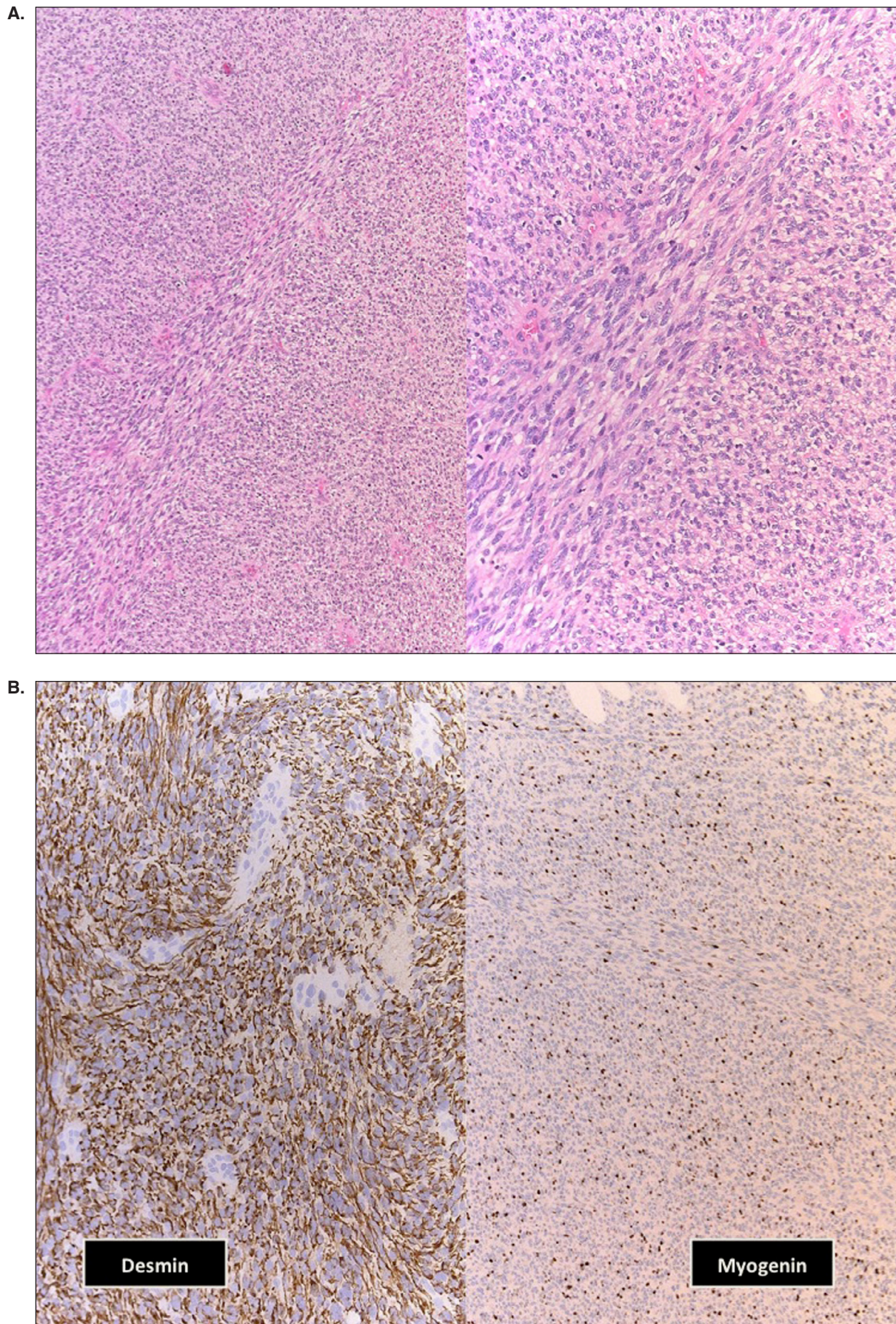
Figure 13. A. 4-year-old girl, tumor on the back. Spindle cell rhabdomyosarcoma (RMS) with long fascicles, mimicking infantile fibrosarcoma (IF). **B.** Tumor cells stain for desmin and myogenin.
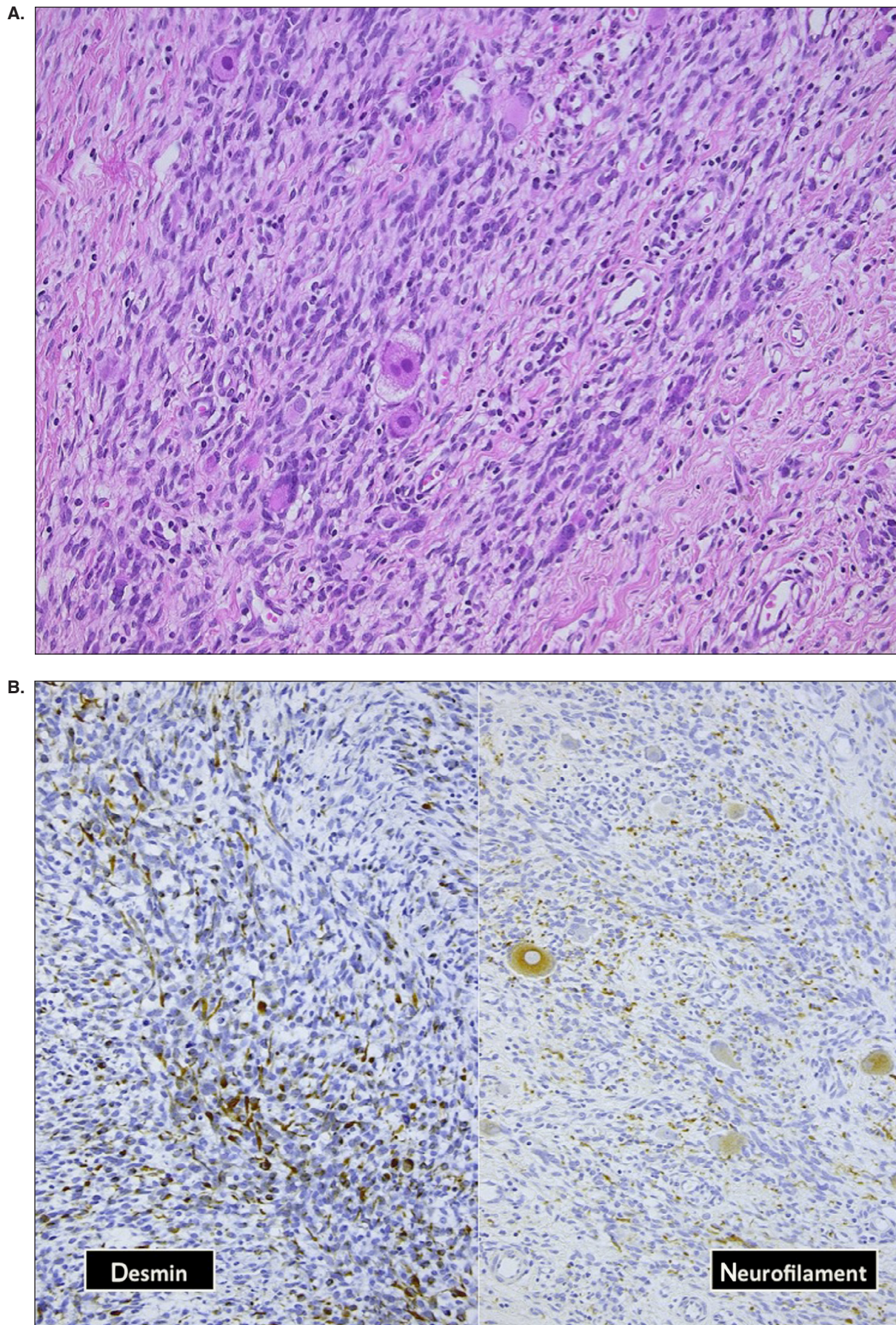
Figure 14. A. Ectomesenchymoma. Male, 8 months, paratesticular mass: fascicles of atypical spindle cells admixed with ganglion cells. **B.** Tumor cells stain for desmin and for neurofilament.

