



Differentiating between congenital rhabdomyosarcoma versus fibromatosis of the pediatric tongue

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ABSTRACT

Congenital rhabdomyosarcoma of the tongue is exceedingly rare. Fibromatosis of the tongue is also rare, and very difficult to distinguish from the spindle cell variant of rhabdomyosarcoma. Both appear histologically as spindle neoplasms replacing normal striated musculature of the tongue. The treatment protocol for the former has been developed by the Intergroup Rhabdomyosarcoma Studies (IRS) I–IV and requires surgery, radiation, and chemotherapy. For fibromatosis, complete surgical excision is usually adequate without additional therapy, although some cases of aggressive fibromatosis also require chemotherapy. With significant differences in appropriate treatment and prognosis, each entity must not be mistaken for the other. We review the differences in radiologic, histologic, and immunohistochemical (IHC) features of both entities.

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1. Introduction

Spindle cell neoplasms account for a unique subset of tumors which may be difficult to diagnose due to histologic similarities. The differential diagnosis in the pediatric population includes benign lesions such as fibromatosis, nodular fasciitis, rhabdomyoma, nerve sheath tumors such as schwannoma and neurofibroma, as well as malignant lesions such as fibrosarcoma, synovial sarcoma, leiomyosarcoma, hemangiopericytoma, and rhabdomyosarcoma (RMS) [1]. We present two cases of congenital spindle cell tumors of the tongue. By reviewing the radiographic, histologic and immunohistochemical (IHC) features of both cases, we will highlight the difficulty in distinguishing between fibromatosis and spindle cell rhabdomyosarcoma of the head and neck.

Case No. 1: A 3.3 kg, 40-week male infant was transferred from an outside hospital shortly after delivery for evaluation of a large, protuberant tongue mass (Fig. 1A). On presentation, the infant was breathing without difficulty despite the size of the tumor. MRI performed on day of life (DOL) 3 demonstrated a 6.3 cm ×

3.7 cm × 3.3 cm heterogeneous mass involving the entire oral and oropharyngeal tongue. The mass enhanced on both T2 and post-contrast T1 images (Fig. 1B and C). On DOL 4, the patient was taken to the operating room for incisional biopsy and tracheotomy. Frozen sections were consistent with a spindle cell neoplasm concerning for rhabdomyosarcoma (RMS). Permanent sections on histological examination revealed sheets of bland spindle cells that infiltrated and effaced the normal striated muscle of tongue (Fig. 2A and B). A few rhabdomyoblastic cells which were both rounded and elongated noted scattered within the spindle cell proliferation. These cells had bright cytoplasmic eosinophilia. However, there were far more numbers of entrapped native striated muscle fibers that showed atrophy and regeneration. IHC staining was patchy and weak for desmin, and negative for CD34 and S-100. There was patchy, but strong nuclear staining for MyoD1 and myogenin (Fig. 2C). Desmin and actin HHF35 were weakly positive in several tumor cells. The tumor was classified as RMS, spindle cell variant. The case was reviewed by Children's Oncology Group (COG) Rhabdomyosarcoma review committee and their review, concurred with the institutional RMS spindle cell variant diagnosis. The infant was subsequently started on vincristine, doxorubicin and cyclophosphamide per the ARST0331 protocol without radiation. Unfortunately, the tumor was minimally responsive to this regimen, and he was switched to COG protocol ARST0431 for additional 6 months. The child has

