Cutaneous Fetal Rhabdomyoma

A Case Report and Historical Review of the Literature

Sarah N. Walsh, MD and Mark A. Hurt, MD†*

Abstract: Fetal rhabdomyomas are well-documented tumors, affecting both children and adults that are composed of immature striated muscle at the sixth to tenth-week stage of development. Although there is often a predilection for the head and neck region, these tumors have been identified in a wide array of anatomic sites. A primary cutaneous presentation, however, has not yet been described. We report the first case of a fetal rhabdomyoma arising in the skin of a 1-year old girl. After the initial biopsy, an incomplete excision was performed with tumor present histologically at multiple surgical margins. In a follow-up period of 54 months, there has been no lesional regrowth or evidence of further progression. This case is detailed, in addition to a literature-based review of the historical and conceptual development of the neoplasm known as fetal rhabdomyoma.

Key Words: fetal rhabdomyoma, juvenile rhabdomyoma, benign neoplasm, case report, 4.5-year follow-up, immunohistochemistry, historical review of literature, first case reported in skin, Triton tumor, pediatric dermatopathology, cutaneous neoplasia, differential diagnosis with rhabdomyosarcoma, nevoid basal cell carcinoma syndrome

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Fetal rhabdomyoma is now a well-recognized neoplasm, first described by Dehner et al[5] in 1972, from the Armed Forces Institute of Pathology (AFIP). The majority of the cases in the original series were identified in boys < 3 years old, showed no evidence of regrowth or malignancy, and were located usually in the subcutaneous tissue of the head and neck, particularly the postauricular region.[5] Since then, there have been 2 other series and numerous case reports that have further defined fetal rhabdomyomas; such articles have documented different histologic types, local regrowth and possible malignancy, a broader age distribution, various immunohistochemical staining patterns, occurrence in particular syndromes, and their presence in a wide assortment of organs and anatomic sites.[1,2,4–8,11,15,16,18,20–25,29,33] To the best of our knowledge, however, fetal rhabdomyoma has never been diagnosed definitively in the skin. We present the first case of a cutaneous fetal rhabdomyoma found in a 1-year-old girl with a lesion on the chin.

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CASE REPORT

The patient was a 1-year-old girl seen by a pediatric dermatologist for a chin lesion that had been present for the past 10 months but had not changed noticeably during that period. On physical examination, there was a 1.4 cm, nontender, slightly firm to rubbery violaceous nodule on the left side of the chin. The clinical differential diagnosis included vascular malformation and tufted angioma. A punch biopsy was performed.

Histologic examination identified a well-delineated mass occupying the reticular dermis and subcutis (Fig. 1); there was no extension into or involvement of the overlying epidermis or papillary dermis (Fig. 2). The lesion expanded the septal planes but did not directly infiltrate the adipose tissue and was present within the midst of mature skeletal muscle (Fig. 3). It consisted of haphazardly arranged short, fascicular bundles of immature cells with small to medium, oval to spindled nuclei, dispersed chromatin, sparse nucleoli, and scant to moderate eosinophilic cytoplasm (Fig. 4). Scattered among these cells were those with evidence of rhabdomyoblastic differentiation characterized by epithelioid nuclei with "straps" of streaming cytoplasm containing definitive cross striations (Fig. 5). A rare mitosis was identified, but there were no pleomorphic nuclei or foci of necrosis.

Special and immunohistochemical stains were performed that showed the strong and diffuse positivity with phosphotungstic acid-hematoxylin (PTAH), actin, desmin, and myoglobin, in the tumor cells (Figs. 6A–D). Approximately 3% to 5% of the tumor cell nuclei marked with Ki-67. An S-100 protein stain was negative.

The patient subsequently had an excision of the tumor, which revealed multiple microscopically positive surgical resection margins. Owing to the location of the tumor on the chin and probable morbidity associated with further resection, the attempt for complete excision with negative margins was abandoned.

Microscopic examination of the resection specimen showed a tumor present in the dermis, subcutis, and between fascicles of skeletal muscle that was morphologically similar to the findings seen on the biopsy. Tumor was present at multiple deep resection margins.

