Pediatric Dermatology Clinical-Pathologic Case “Mimickers”

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Abstract Herein are presented a collection of pediatric dermatology “mimickers.” We have selected three cases in which the suspected clinical diagnosis was overturned by the histopathology findings.

Keywords Stiff skin syndrome · Morphea · Fibrillin · Rhabdomyosarcoma · Vascular birthmark · Clear cell papulosis · Flat warts · Toker cells

Introduction

We present three patients who presented to pediatric dermatology with rare conditions. The first case is of stiff skin syndrome that was diagnosed previously and treated as linear morphea for many years. The second case is that of an infantile rhabdomyosarcoma misdiagnosed as a vascular birthmark, and the third case is that of clear cell papulosis in a toddler, mimicking flat warts. In all three cases, the clinician was prompted to perform a skin biopsy, because the clinical presentation did not “quite fit” with the suspected or presumed diagnosis; and in each case, the histopathology was crucial in making the correct diagnosis.

Case 1: Stiff Skin Syndrome Mimicking Linear Morphea

An 18-year-old female was referred to pediatric dermatology for a discussion of ongoing care for her “linear morphea.” She had hard skin on the right thigh since the age of 4 years with

progressive expansion over time despite treatment with methotrexate and intravenous corticosteroids. Her original biopsy was read as “consistent with morphea.” At presentation, she was taking oral methotrexate, with the plan to taper off the medication over time, but her skin had not softened or responded to the medication as expected. No family members had similar disease. On examination, she had a stony hard somewhat pebbly plaque that extended down the right thigh (Fig. 1). Parts of the lesion were associated with increased dark hair growth.

A repeat deep incisional skin biopsy was performed given the unusual morphology of her skin lesions as well as the lack of response to therapy. Histopathology revealed normal follicular and eccrine structures with no adnexal atrophy or entrapment of eccrine coils. There were thickened but not sclerotic collagen bundles in the deep reticular dermis that extended through the subcutis in a lattice-like woven configuration. There was no inflammation present (Fig. 2). The diagnosis of stiff skin syndrome (congenital fascial dystrophy) was made based on this biopsy.

Distinguishing between stiff skin syndrome and morphea both clinically and histopathologically is outlined in Tables 1 and 2. The repeat biopsy was performed on this patient because the clinician questioned the diagnosis of morphea based on the “rock hard” feel of the skin, the lack of dyspigmentation, and the increased hair growth within the lesion (not seen in photos/figures, as the patient shaved the excess hair.) Also, the patterning of the skin lesion, with a Y-shaped bifurcation on the thigh, did not follow the patterning typical of morphea along the lines of Blaschko [1]. The most important clue to the diagnosis of stiff skin syndrome on histopathology was the finding of a lattice-like array of thickened, horizontally oriented collagen bundles, proposed to be the histopathological hallmark of this condition [2•].

Most cases of stiff skin syndrome are sporadic [3, 4]. Loeys et al. sequenced the fibrillin-1 (FBN1) gene in affected individuals from four unrelated families with autosomal dominant

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Fig. 1 An 18-year-old female with progressive expansion of a stony hard somewhat pebbly plaque, extending down the right thigh since the age of 4 years

inheritance of stiff skin syndrome, and they found heterozygous missense mutations all within exon 37 of the gene for the extracellular matrix molecule fibrillin, in an area that affects interactions with neighboring cells [5•].

The tight skin mouse (Tsk/+) has similar fibrosing cutaneous disease inherited as an autosomal dominant trait. A duplication of the murine fibrillin-1 gene has been identified and the abnormal protein is thought to affect TGF-beta synthesis and alter matrix expression [6]. Fibrillin-1 is an important component of microfibrils, affecting protein-protein interactions and extracellular matrix synthesis. The Tsk1/+ mice have increased cutaneous TGF-beta, increased binding of TGF-beta to fibrillin in vitro, and increased cutaneous collagen synthesis, leading to skin fibrosis. Of note, a fibrillin mutation was not detected in this patient, who likely has a sporadic form of this condition.