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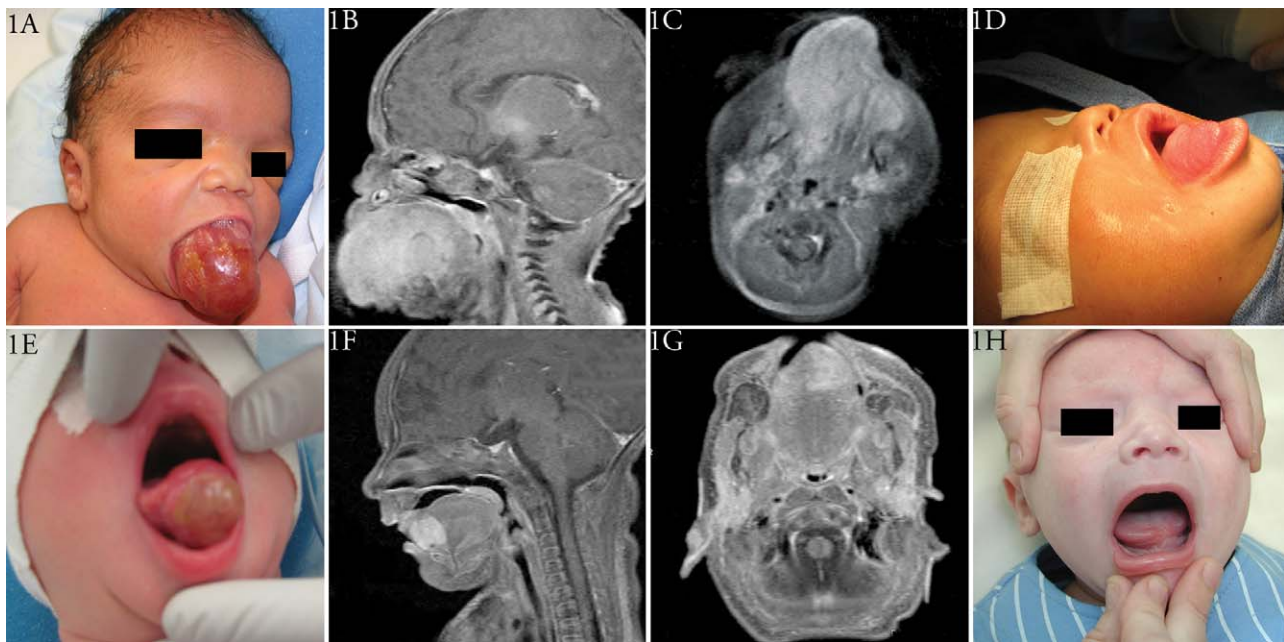


Fig. 1. (A) Case 1 spindle cell rhabdomyosarcoma, clinical pre-operative photo. (B) Case 1 T1-weighted post-contrast MRI, sagittal view. (C) Case 1 MRI, axial view. (D) Case 1, clinical photo after several surgical debulking procedures and chemotherapy. (E) Case 2 fibromatosis, clinical pre-operative photo. (F) Case 2 T1-weighted post-contrast MRI, sagittal view. (G) Case 2 MRI, axial view. (H) Case 2, clinical photo after complete surgical resection.

undergone multiple surgical debulking procedures to reduce the tumor burden (Fig. 1D). He is currently 14 months post completion of chemotherapy. At a recent follow-up examination there was no gross evidence of tumor in the tongue by clinical examination.

Case No. 2: A 3.4 kg, 39-week male infant was transferred from and outside hospital approximately 24 h after birth for evaluation of a tongue mass (Fig. 1E). On presentation, the child exhibited no signs or symptoms of respiratory distress and was able to feed from a bottle without difficulty. The patient's physical examination was unremarkable except for a two centimeter submucosal mass in the anterior tongue just left of the midline. On DOL 2, the child was taken to the operating room for incisional biopsy to rule out malignancy. Frozen sections were consistent with a spindle cell neoplasm concerning for RMS. The permanent sections of the biopsied tissue showed fascicles of bland, spindle cells infiltrating and focally replacing tongue musculature (Fig. 2D and E). IHC staining showed focal nuclear staining of MyoD1 and myogenin (Fig. 2F). A beta-catenin immunohistochemical stain was negative for nuclear staining. A diagnosis of spindle cell neoplasm favoring spindle cell RMS was made. However, as the possibility of fibromatosis was raised by an intra-departmental pathologist, an outside expert consultation was sought. The expert consultant diagnosed the spindle cell neoplasm as "low grade myofibroblastic neoplasm most compatible with infantile fibromatosis." MRI performed on DOL 3 demonstrated a 1.2 cm × 1.5 cm × 1.1 cm mass in the left anterior tongue which enhanced on T2 and post-contrast T1 images (Fig. 1F and G). The remainder of the metastatic workup was negative, and the infant returned to the OR on DOL 15 for partial glossectomy. A larger, protuberant mass was noted to occupy the previous biopsy site at the time of the procedure. This was resected completely with negative margins. Microscopic examination of the specimen revealed similar appearance of spindle cell fascicles, regenerating striated muscle and granulation tissue. IHC staining showed focal nuclear staining of MyoD1 and myogenin, desmin and calponin were focally positive, smooth muscle actin was positive and beta-catenin was negative in the nuclei of lesional cells. Actin HHF35 was diffusely positive in the lesional cells. The lesion was again worrisome for a spindle cell