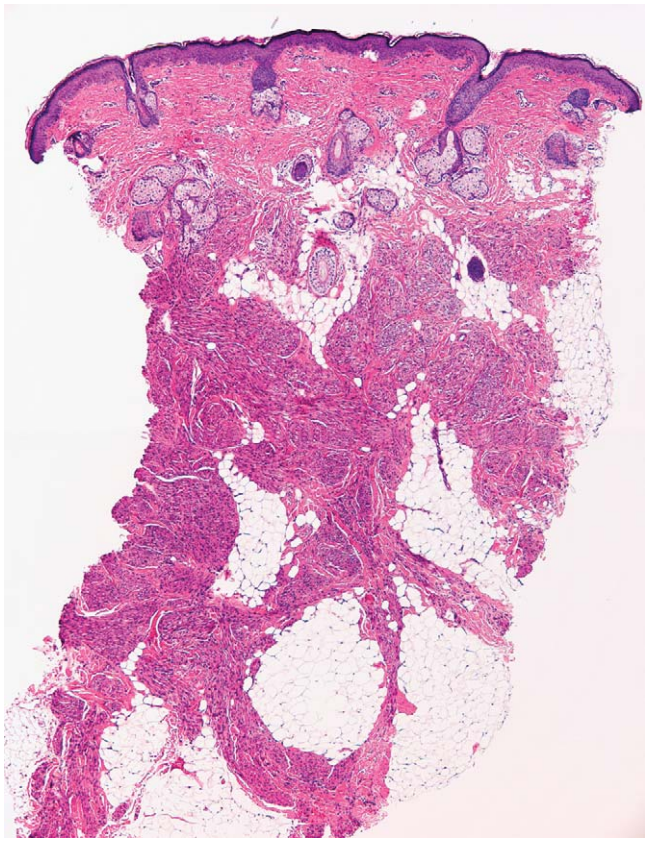

FIGURE 1. A well-delineated neoplasm present within the reticular dermis and subcutis is seen at scanning magnification.

In a 54-month period of follow-up, the patient was alive and well with no evidence of lesion regrowth or progression, despite microscopically residual tumor.

DISCUSSION

Before 1972, an immature or fetal counterpart of rhabdomyoma had not been described. In a series of 9 cases from the AFIP, Dehner et al[5] identified a lesion

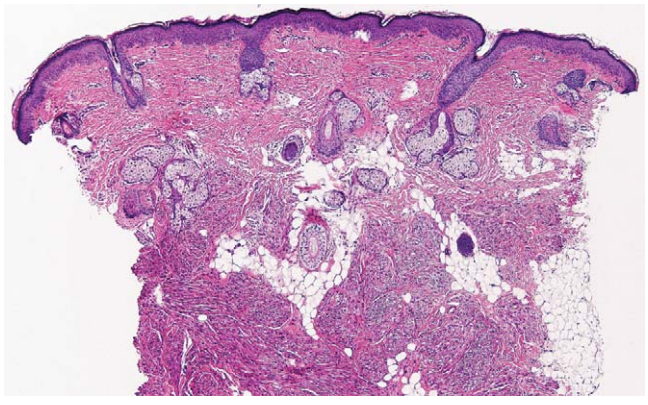

FIGURE 2. Epidermis and dermis with the lesion occupying the lower part of the dermis.

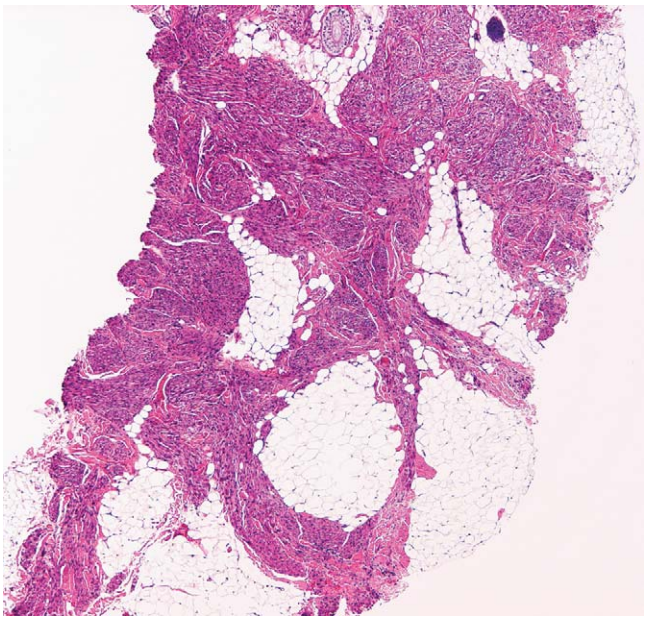

FIGURE 3. A higher magnification highlights neoplastic expansion of the septal planes. Note the sparing of the adipose tissue lobules and the uninvolved native mature skeletal muscle.