myogenin in embryonal RMS is often less prominent than in the alveolar subtype. Numerical chromosomal changes are frequent in embryonal RMS. Recently, embryonal RMS has been reported in association with DICER1 syndrome, a pediatric cancer predisposition condition causing a variety of tumor types in children and young adults [29]. The prognosis is influenced by the stage, the type, the site and the age at presentation. The botryoid variant has a superior outcome (> 90% survival), the anaplastic subtype a worse outcome (± 45% survival) versus the classical type (± 70% survival). Children between 1 and 9 years have better outcomes and the orbital and genitourinary ones do better. A multidisciplinary approach combining chemotherapy, surgery and selectively radiotherapy has proven successful in the treatment of maxillofacial RMS [29].

Spindle cell RMS

The spindle cell variant of RMS is now considered to be a separate entity, and the one that occurs in children is most often seen in the paratesticular/head and neck region in young children (< 10 years) and adolescents [30]. Males are more affected than females. The histological picture of spindle cell RMS is characterized by long intersecting fascicles of eosinophilic spindle cells, resembling leiomyosarcoma and IF (**Fig. 13A**). Rhabdomyoblasts are usually rare. The immunohistochemical pattern is charcterized by reactivity of spindle cells for muscle-specific actin, desmin and myogenin (**Fig. 13B**). At the genetic level, NCOA2 or VGLL2 gene rearrangements have recently been described. MYOD1 (L122R) mutations are associated with spindle cell and sclerosing RMSs with aggressive clinical outcomes [31, 32]. The overall prognosis is good (5 year survival > 90%).

Malignant ectomesenchymoma

Malignant ectomesenchymoma (MEM) is a rare pediatric mixed sarcoma composed of an RMS, usually of the embryonal type, and a neuroectodermal component showing differentiation towards ganglion cells, ganglioneuroma, ganglioneuroblastoma or neuroblastoma (**Fig. 14**). Rarely, areas of ependymoma and/or astrocytoma have been reported in MEM [33]. MEM is generally believed to arise from pluripotent cell precursors migrating from the neural crest. It is seen in children under the age of 5. MEM frequently arises in the pelvic region [34]. After resection, recurrences are frequent as well as distant metastases. The genetic profile of MEM has been shown to reflect rhabdomyosarcomatous differentiation [35]. Recently, a close genetic link of MEM to embryonal RMS, resulting of common HRAS mutations and composite gene signature, associated with up-regulation of skeletal muscle and neuronal genes, has been reported [36].

Declaration of interest

The Authors declare that there is no conflict of interest.

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