RMS versus fibromatosis. Since there was lack of unanimity among institutional pathologists, the case was labeled as "spindle cell proliferative tumor with infiltrative pattern and myoblastic phenotype" and sent to an expert consultant for review. The consultant rendered a diagnosis of "infantile fibromatosis, diffuse type." Thus, two independent, external consultants who separately reviewed the biopsied tissue concurred that the tongue lesion actually represented diffuse type infantile fibromatosis (IF). A cytogenetic analysis of the lesional tissue revealed a ringed chromosome 9 with partial deletion of 9q. The patient is now being followed clinically with no evidence of recurrence 16 months after his partial glossectomy (Fig. 1H).

2. Discussion

While most congenital lesions of the head and neck are benign, it is imperative to rule out malignancy in order to prescribe appropriate therapy. Similar histologic features amongst soft tissue lesions can often create diagnostic uncertainty. Even with a battery of radiographic and immunohistochemical studies, it can be difficult to differentiate between benign and malignant lesions, as is demonstrated by our case studies.

2.1. Epidemiology

RMS rarely presents in the tongue despite the fact that approximately one-third of all head and neck RMS has its origin in intraoral and pharyngeal structures [2]. While there have been cases of infantile tongue RMS reported, congenital rhabdomyosarcoma of the tongue is exceedingly rare with few cases ever reported [1–4]. In the Intergroup Rhabdomyosarcoma Studies I, II and III only seven rhabdomyosarcomas of the tongue were registered, representing 0.34% of IRS participants [5,7]. In infants and young children, embryonal rhabdomyosarcoma (ERMS) is more common in the head and neck than the alveolar type (ARMS). Spindle cell RMS is a rare variant of ERMS that accounts for 4% of all RMS. It is thought to carry a more favorable prognosis than other forms of RMS. While it occurs most frequently in the paratesticular