which was mainly solitary and found usually in boys < 3 years old. Clinically, the lesions were identified from shortly after birth to up to 2 years, were nontender, well circumscribed, and freely mobile, ranged in size from 1.2 to 8 cm in greatest dimension, and were located in the subcutaneous tissue, most commonly, of the head and neck region. Microscopically, they were described as having both oval to spindled, ''undifferentiated'' mesenchymal cells and haphazardly arranged irregular bundles of immature muscle fibers, some with cross

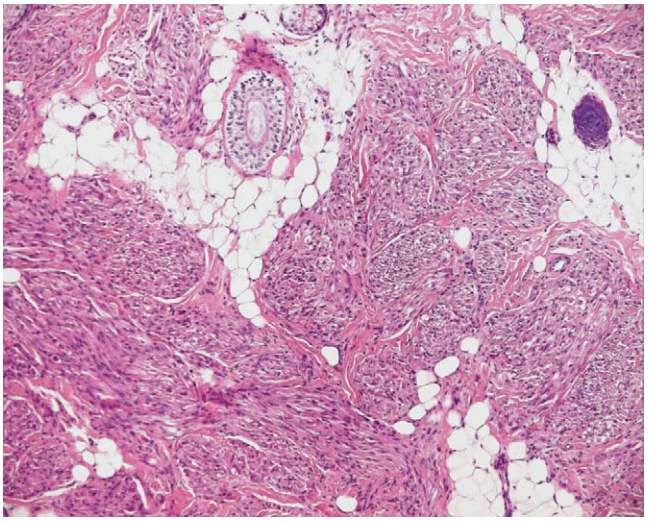

FIGURE 4. A medium power view shows the haphazardly arranged irregular bundles of oval and spindled cells.

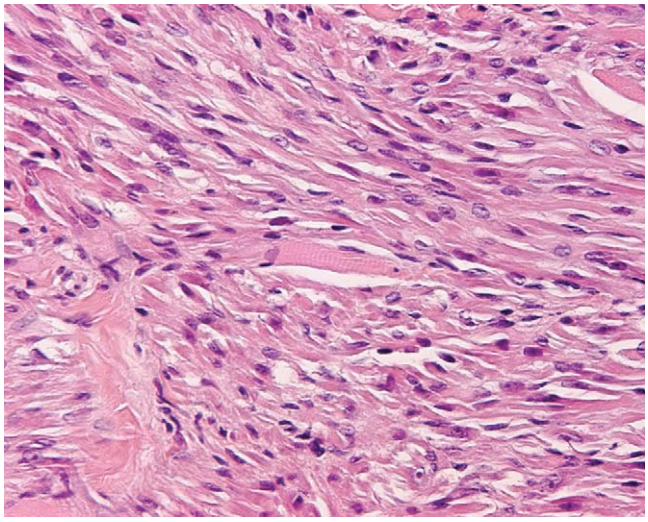

FIGURE 5. At high power, rhabdomyoblastic differentiation is confirmed by the presence of cross striations.

striations, that resembled striated muscle in the sixth to tenth-week stage of intrauterine development. Treatment involved only local excision in 8 of the 9 cases, and in all, there was no evidence of local persistence or disease progression in a follow-up period of up to 10 years. The name given to this newly described proliferation was fetal rhabdomyoma.

Since this seminal paper in 1972, various features of fetal rhabdomyoma have been elaborated. The second largest series, which included 15 cases, was published in 1980 by Di Sant'Agnese and Knowles.[6] In this article, fetal rhabdomyoma was divided into myxoid and cellular types. The myxoid type was found to occur in the vulvovaginal region of middle aged women or in the postauricular region of infant boys, whereas the cellular type most often resided in the head and neck area of men. Histologically, the myxoid type was analogous to that originally described by Dehner et al whereas the "new" cellular type was thought to closely resemble the classic adult rhabdomyoma, containing a high degree of cellularity, predominance of immature spindle cells, and variable differentiation toward skeletal muscle, including rhabdomyoblasts with cross striations and large round rhabdomyocytes.