Case 2. Rhabdomyosarcoma Mimicking a Vascular Birthmark

A 12-month-old boy presented to dermatology for a birthmark on his chest. The skin lesion was a 3.5-×2-cm hyperpigmented crescent-shaped patch underlying which were three firm but not hard nodules that were freely mobile and nontender with a somewhat “spongy” feeling (Fig. 3a).

The skin lesion was reportedly present at birth but was flatter, and the subcutaneous component by report was not multinodular as it was at the time of examination. The skin over it had always been brown, but it was getting darker. Biopsy was attempted at the time of the first visit, and the lesion bled profusely leading the clinician to consider a vascular malformation as the diagnosis.

Fig. 2 Histopathology showing a lattice-like array of thickened, horizontally oriented collagen bundles in the deep reticular dermis, extending into the subcutis, characteristic of stiff skin syndrome (upper panel: magnification 2×; middle and lower panels: magnification 10×)

Ultrasound was obtained, which showed a hypoechoic lesion in the skin and subcutaneous soft tissue of the chest. There appeared to be color flow on Doppler. The radiologist’s comment was “a vascular malformation is a definite consideration.”

The patient returned in follow-up, at which time the lesion had grown to 4×3 cm with a 2.7×2.2 mass in the subcutaneous tissue that was slightly firm but mobile (Fig. 3b). Urgent referral was made to a pediatric plastic surgeon for definitive biopsy.

On pathology, there were clusters of atypical small round blue cells resembling lung alveoli. Tumor cells were shed into center of alveolar spaces. Characteristic giant cells with

Table 1 Clinical presentation of stiff skin syndrome vs. morphea

Stiff skin syndrome	Morphea
Rock or stony hard, pebbly skin	Skin is sclerotic but often smooth
Usually no dyspigmentation	Often see hyper- or hypopigmentation
Often associated hypertrichosis	Often associated with alopecia
Found on thigh, buttocks, and hip but no patterning	Characteristic patterning in linear morphea, following lines of Blaschko [1]
No serological, immunological, and vascular abnormalities	Can be associated serological, immunological, and vascular abnormalities
Lack of response to traditional morphea treatment or any treatment	Often responds to anti-inflammatory treatment, especially if identified early

wreath-like nuclei were present (Fig. 4). The diagnosis was “alveolar rhabdomyosarcoma.”

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. The incidence is approximately 4–6 cases per 1,000,000 population per year, and approximately 350 new cases are diagnosed in the United States each year in individuals younger than 20 years of age [7].

Rhabdomyosarcoma is one of the small, round blue-cell tumors of childhood, thought to be derived from primitive mesenchyme that retains the capacity for skeletal muscle differentiation. Rhabdomyosarcoma cells tend to have variable differentiation along the myogenesis pathway and may appear as strap cells or myotubes that sometimes contain muscle cross-striations. Rhabdomyosarcoma cells may demonstrate positive immunohistochemical results for muscle-specific markers, such as myoglobin, actin, and desmin. Additional immunostains include myogenin and MyoD1.

Table 2 Histopathology of stiff skin syndrome vs. morphea

Stiff skin syndrome	Morphea
Noninflammatory	Often lymphocytic or lymphoplasmacytic infiltrate at the junction of the dermis and subcutis
Thick collagen is deeper, usually in the subcutis and fascia	Sclerotic collagen in the deep reticular dermis
No distortion of adnexal structures	Usually see “entrapment” of adnexal structures and atrophy of hair follicles
Lattice-like array of thickened, horizontally oriented collagen bundles may be characteristic feature [2••]	Densely packed sclerotic collagen, no lattice-like array
Increased deposition of both fibrillin-1 (FBN-1) and elastin in papillary dermis	Increased normal collagen; decreased CD34+ cells in areas of sclerosis

Fig. 3 *a* A 12-month-old male with a hyperpigmented crescent shaped patch on the chest with underlying nodules, present since birth. *b* Follow-up examination of the skin lesion several months later at which time the lesion was larger and there was an appreciable firm mass in the subcutaneous tissue