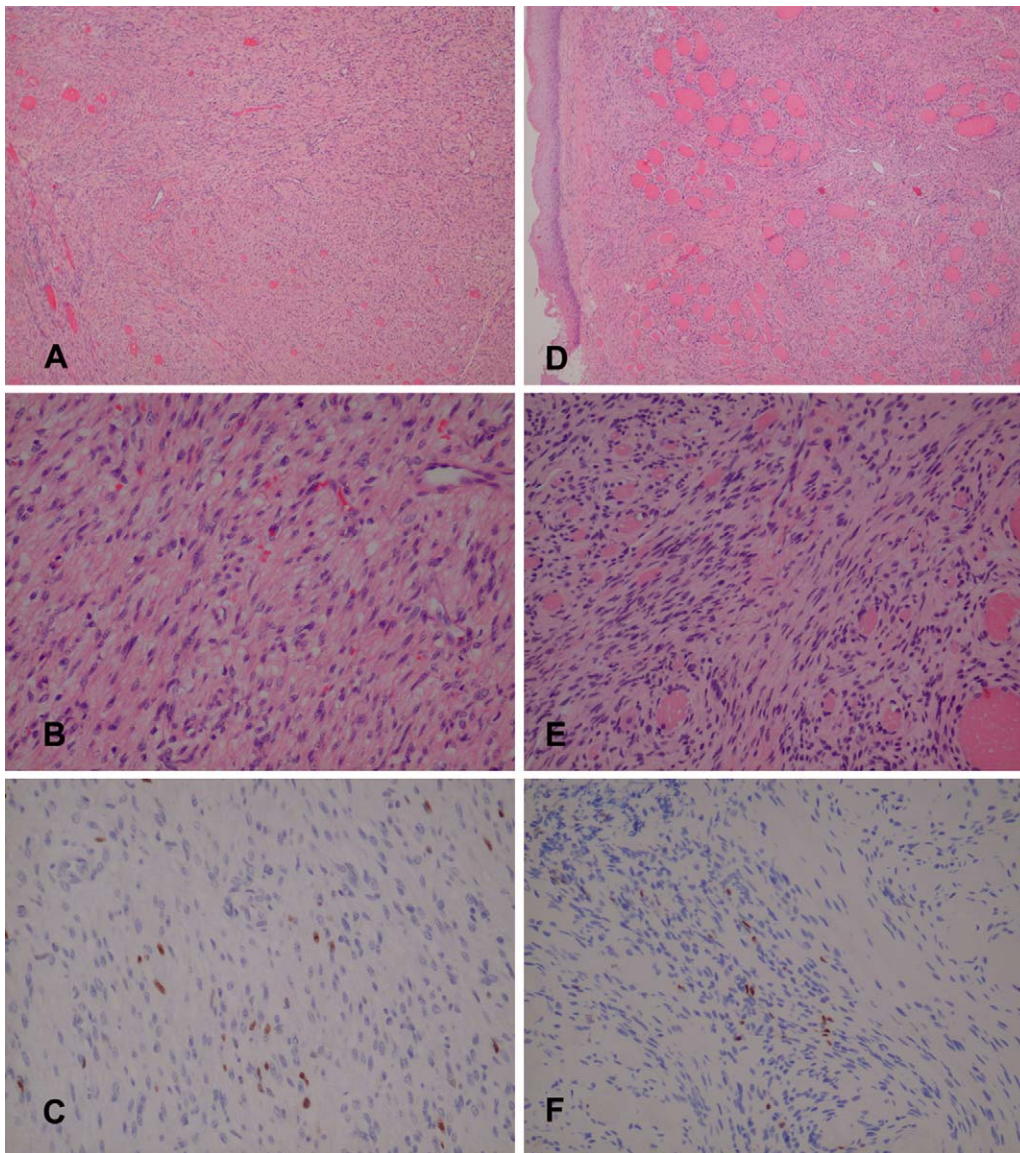


Fig. 2. (A–C) Case 1 Spindle cell rhabdomyosarcoma. (A) H&E stain, 40 \times magnification, shows fascicles of spindle cells with a mass effect that effaces native tissue. (B) H&E stain, 200 \times magnification, shows bland spindle cells with no striated muscle differentiation. (C) Myogenin immunostain shows scattered tumor cells with positive nuclear stain. (D–F) Case 2 Fibromatosis. (D) H&E stain, 40 \times magnification, shows fascicles of spindle cells that percolate between native tongue striated muscle cells. (E) H&E stain, 200 \times magnification, shows bland spindle cells with entrapped native striated muscle. (F) Myogenin immunostain shows scattered tumor cells with positive nuclear stain, which probably represent regenerating myoblasts/muscle cells.

region, it has been reported in the head and neck [6–9]. Infantile fibromatosis is a rare lesion that in the newborn frequently involves extremities, head and neck. The IF can present as superficial fibromatosis or as desmoid (deep) fibromatosis. Only 10–15% of extra-abdominal desmoids in general population occur in the head and neck [8–10]. The infantile form of the disease, however, has a propensity for the region, with 25–30% of lesions occurring in this location. The tongue, mandible and maxilla are favored sites [11].

2.2. Radiography

Soft tissue tumors have a tendency to look very similar in radiographic studies, which limits their usefulness as a tool for narrowing the differential diagnosis. As can be seen in our Case 1 images, RMS demonstrates characteristic hypo- to isointensity relative to muscle on T1 images, while T2 images tend to be hyperintense with avid, though heterogeneous, enhancement on

T1 contrasted images. The tumor typically invades surrounding tissues [12,13]. Similarly, IF appears as a hypointense to isointense mass on T1 images with heterogeneous enhancement on T2 and T1 contrasted images [13]. While fibromatosis is generally considered to be a localized lesion, the margins can appear infiltrative in over 50% of cases, contributing to the malignant appearance of the mass as demonstrated in the images from Case 2.

2.3. Microscopy

The two major subtypes of RMS: alveolar and embryonal, are well characterized and have distinctive cytogenetic features. ERMS has the histologic appearance of muscle cells in various phases of differentiation, ranging from stellate mesenchymal cells to well-differentiated muscle fibers [14]. The spindle cell variant of ERMS, however, has a uniform appearance that resembles smooth muscle tumors. Spindle-shaped cells with elongated nuclei are arranged in tight fascicles, in a background of variable collagen matrix [15]. The

presence of rhabdomyoblastic cells should be sought in such a spindle cell proliferation as their presence will clue in to the diagnosis of rhabdomyosarcoma. The rhabdomyoblastic cells may be rare and hard to find or sometimes in abundant numbers, and are recognized by a rounded to polygonal appearance, with bright eosinophilia and eccentric nucleus. As they become more differentiated, multiple nuclei and cross-striations are noted within the cells. The tumor is infiltrative, and normal tissue is replaced by neoplasm. Histologically, IF presents as fascicles of monomorphic fascicles of spindle-shaped cells. Mitoses and nuclear pleomorphism are rare. The tumor cells often appear to infiltrate and entrap normal tissue, but without obvious destruction, a subtle and easily missed distinction from RMS. When the fibromatosis is diffuse and very cellular simulating a low grade fibrosarcoma, the designation of aggressive fibromatosis is applied. The bland appearance of spindle cell in both spindle cell RMS and fibromatosis, and paucity of rhabdomyoblastic differentiation in spindle cell RMS, is what creates much of the diagnostic dilemma in these scenarios. On the other hand, the presence of entrapped striated muscle within fibromatosis may mimic rhabdomyosarcoma, but the distinctive appearance of rhabdomyoblastic cells and their nuclear features help to distinguish them from entrapped striated muscle fibers.

2.4. Immunohistochemistry

Immunohistochemistry has been an immensely helpful tool in ascertaining a diagnosis for challenging and otherwise histologically indistinct soft tissue tumors. The key to successful use of IHC is appreciating the potential advantages and pitfalls for any given marker. As seen in Case 2, this understanding is essential to interpreting confounding data. HHHF35 actin is a marker for the alpha isomer of actin. While it stains cytoplasmic actin in skeletal, cardiac and smooth muscle, it does not bind the beta isomer of actin found in fibroblasts and other non-muscle cells of mesenchymal origin [16]. It is, therefore a useful marker for identifying neoplasms that arise from muscle. Beta-catenin is a transcription factor that is stored as an inactive protein complex in the cytoplasm of the cell. When activated, it translocates to the nucleus to drive cell proliferation. 80–100% of desmoids stain positively for nuclear beta-catenin, with significantly less staining in superficial fibromatosis (56%) and low grade myofibrosarcoma (30%) [17]. Calponin is a cytoplasmic protein that binds to actin in myoepithelial and smooth muscle cells. Nodular fasciitis, fibromatosis and myofibrosarcoma, leiomyoma and leiomyosarcoma all typically demonstrate intermediate to strong cytoplasmic staining for the marker [18]. Myogenin and MyoD1 are regulatory proteins which drive mesenchymal differentiation into mature skeletal muscle. While nuclear staining for MyoD1 is very sensitive, there have been issues with nonspecific cytoplasmic staining resulting in some degree of diagnostic ambiguity [19,20]. While nearly 100% of RMS will stain positively for myogenin, ARMS stains more strongly than ERMS, 75–100% of nuclei compared 25–50% of nuclei, respectively [21]. While myogenin studies typically do not suffer from the nonspecific cytoplasmic staining issues encountered with MyoD1, it is not 100% specific. Focal staining can be seen in desmoid, infantile myofibromatosis and infantile fibrosarcoma, although this is felt to represent entrapped, regenerating normal muscle and not tumor [22]. Desmin is an intermediate filament found in skeletal, cardiac and smooth muscle. It is expressed in 95% of RMS, but can also be seen in up to 17% of non-myogenic neoplasms such as malignant fibrous histiocytoma and benign fibromatosis [23]. Using the above-mentioned IHC markers in most instances, it is possible to distinguish spindle cell RMS from fibromatosis as shown in Table 1. However, in some cases especially when the fibromatosis involves striated muscle, the

Table 1

Comparing immunohistochemistry of IF and RMS and in both cases.

Marker	Fibromatosis	RMS	Case 1	Case 2
MyoD1 (N)	–	+	+(patchy)	+(focal)
Myogenin (N)	–	+	+(patchy)	+(focal)
Desmin (C)	–/+	+	+(weak)	+
Beta-Catenin (N)	+	–	N/C	–
HHF35 Actin (C)	–/+	+	+(weak)	+
Calponin (C)	+	–	N/C	+/-

N = nuclear staining; C = cytoplasmic staining; N/C = not performed.

Table 1 is a summary of the expected IHC staining patterns for IF and RMS, as well as a summary of our case findings.

distinction may become difficult as exemplified by our case 2. The positive expression of MyoD1 and myogenin in the regenerating muscle and focally, in some entrapped atrophic muscle of our case 2 were distracting.

2.5. Treatment

The importance of differentiating between these two morphologically similar lesions lies in the issue of treatment. Protocols for treating RMS have been developed over the last 20 years through the work of the Intergroup Rhabdomyosarcoma Studies (IRS) I-IV [24]. Surgical excision is recommended only to the extent that it does not cause significant functional morbidity. The cornerstone of treatment is an almost a year-long course of chemotherapy using vincristine, actinomycin D and cyclophosphamide (VAC). Depending on the staging and grouping of the disease, radiation therapy may be included in the treatment regimen. In infants with RMS, radiation therapy is often avoided. Recently, brachytherapy has been reported as an alternative to conventional external beam radiation [25,26]. Though multimodality therapy has improved local control rates and disease free survival, the potential for long-term sequelae exists, especially to the underdeveloped organs of the neonate. Infantile fibromatosis, while locally aggressive, does not have the potential to metastasize. Treatment consists of resection with negative margins. This can be difficult in the head and neck, as significant functional morbidity can result from excision of desmoids in this region. Patients must be followed closely, as recurrence rates are near 70% in the head and neck [27]. Chemotherapy and radiation, which are mainstays in the treatment of RMS, are reserved for only the recurrent and most recalcitrant cases. Several studies have shown a role for chemotherapy and radiation in such cases [28–30]. Interestingly, the chemotherapeutic agents used for aggressive fibromatosis, which include vincristine, actinomycin D, and cyclophosphamide are similar to that used for RMS.

3. Conclusions

Spindle cell tumors are a rare group of neoplasms that can be challenging to diagnose. Radiographically, even benign lesions can have a malignant and infiltrative appearance. Histologically, these tumors look very similar, with only subtle morphologic differences. Immunohistochemistry continues to be a powerful tool for pathologic diagnosis, but is not without pitfalls. All available information should be carefully reviewed in a potential new cancer to ensure correct diagnosis and appropriate therapy is given.

References

- [1] A. Gupta, J. Maddalozzo, T. Win Htin, et al., Spindle cell rhabdomyosarcoma of the tongue in an infant: a case report with emphasis on differential diagnosis of childhood spindle cell lesions, *Pathol. Res. Pract.* 200 (7–8) (2004) 537–543.
- [2] P.S. Liebert, S.E. Stool, Rhabdomyosarcoma of the tongue in an infant, *Ann. Surg.* (November) (1973) 621–624.

- [3] V.A. Skelton, A. Goodwin, Perinatal management of a neonate with airway obstruction caused by rhabdomyosarcoma of the tongue, *Br. J. Anaesth.* 83 (December(6)) (1999) 951–955.
- [4] A. Cirocco, F. Gonzalez, A.M. Saenz, et al., Embryonal rhabdomyosarcoma of the tongue, *Pediatr. Dermatol.* 22 (May–June(3)) (2005) 218–221.
- [5] R. Kodet, J. Fajstavr, Z. Kabelka, et al., Is fetal cellular rhabdomyoma an entity or a differentiated rhabdomyosarcoma? *Cancer* 67 (June(11)) (1991) 2907–2913.
- [6] A.Q. Cavazzana, D. Schmidt, V. Nifo, et al., Spindle cell rhabdomyosarcoma. A prognostic favourable variant of rhabdomyosarcoma, *Am. J. Surg. Pathol.* 16 (1992) 229–235.
- [7] I. Leuscher, W.A. Newton Jr., D. Schmidt, et al., Spindle cell variants of embryonal rhabdomyosarcoma in the paratesticular region. A report of the Intergroup Rhabdomyosarcoma Study, *Am. J. Surg. Pathol.* 17 (1993) 221–230.
- [8] M. Abdelkader, M. Riad, A. Williams, Aggressive fibromatosis of the head and neck (desmoid tumors), *J. Laryngol. Otol.* 115 (10) (2001) 772–776.
- [9] N.S. Siegel, C.R. Bradford, Fibromatosis of the head and neck: a challenging lesion, *Otolaryngol. Head Neck Surg.* 123 (3) (2000) 269–275.
- [10] S.W. Weiss, J.R. Goldblm (Eds.), *Fibrous tumors of infancy and childhood*. Enzinger and Weiss's Soft Tissue Tumors, 4th ed., Mosby, St. Louis, 2001, pp. 347–408.
- [11] R.R. Van Rijn, J.C.H. Wilde, J. Bras, et al., Imaging findings in noncraniofacial childhood rhabdomyosarcoma, *Pediatr. Radiol.* 38 (2008) 617–634.
- [12] H.R. Harnsberger, *Diagnostic Imaging: Head and Neck*, Amirsys, Manitoba, 2006, pp. IV 1–53.
- [13] J.M. Ahn, H.K. Yoon, Y.L. Suh, et al. *Clin. Radiol.* 55 (January) (2000) 19–24.
- [14] D.M. Parham, The molecular biology of childhood rhabdomyosarcoma, *Semin. Diag. Pathol.* 11 (1994) 39–46.
- [15] D.M. Parham, D.A. Ellison, Rhabdomyosarcomas in adults and children: an update, *Arch. Pathol. Lab. Med.* 130 (2006) 1454–1465.
- [16] T. Tsukada, D. Tippens, D. Gordon, et al., HHF35, a muscle-actin-specific monoclonal antibody, *Am. J. Pathol.* 126 (1987) 51–60.
- [17] J.W. Carlson, C.D.M. Fletcher, Immunohistochemistry for beta-catenin in the differential diagnosis of spindle cell lesions: analysis of a series and review of the literature, *Histopathology* 51 (2007) 509–514.
- [18] M.D. Perez-Montiel, J.A. Plaza, H. Dominguez-Malagon, et al., Differential expression of smooth muscle myosin, smooth muscle actin, H-caldesmon and calponin in the diagnosis of smooth muscle lesions of skin and soft tissue, *Am. J. Dermatopathol.* 28 (April) (2006) 105–111.
- [19] M.H. Cessna, C. Coffin, S. Perkins, et al., Myogenin (MYOG) and MyoD1 (MD1) expression in rhabdomyosarcoma (RMS) and spindle cell mimics: a study of 135 cases, *Lab. Invest.* 81 (2001) 36.
- [20] M.H. Cessna, H. Zhou, S. Perkins, et al., Are myogenin and myoD1 expression specific for rhabdomyosarcoma: a study of 150 cases with emphasis on spindle cell mimics, *Am. J. Surg. Pathol.* 25 (2001) 1550–1557.
- [21] S. Kumar, E. Perlman, C.A. Harris, et al., Myogenin is a specific marker for rhabdomyosarcoma: an immunohistochemical study in paraffin-embedded tissues, *Modern Pathol.* 13 (2000) 993–998.
- [22] M.J. Sebire, M. Malone, Myogenin and MyoD1 expression in paediatric rhabdomyosarcoma, *J. Clin. Pathol.* 56 (2003) 412–416.
- [23] L.D. Truong, S. Rangdaeng, P. Cagle, et al., The diagnostic utility of desmin. A study of 584 cases and review of the literature, *Am. J. Clin. Pathol.* 93 (1990) 305–314.
- [24] R.B. Raney, H.M. Maurer, J.R. Anderson, et al., The Intergroup Rhabdomyosarcoma Study Group: major lessons from the IRS-I through IRS-IV studies as background for the current IRS-V treatment protocols, *Sarcoma* 5 (2001) 9–15.
- [25] S. Nag, J. Grecula, F.B. Ruymann, Aggressive chemotherapy, organ-preserving surgery, and high-dose-rate remote brachytherapy in the treatment of rhabdomyosarcoma in infants and young children, *Cancer* 72 (November(9)) (1993) 2769–2776.
- [26] S. Nag, R. Martinez-MOngé, F. Ruymann, et al., Innovations in the management of soft tissue sarcomas in infants and young children: high-dose-rate brachytherapy, *J. Clin. Oncol.* 15 (September(9)) (1997), 3-75-84.
- [27] J.K. Masson, E.H. Soule, Desmoid tumor of the head and neck, *Am. J. Surg.* 12 (1966) 615–622.
- [28] S. Buitendijk, C.P. van de Ven, T.G. Dumans, et al., Pediatric aggressive fibromatosis: a retrospective analysis of 13 patients and review of literature, *Cancer* 104 (2005) 1090–1099.
- [29] S.X. Skapek, W.S. Ferguson, L. Granowetter, et al., Vinblastine and methotrexate for desmoid fibromatosis in children: results of a Pediatric Oncology Group Phase II Trial, *J. Clin. Oncol.* 25 (2007) 501–506.
- [30] C. Meazza, G. Bisogno, A. Gronchi, et al., Aggressive fibromatosis in children and adolescents: the Italian experience, *Cancer*, November 30 (Epub ahead of print).