In 1982, Konrad et al[21] documented the first local regrowth of a fetal rhabdomyoma. The case involved a 9-year-old boy with a mass in the right eyebrow. On microscopic examination, the tumor was noted to have "moderate" pleomorphism and cellular immaturity. In 7 years of follow-up, however, there was no evidence of malignancy.

A fetal cellular rhabdomyoma that persisted and "transformed" into a mixed embryonal/alveolar rhabdomyosarcoma over 22 months was described by Kodet et al[19] in 1990. In this case, an 18-month old presented with a 4.5-cm mass in the base of the tongue that showed marginal infiltration into surrounding muscle and minor salivary glands. The tumor was not completely excised, and it regrew 10 months later, showing some degree of nuclear pleomorphism and an increased mitotic index. The margins were positive microscopically for residual tumor. Twelve months later, a second regrowth now showed a mixed embryonal/alveolar rhabdomyosarcoma. After multiple excisions for local persistence of rhabdomyosarcoma, the patient was apparently tumor-free 47 months after the initial diagnosis.

A third series of 24 cases of fetal rhabdomyoma was published, once again, from the AFIP. In this 1992 article, Kapadia et al[18] defined a broader age range for these tumors (46% in their series were older than 15 y of age) and expanded the histologic definition to allow for focal infiltration, increased mitotic index (up to 14 mitoses/50 HPF), and focal necrosis. Instead of dividing the tumors into myxoid and cellular types, they split them into "classic" and "intermediate" variants. Again, the classic subtype was similar to the myxoid type termed by DiSant'agese et al and that of Dehner et al's original description. The intermediate type had a higher cellularity with more advanced and extensive skeletal muscle maturation, but retained foci of the classic fetal rhabdomyoma. Immunohistochemistry showed the tumors were positive for myoglobin, desmin, muscle-specific actin, and vimentin, supporting a 1987 article by Seidal et al.[26] However, 7 of the 11 cases were positive for smooth muscle actin, 6 of 12 for S-100 protein, and 5 of 10 for glial fibrillary acidic protein, all which were findings that had not been reported previously. Possible explanations for this included a multipotential character of the primitive mesenchymal cells or possible relation to Triton tumor (neuromuscular hamartoma).[24] Only one tumor in this series, an intermediate type, persisted after 3 months but did not have further progression after 43 months.

In a 1993 article by Crotty et al,[3] the previously termed "cellular" form of fetal rhabdomyoma was thought to represent a more differentiated lesion than the classic fetal rhabdomyoma and, therefore, a distinct variant that they termed "juvenile rhabdomyoma." Two cases were highlighted; they presented in the buccal soft tissues of children and were characterized by nodules of spindle cells with abundant cross striations and no immature mesenchymal cells, nuclear pleomorphism, or mitotic figures. A period of 46 and 7-month follow-up showed no persistence, regrowth, or progression.

Fetal rhabdomyoma found in patients with nevoid basal cell carcinoma syndrome has been documented throughout the years[7,17]; it was first elucidated by Dahl et al[4] in 1976. Watson et al[32] described a case in the tongue in 2004, bringing the literature tally to 6 patients, who also had fetal rhabdomyomas in various locations, with this syndrome.

As detailed above, numerous changes and developments have occurred in defining the different aspects of fetal rhabdomyoma, from patient age to histology to tumor behavior. In addition to that already discussed, a wider spectrum of tumor location has also been a major contribution. In the original series from the AFIP, 8 of