The rhabdomyosarcoma subtypes have the following distinctive features:

- Embryonal (55 % of cases): small round blue cells resembling embryonic skeletal muscle
- Botryoid (5 % of cases): clinically resembles clusters of grapes. Microscopically, cells are undifferentiated, round or spindled with sparse cytoplasm. Mitotic figures are usually numerous.
- Alveolar (20 % of cases): cells line up along membranes that may be imperceptibly thin or that may be obvious collagen bands resembling the lung alveoli. A tumor should be classified as this type if any portion of it appears to be alveolar. Tumor cells are shed into the center of alveolar spaces. The alveolar rhabdomyosarcoma contains variable eosinophilic rhabdomyoblasts and giant cells with wreath-like nuclei.
- Undifferentiated (20 % of cases): diagnosis depends on immunostaining and molecular studies.

The embryonal subtype has the most favorable prognosis, whereas the alveolar subtype is the most aggressive subtype.

Molecular genetic testing is now widely used to help classify these tumors, determine outcomes, and guide therapy. In 60 % of cases of alveolar rhabdomyosarcoma, there is a

Fig. 4 Histopathology showing clusters of atypical small round blue cells resembling lung alveoli with tumor cells being shed into the centers of alveolar spaces (upper panel: magnification 10×) and characteristic giant cells with wreath-like nuclei (lower panel: magnification 40×)

tumor-specific chromosomal translocation $t(2;13)(p35;q14)$ leading to the expression of a PAX3-FOXO1 fusion protein, detectable by classic karyotyping, RT-PCR (reverse transcriptase polymerase chain reaction) or FISH (fluorescence in situ hybridization). Twenty percent of cases of alveolar rhabdomyosarcoma have a PAX3-FOXO1 phenotype, and another 20 % of cases do not have evidence of either translocation. PAX is a neuromuscular transcription factor and FOXO1 is another relatively ubiquitous transcription factor. The fusion molecule is a potent transcription factor. It has been shown that patients with metastatic alveolar rhabdomyosarcoma with a PAX3-FOXO1 fusion have a significantly poorer prognosis than those with a PAX7-FOXO1 fusion. There is also some evidence suggesting that tumors classified as alveolar on histopathology with no chromosomal translocation often behave more like embryonal rhabdomyosarcoma, exhibiting better outcomes [8].

Rhabdomyosarcoma usually manifests as an expanding mass, and clinical presentation is dependent on the location of the tumor. Alveolar rhabdomyosarcoma tends to occur in older patients with a mean age of 15–20 years, and it typically arises in the deep musculature of an extremity [9]. Misdiagnosis of infantile rhabdomyosarcoma as a vascular birthmark, namely a hemangioma of infancy, has been reported [10, 11].

The histopathologic differential diagnosis for infantile rhabdomyosarcoma includes:

- Ewing sarcoma and other primitive neuroectodermal neoplasms
- Liposarcoma
- Neuroblastoma
- Pheochromocytoma
- Wilms tumor

The patient's initial staging work-up was negative for distant metastatic disease but notable for regional lymph node involvement. He underwent complete excision of the skin lesion, had lymph node dissection and was treated with chemotherapy. FISH analysis revealed a PAX3-FOXO1 gene rearrangement. Two years after diagnosis, he presented with pulmonary nodules confirmed to be alveolar rhabdomyosarcoma, indicating relapse with metastatic disease. He is currently being treated with chemotherapy for this relapse.

Case 3: Clear Cell Papulosis Mimicking Flat Warts

A 14-month-old girl presented to dermatology with multiple 2- to 3-mm, flat, white papules in the vulvar and suprapubic area as well as on the buttocks. These were first noted at 6–8 months of age and were becoming more numerous (Fig. 5). They were thought to be flat warts clinically but were unusual in appearance and location.