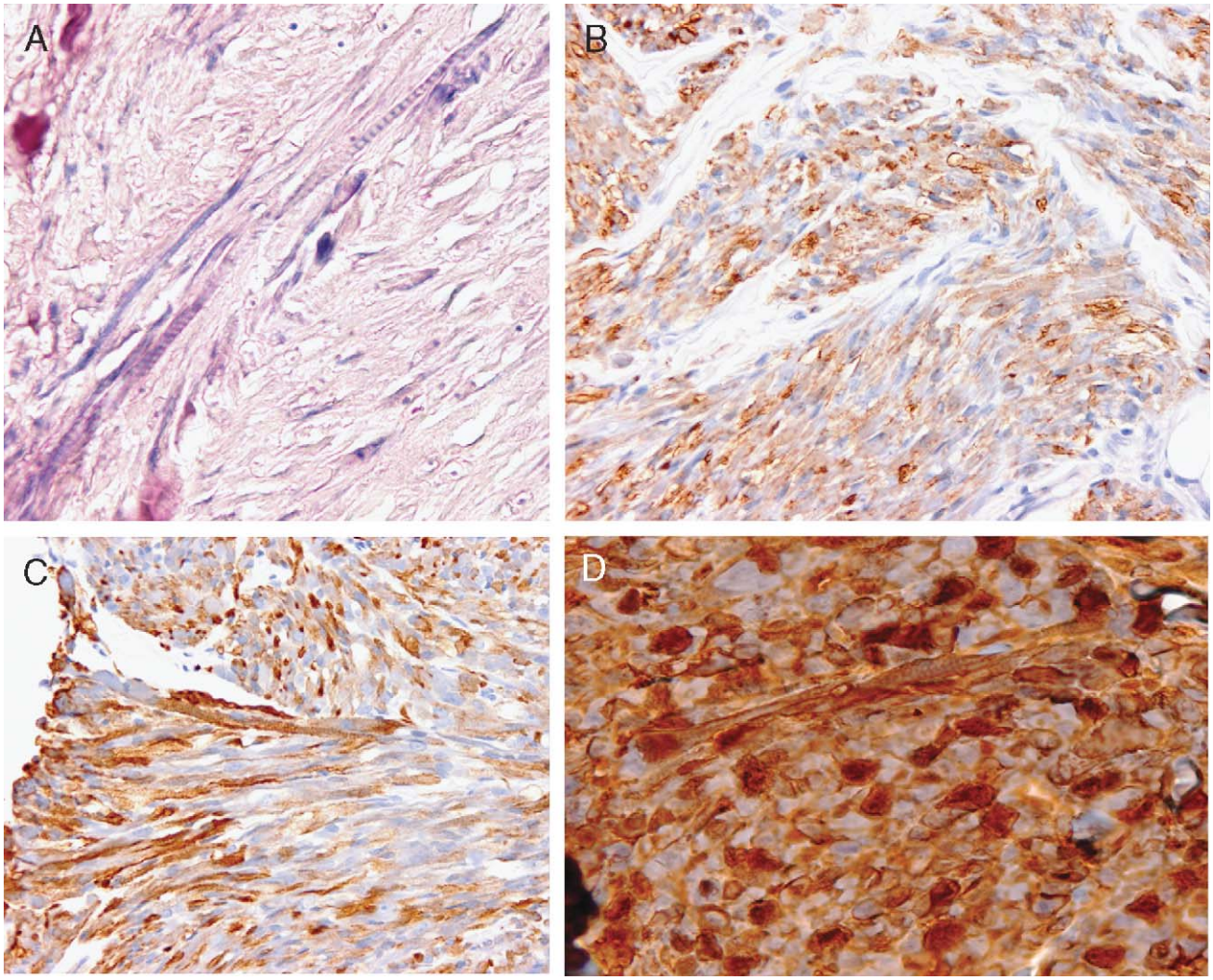

FIGURE 6. A to D, A skeletal muscle origin is illustrated by positive staining with PTAH, actin, desmin, and myoglobin (PTAH-A, actin-B, desmin-C, and myoglobin-D).

the 9 cases were found in the head and neck (5 in the postauricular area).[5] Since then, fetal rhabdomyomas have been identified in numerous anatomic sites, ranging from the chest wall to the perianal region (Table 1). We did not, however, find a definitive case that had been previously reported in the skin. A case report from Sweden authored by Dahl et al in 1976 described a newborn girl, who was subsequently diagnosed with nevoid basal cell carcinoma syndrome and who presented with a congenital polypoid cutaneous mass of the left thigh and a separate new deep chest wall mass at 6 months of age.[4] The chest wall mass had convincing histologic and electron microscopic features of fetal rhabdomyoma. However, the cutaneous left thigh mass showed no cross striations on hematoxylin and eosin (H&E) and had no cross banding or thick or thin fibers on electron microscopy. Although it has been documented that in rare cases of fetal rhabdomyoma, cross striations may not be seen on H&E, such cases had other clear cut evidence of skeletal muscle differentiation, namely identified by electron microscopy.[5] Dahl noted that "a suggestion of Z line formations" and the position of the nuclei "seem(ed) to justify the classification of this tumor as a fetal rhabdomyoma."[4]

The case we present herein had irregular bundles of cells with oval to spindle-shaped nuclei and scant to moderate eosinophilic cytoplasm. Cross striations were identified easily on the H&E stain, and were confirmed by a PTAH stain. Desmin, myoglobin, and actin were all positive. There was no bizarre nuclear pleomorphism or foci of necrosis. The mitotic index was low, as evidenced by the Ki-67 stain. This combination of findings are features that have been documented consistently in cases of fetal rhabdomyoma, and thus, with certainty, we believe our case represents the first report of an example documented within the skin.

TABLE 1. Various Organs and Anatomic Sites in Which Fetal Rhabdomyomas Have Been Described

Location	Age	Sex
Head and neck		
Postauricular[1]	Newborn—13 mo	M/F
Posterior cervical neck[1]	3 y	M
Parotid[1]	56 y	M
Anterior cervical neck[14]	< 1 y	n/a
Tongue[4]	37 y	M
Face[5]	9 y	M
Larynx[4]	53-65 y	M/F
Orbit[4]	20 y	F
Buccal mucosa[8]	20 y	F
Nasopharynx[8]	1-17 y	M
Occipital region[1]	2 mo	F
Preauricular[8]	6 y	M
Soft palate[8]	37 y	M
Chest wall/costal margin[1,2]	6 mo/1.5 y	F/M
Axilla[1]	15 mo	M
Vulvovaginal region[4]	23-45 y	F
Abdominal wall[3]	Newborn	F
Retroperitoneum[7]	Newborn	F
Anus/perianal[4,10]	Newborn/1 mo	M/F
Upper/lower extremity[2,11]	n/a/Newborn	n/a/F
Spermatic cord[13]	Infant	M
Stomach[4]	3 y	M
Urinary bladder[17]	n/a	n/a
Urethra[19]	Child	n/a
Posterior mediastinum[18]	6 y	F

Cases in the table represent those first known to be reported for the various anatomic regions.

One controversy that continues to arise is the exact nature, nosologically, of fetal rhabdomyoma. The conundrum centers on whether it represents a developmental malformation, hamartoma, or a neoplasm. Some authors, such as Dahl et al, favor a malformation. His case was found to occur in a patient with other aberrations of tissue development (in a patient with nevoid basal cell carcinoma syndrome); therefore, they inferred that such an environment "lends credence to the opinion that fetal rhabdomyomas are malformations rather than true neoplasms."[4] Simha et al[27] demonstrated electron microscopic evidence of various stages of formation and organization of myofilaments into striated muscle fibers in a postauricular lesion diagnosed as fetal rhabdomyoma.[27] Therefore, ultrastructurally, they believed fetal rhabdomyoma was a "hamartomatous swelling rather than a true neoplasm."[27] Most other articles have skirted the issue.

We believe the designation of fetal rhabdomyomas as a "malformation" or "hamartoma" is quite curious. A malformation, as defined in Dorland's Medical Dictionary is "a morphologic defect of an organ or larger region of the body, resulting from an intrinsically abnormal developmental process."[9] Although this definition initially seems reasonable in that fetal rhabdomyoma may represent abnormal development of skeletal muscle, it does not explain the lesion's ability to persist and regrow. Hamartoma, again as defined by Dorland's Medical Dictionary, is a "benign tumorlike nodule composed of an overgrowth of mature cells and tissues normally present in the affected part but with disorganization."[9] Fetal rhabdomyoma, by definition, does not fit into this category because it is composed of *immature* rhabdomyocytes in various stages of skeletal muscle differentiation. A neoplasm is defined as a "tumor; any new and abnormal growth, specifically one in which cell multiplication is uncontrolled and progressive."[9] Benign neoplasms, as a rule, are limited in their ability to grow and progress, in contrast with malignant neoplasms, and they are usually composed of immature cells of a given type. Logically, neoplasia is the only classification that seems to fit the spectrum of lesions described under the banner of fetal rhabdomyoma.

The most important reason to recognize and diagnose fetal rhabdomyoma in its various forms and locations is to avoid misinterpretation of it as a malignant neoplasm, namely rhabdomyosarcoma. The main considerations in the histologic differential diagnosis are rhabdomyosarcoma, both embryonal and spindle cell types, adult rhabdomyoma, Triton tumor (neuromuscular hamartoma), and rhabdomyomatous mesenchymal hamartoma of the skin. Numerous other cutaneous spindle cell neoplasms could potentially be a fleeting thought, such as dermatofibroma sarcoma protuberans, but once definitive skeletal muscle differentiation is identified, such conditions are excluded easily.

Adult rhabdomyoma has been reported in the skin, albeit rarely, and it should not be difficult to distinguish from its fetal counterpart, given the distinctive cells that compose this tumor.[10] There are characteristic "spider" cells scattered among the predominant large round to polygonal cells with vesicular nuclei containing central nucleoli and abundant eosinophilic cytoplasm.[14]

Two of the other considerations in the differential diagnosis are both hamartomas. Triton tumor should be considered, especially given the positivity for S-100 protein and glial fibrillary acidic protein found in a minority of true fetal rhabdomyomas.[18] However, Triton tumor is composed of mature striated skeletal muscle admixed with nerve fascicles, and in rhabdomyomatous mesenchymal hamartoma, there are abnormally arranged mature striated skeletal muscle fibers scattered among normal dermal elements.[30] In both proliferations, the presence of mature skeletal muscle intermingled with other mature components seals the diagnosis of hamartoma. There was a single case report by Hardisson et al[17] in 1996 of a so-called neural variant of fetal rhabdomyoma in a patient with nevoid basal cell carcinoma syndrome. The description was that of well-differentiated nerve fibers admixed with immature skeletal muscle. It is unclear whether this was a true fetal rhabdomyoma, and, because this variant has not been further reported or described, it should be diagnosed with some hesitancy, if at all.

The most critical of those lesions from which to distinguish a fetal rhabdomyoma is rhabdomyosarcoma, for obvious reasons, given that the former is benign

and the latter is malignant. This distinction can be quite difficult in that fetal rhabdomyomas can be of variable cellularity with differing degrees of skeletal muscle differentiation and have a range of cell types. Architecture is one clue in avoiding misdiagnosis. Spindle cell rhabdomyosarcoma is composed of cellular spindled fascicles with a cartwheel pattern, at least focally.[13] In both embryonal and spindle cell types, there is diffuse cellular immaturity which is much more pronounced than that seen in fetal rhabdomyoma.[12] Although it has been shown that rare foci of necrosis, focal infiltration, and sparse number of mitotic figures can be seen in fetal rhabdomyoma, these features are much more exaggerated and pronounced in rhabdomyosarcoma. In addition, marginal infiltration at the tumor edge remains distinct from frank destruction of adjacent tissues and structures, which occurs in rhabdomyosarcoma but not in fetal rhabdomyoma. Finally, the feature identified time and time again, which was best stated by Kapadia et al[18] in the largest series of fetal rhabdomyomas to date, "found the lack of striking nuclear atypia to be the single most important criterion allowing us to distinguish fetal rhabdomyoma from rhabdomyosarcoma."

It is well established that fetal rhabdomyoma can persist and regrow when excised incompletely.[18,20,21,28,31] Although there has been one report of a cellular fetal rhabdomyoma theoretically "transforming" into a mixed embryonal/alveolar rhabdomyosarcoma, no other cases have yet been reported to lend support to this notion.[19] As this remains the solitary example, we question the validity of this concept. This point was acknowledged even by those who authored the article, who stated that "either a malignant change may occur in a rhabdomyoma or that a highly differentiated rhabdomyosarcoma may be difficult to distinguish from rhabdomyoma."[19] We favor the latter to be true and therefore believe that fetal rhabdomyoma follows a uniformly benign course, despite occasional local persistence and regrowth when those neoplasms are excised incompletely.

In summary, fetal rhabdomyoma is a benign neoplasm of rhabdomyoblasts that is found in both children and adults, is usually solitary, has a spectrum of morphologic features unified by the presence of immature skeletal muscle, can persist and regrow, and is located in various organs and anatomic regions throughout the body. To our knowledge, ours is the first case conclusively reported to involve the skin, and it has followed the anticipated benign clinical course without evidence of regrowth or progression in a follow-up period of 54 months. Recognition of fetal rhabdomyoma is essential to convey accurate information about tumor behavior and to avoid both under and over treatment.

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CORRECTION

Torlakovic EE, Gomez JD, Driman DK, et al. Sessile serrated adenoma (SSA) vs. traditional serrated adenoma (TSA). *Am J Surg Pathol*. 2008;32:21–29.

In the article on page 21, the authors inadvertently did not include their support information. It is listed below:

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