A shave biopsy was performed and the pathology showed a small papular area with large clear pagetoid cells without nuclear atypia along the basal layer of the epidermis. The clear cells stained positive for cytokeratin 7 (CK7), and the CK7+ cells were found in the papular area of the lesion but not in the adjacent epidermis. There were no granular layer changes to suggest flat warts (Fig. 6). The diagnosis of clear cell papulosis was made based on this biopsy.

Fig. 5 A 14-month-old girl with multiple 2- to 3-mm flat white papules in the vulvar, suprapubic area, and buttocks, first noted at 6–8 months of age and becoming more numerous

Fig. 6 Histopathology showing a small papular area with large clear pagetoid cells without nuclear atypia (arrows) (upper panel: magnification 20×). The clear cells stained positive for cytokeratin-7 (CK7), and the CK7+ cells were found along the basal keratinocyte layer in the papular area of the lesion but not in the adjacent uninvolved epidermis (middle and lower panels: magnification 10×)

Clear cell papulosis is a rare and newly described entity, first reported in 1987 [12]. The disease is characterized clinically by multiple small, hypopigmented, flat-topped maculopapules distributed on the lower abdomen and along the milk line in young children. The clinical differential diagnosis often includes tinea versicolor, postinflammatory hypopigmentation, vitiligo, flat warts, and pityriasis lichenoides.

Histologically, clear cell papulosis is characterized by the presence of large, benign pagetoid cells in the epidermis resembling the clear cells of the nipple [13]. The clear cells are intraepidermal glandular secretory cells called Toker cells, found in normal nipples, accessory nipples, and along the milk line/anogenital regions in both males and females [14, 15]. The histologic differential diagnosis and immunostaining patterns for pagetoid cells in the epidermis are outlined in Table 3. Of note, these clear cells seen in clear cell papulosis can be missed easily or mistaken for other entities (i.e., melanocytes.) Therefore, a high index of suspicion on the histopathologist's part is necessary so that the correct immunohistochemical studies can be obtained to make a definitive diagnosis of clear cell papulosis [16•]. Those stains include variable positivity for the following: mucin, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), cytokeratin A1 and/or A3, gross cystic disease fluid protein-15, cell adhesion molecule-5.2 (CAM-5.2), cytokeratin-7 (CK-7), and colloidal iron. Immunostaining is negative for S100 protein.

The clinical significance of clear cell papulosis also lies in its potential histogenetic link with Paget's disease of the skin, but a recently published study with long-term follow-up of these patients suggests that the skin lesions in many of these patients remit with time and there is no malignant potential. Tseng et al. reported that after a median follow-up duration of 11.5 years, regression of skin lesions was observed in 85.7 % of patients [17••].

Table 3 Immunostaining of Pagetoid cells in the epidermis

Type of cell	Disorder	S100 protein	Cytokeratin	Other
Melanocytes	Melanoma in situ	Positive	Negative	MART-1 and MelanA positive
Keratinocytes	Squamous cell carcinoma in situ	Negative	High MW cytokeratin AE1/AE3 positive	
Langerhans cells	Langerhans cell disease	Positive	Negative	CD1a positive
Epithelial cells of underlying adenocarcinoma	Mammary or extramammary Paget's disease	Negative	Low MW cytokeratin CK7-positive Cam 5.2 ± positive	Often Her2/Neu ER/PR-positive in mammary Paget's
Toker cells	Normal finding in nipple and milk line Clear cell papulosis	Negative	CK7-positive	Her2/Neu ER/PR negative

Bolded text represents key immunostains for the diagnosis.

Conclusions

We have presented three cases of rare pediatric dermatologic conditions in which the clinician was prompted to perform a skin biopsy because the clinical presentation did not “quite fit” with the suspected or presumed diagnosis. Performing a skin biopsy on a pediatric patient can be challenging. However, the clinician should not hesitate to perform a skin biopsy when the clinical presentation is unusual, because histopathology can be crucial in making an accurate diagnosis.

Compliance with Ethics Guidelines

Conflict of Interest Amy E. Gilliam declares no conflicts of interest.
Anita C. Gilliam declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance