The Stiff Skin Syndrome

Case Series, Differential Diagnosis of the Stiff Skin Phenotype, and Review of the Literature

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Background: Stiff skin syndrome is a sclerodermalike disorder that presents in infancy or early childhood with rock-hard skin, limited joint mobility, and mild hypertrichosis in the absence of visceral or muscle involvement, immunologic abnormalities, or vascular hyperreactivity.

Observations: We describe 6 children who fit criteria for stiff skin syndrome. A review of the clinical range of this disorder and discussion of the differential diagnosis is presented. The age at onset in our cases ranged from infancy to 6 years of age. Stony-hard skin was noted mostly on the thighs, buttocks, and lower back with shoulder and arm involvement in 2 cases. There was associated hypertrichosis in 3 of 6 cases. Extracutaneous manifestations consisted primarily of joint restriction, and several patients had resulting postural and thoracic wall irregularities. Histopathologically, our cases showed areas of fascial sclerosis or showed increased fibroblast cellularity with thickened, sclerotic, horizontally oriented collagen bundles in the deep reticular dermis and/or subcutaneous septa without associated inflammation.

Conclusions: Stiff skin syndrome is characterized by an early, insidious onset of stony-hard skin, often with associated contracturelike joint restriction, hypertrichosis, and postural and thoracic wall abnormalities. Supportive histopathologic findings consisting of either fascial sclerosis or increased fibroblast cellularity with sclerotic collagen bundles in the deep reticular dermis and/or subcutaneous septa may help to confirm this diagnosis.

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TIFF SKIN SYNDROME (SSS) is a sclerodermalike disorder characterized by stony-hard skin, limited joint mobility, and mild overlying hypertrichosis. We report 6 cases of SSS, emphasizing the clinical presentations, histopathologic features, and differential diagnosis of this rare disorder. Cases 3 to 6 are presented briefly to highlight the salient features of each case.

He has had no visceral symptoms, no Raynaud phenomena, and no intellectual impairment. His medical history included asthma, frequent ear infections, and a patent ductus arteriosus. There were no affected family members.

On physical examination, he had a very dense, woody, ill-defined induration encircling his right thigh to just above the patella extending to his right buttocks, back, and shoulder. The left thigh and buttocks were involved to a lesser extent from the iliac crest down through the lateral and posterior thigh to below the knee joint. He had restricted range of motion of his hips and knees and a slightly protruding barrel chest, and his thorax was thinned with respect to his arm girdle. He had hypertrichosis in his lumbosacral area (Figure 1A).

His laboratory evaluations included a negative antinuclear antibody and normal skeletal films. A thoracic computed tomography scan and magnetic resonance imaging of the abdomen, pelvis, and lower extremities only revealed a nonspecific soft tissue enhancement. Findings from pulmonary functional studies were normal. A deep fascial biopsy revealed a fascial thickening and sclerosis with only a subtle increase in over-
all cellularity (Figure 1B). There was a subtle increase in deep dermal cellularity as well. The superficial dermis and epidermis were normal, and there was little to no increase in interstitial mucin in the dermis.

The progression of his skin disease was followed using clinical drawings that delineated regions affected by skin thickening. During the first 6 months of follow-up, the areas of clinical induration progressed to involve more of the upper back, right lateral arm, neck, abdomen, and lower legs bilaterally. After consultation with the pediatric rheumatology service, treatment with monthly intravenous pulses of methylprednisolone (20 mg/kg) for 3 months along with weekly doses of methotrexate, 25 mg, subcutaneously was initiated. One year later, no further areas of progression were observed and some of the more mildly affected areas appeared to be softening. However, long-term follow-up examination at age 15 years revealed that the patient’s skin disease continued to slowly progress to involve new areas despite trials of other therapeutic modalities, including psoralen with UV-A light and oral penicillamine.

CASE 2

An 8-year-old Hispanic girl presented with a skin lesion on her left lateral thigh that had been present for 1 to 2 years. Her father reported that the lesion was initially small but had been gradually widening out of proportion to her growth. There was no associated pain or pruritus. The child was otherwise healthy with normal growth and development, and there was no family history of similar skin conditions or autoimmune disease.

On skin examination, she had a 30 x 10-cm area of thickened, sclerotic skin located on the left thigh with associated hyperpigmentation and hypertrichosis (Figure 2A). At the periphery of the lesion, deep nodular components could be palpated. The lesion extended from her left flank and hip along the lateral thigh and involved the left posterior calf.

Laboratory evaluations included negative findings for antinuclear antibodies and anti–double-stranded DNA as well as a normal complete blood cell count, erythrocyte sedimentation rate, and C-reactive protein level. An excisional biopsy from the involved skin revealed deep dermal and subcutaneous sclerosis with thickened, horizontally arranged collagen bundles with diminished spaces between them. There was a slight increase in spindled cellularity throughout the reticular dermis with the absence of an associated lymphocytic or plasmacytic infiltrate. The intervening fatty lobules appeared normal (Figure 2B). These histopathologic findings were interpreted as consistent with SSS.

The patient returned for follow-up examination 1 year after her initial presentation, at which time progression of her disease was noted. The skin involvement had extended to include her hip and waist, encompassing an area of 25 x 58 cm. She complained of limitation of her range of motion and pain with exercise. A physical therapy evaluation had been requested after the first visit, and the family had not followed through with this. Physical therapy was again recommended with the addition of ibuprofen for pain, and the patient has since been lost to follow-up.

CASE 3

A 6-year-old white girl with an unremarkable medical and family history presented with firm skin that started on the right leg for 1 year. She had thickened skin with overlying hyperpigmentation that involved her lower hip girdle, lower back, lateral thighs, and entire legs. She had a pseudohypertrophic stance and toe-walked with her right leg. She had a protuberant chest, retracted arms, and thin, atrophic shoulders. There was also increased dense hair growth over the lumbosacral area. A punch biopsy revealed a subtle increase in density of fibrocyte nuclei and a marked increase in interstitial mucin in the deep reticular dermis. The fascia was not visualized.

CASE 4

A 9-year-old girl presented with a 6-year history of indurated skin starting in the left deltoid. She had not responded to therapy with topical calcipotriene, triamcino-
lone, and betamethasone dipropionate. She had a brother with a similar lesion on the buttock, but he had not been examined by us. The involved areas of her skin had a sensation of skin “tightness” and occasional tenderness after physical exertion. She had markedly thickened skin involving the left shoulder and arm area, the left lumbar back, and the right back. Multiple biopsies finally revealed thickened, sclerotic collagen bundles in horizontal array in the deep reticular dermis and superficial subcutaneous septa without inflammation or distortion of the adnexa. Dermal and subcutaneous septal cellularity was slightly increased. The fascia was not visualized.

CASE 5

A 2-year-old girl presented with a growing lesion on her left buttock that had been present since birth. She had an otherwise unremarkable medical and family history. The lesion was asymptomatic and did not interfere with ambulation. She had a deep induration on the lateral aspect of the left buttock with overlying hypertrichosis. Skin biopsy results showed broadened and elongated collagen bundles in horizontal array in the deep reticular dermis and superficial subcutaneous septa without inflammation or distortion of the adnexa. Dermal and subcutaneous septal cellularity was slightly increased. The fascia was not visualized.

CASE 6

A 7-year-old white girl presented with thick skin on the right buttock for 4 years. A skin biopsy specimen had previously shown dermal fibrosis without inflammation, and she was treated with topical calcipotriene and clobetasol ointments for presumed morphea. She experienced minimal softening of her skin in that area according to parental report. She had an otherwise unremarkable medical and family history. There was a 4 × 5-cm, ill-defined, indurated plaque of deep sclerosis that involved the right buttock, the lower back, and the right hip. She had no limitation of range of motion at the right hip. An excisional skin biopsy specimen showed abnormally horizontally oriented, thickened collagen bundles with a subtle increase in fibrocytes in the deep reticular dermis. The elastic tissue was normally preserved, and fascia was not observed in the sections.

COMMENT

Stiff skin syndrome is a rare disorder originally described by Esterly and McKusik. It is characterized by stony-hard skin, limited joint mobility, and mild overlying hypertrichosis. Jablonska et al further characterized this condition as a generalized, noninflammatory fascial disorder in the absence of visceral involvement, muscle involvement, immunologic abnormalities, or vascular hyperreactivity and proposed the name “congenital fascial dystrophy.” At least 37 cases of SSS have been published since the initial report by Esterly and McKusik. Table 1 summarizes the clinical features in these 37 published cases of SSS in addition to the 6 cases presented herein.

CLINICAL FEATURES

The cutaneous findings present in infancy or in early childhood with rock-hard skin bound firmly to the underlying tissues that is most prominent in areas with abundant fascia such as on the buttocks and thighs. The overlying skin can be normal in appearance or may have
mild hypertrichosis and hyperpigmentation overlying the affected areas of skin. Our patients had cutaneous involvement primarily or exclusively in the pelvic and shoulder girdle areas. The indurated skin felt like a well-demarcated, large, sometimes nodular subcutaneous tumor. All of the cases have had an insidious onset in infancy or early childhood.

Extracutaneous features of SSS include contractures, especially of the large joints, often resulting in scoliosis, a tiptoe gait, and a narrow thorax in relation to the arm girdle. Several reported cases have had associated restrictive pulmonary changes and growth retardation. Notably lacking are visceral, bone, or muscular involvement; immunologic abnormalities; vascular disturbances; or mucopolysacchariduria. The disease is slowly progressive and nonfatal. A genetic basis has been suggested by the reports of other affected family members, and/or evidence of associated consanguinity. Therapy thus far has been limited to supportive and rehabilitative care. In our cases, joint restriction was common but not universal. Postural and thoracic wall irregularities occurred sporadically. None of our cases had other associated abnormalities. All of our cases were isolated with the possible exception of case 4, whose family reported a sibling with a similar skin condition, which was not brought to medical attention.

### HISTOPATHOLOGIC FEATURES

Several histologic patterns have been described in previous reports. Early reports described increased dermal mucin and large, bizarre fibroblasts that stained metachromatically with toluidine blue. Jablonska et al described underlying fascial thickening “four times beyond normal” with “amianthoid-like” collagen fibers and bundles composed of incompletely organized microfibrils. Several subsequent reports confirmed a thickened fascia, but others reported normal fascia. One of our patients (case 1) had a biopsy of the fascia, which revealed fascial sclerosis. In the remaining 5 cases, the diagnosis was microscopically supported via deep incisional or punch biopsies that did not include the fascia. In one of our patients (case 2), the biopsy revealed increased cellularity and an increase in interstitial mucin in the deep reticular dermis. These findings, in conjunction with the characteristic postural and thoracic wall changes, led to the diagnosis of SSS. In the remaining 4 cases, biopsy specimens showed thickened, sclerotic collagen bundles in the deep reticular dermis and/or subcutaneous septa with no inflammation or distortion of adnexa. The collagen was usually horizontally oriented with diminished spaces between them, although 1 case exhibited a haphazard arrangement in the mid to deep reticular dermis. Slightly increased cellularity was present in 3 of these 4 cases and 5 of the 6 total cases. Several patients needed repeated deeper biopsies performed because prior superficial biopsies were nondiagnostic. Possibly, SSS exhibits a spectrum of histopathologic findings, with interstitial mucin representing early disease and the deep dermal sclerosis signifying a later stage.

### DIFFERENTIAL DIAGNOSIS

Several entities have clinical features that resemble SSS. Scleredema, in particular, can have many overlapping features with SSS. Scleredema results in nonpitting edema due to mucin in the dermis. It typically presents with skin tightness and induration beginning...
on the neck or face and spreading symmetrically to involve the arms, shoulders, back, and chest.\textsuperscript{25} It may have an acute onset following an upper respiratory tract infection or an insidious onset without preceding infection, with or without diabetes mellitus. Classically, it is a disease of adults, but several pediatric cases have been reported. Microscopically, there is increased mucin deposition in the reticular dermis as well as broadening of collagen bundles, but the bundles are separated by fenestrations.\textsuperscript{22-25} Sclerotic fascia has not been reported in scleredema.

Several features can help differentiate SSS and scleredema. In SSS, disease is centered on or around the pelvic and shoulder girdle, whereas scleredema is centered on the face, head, neck, and back\textsuperscript{24} and with rare exception\textsuperscript{25} only involves the pelvic or shoulder girdle with concomitant involvement of the face, neck, or upper back.\textsuperscript{24} Joint restriction, although common in SSS, is rare in scleredema and is more often due to a “bulk” effect of the thick skin usually affecting the eyelids, neck, mouth, and shoulder.\textsuperscript{18,26-29} The skin stiffness in SSS, in our experience, is often well demarcated, uneven, or lumpy and may not involve an entire anatomic unit, while the stiffness in scleredema is more uniform, typically encompassing an entire involved anatomic unit. The abrupt onset often seen in scleredema is not a feature of SSS. The histopathologic features overlap, but increased fibroblast cellularity, thickened collagen bundles in a horizontal arrangement, and diminished spaces between individual bundles, if present, can help differentiate biopsy results of SSS from scleredema. Typically in scleredema, the collagen bundle pattern is nearly normal.

Recently, 2 cases with overlapping features of both scleredema and SSS were published as a diagnostic dilemma.\textsuperscript{30} One patient had a 3-day history of right leg swelling, diffuse induration of the right flank, waist, and entire right leg from ankle to hip, and histopathologic findings that demonstrated bundles of irregular dense collagen extending deep into the sweat ducts and separated by mucin and a normal fascia. The abrupt onset and diffuse uniform involvement in this case make scleredema, albeit in an atypical distribution, the most likely diagnosis. The second case was a 9-year-old girl with a 5-year history of progressive firmness on the right thigh, torso, shoulder, and bilateral buttocks, with loss of range of motion of the right knee and hip and an uneven plaque-like induration of the right thigh and flank. Findings from histopathologic examination demonstrated slight separation of thickened collagen bundles (suggestive of scleredema) but also an increased fibrocyte density favoring classification as SSS, and these features, particularly with joint contracture and the uneven, irregular induration on the right leg, are those of SSS.

Cases of SSS are often initially diagnosed as sclerodermatomyositis, systemic sclerosis, or localized scleroderma. Sclerodermatomyositis is an overlap syndrome with features of dermatomyositis and systemic sclerosis\textsuperscript{30} that typically presents with arthralgias, arthritis, sclerodermoid skin lesions, and joint restriction. Features that distinguish this entity from SSS are evidence of muscle involvement (eg, elevated serum muscle enzyme level and abnormal electromyography), autoantibodies, and vascular hyperreactivity. Systemic sclerosis is very rare in childhood and has many features including “hidebound” skin changes in the hands and face, Raynaud phenomenon, periungual telangiectasias, and immunologic abnormalities that help distinguish it from SSS.\textsuperscript{2} Localized scleroderma (morphea) tends to have a later onset as well as more localized and asymmetric involutions and alterations of the skin.\textsuperscript{2}

Deep morphea, a form of localized scleroderma, must also be distinguished from SSS. This can sometimes be difficult, given the clinical similarities between the 2 disorders. However, the histopathologic findings of deep morphea (as well as those of systemic sclerosis and localized scleroderma) are distinct from those of SSS. In deep morphea, there is typically a lymphocytic or lymphohistiocytic infiltrate at the junction of the dermis and subcutis with abnormal, sclerotic collagen in the deep reticular dermis or subcutaneous septa, and fascial involvement is exceptional. In contrast, in SSS there is typically fascial sclerosis with slightly increased fibrocyte cellularity, and thickened collagen bundles, often with a horizontal orientation, are sometimes also present in the deep reticular dermis and/or subcutaneous septa. There is characteristically no inflammation or distortion of adnexa in SSS. In addition, many of the clinical features of SSS, such as the characteristic distribution involving the pelvic area and/or shoulder girdle and the often-present hypertrichosis, are typically not observed with deep mor-
Finally, patients with SSS rarely respond to anti-inflammatory treatments compared with those with deep morphea (Table 2). Case 1 was treated with pulsed methylprednisolone sodium and methotrexate owing to relentless disease progression and a lack of therapeutic alternatives. While disease activity appeared to slow down within the first few years after treatment, long-term follow-up has demonstrated continued slow disease progression with involvement of new areas despite trials of other therapeutic modalities. While there are similari-

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<th>Features Overlapping With Stiff Skin Syndrome</th>
<th>Other Features</th>
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<td>Mucopolysaccharidoses</td>
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<td>Hunter syndrome</td>
<td>Early onset; focal, pebbly thickened skin; joint stiffness</td>
<td>Neurologic abnormalities; skeletal abnormalities</td>
<td>Urine mucopolysacchariduria</td>
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<td>Hurler syndrome</td>
<td>Early onset; focal, pebbly thickened skin; joint stiffness</td>
<td>Neurologic abnormalities; skeletal abnormalities</td>
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<td>Scheie syndrome</td>
<td>Early onset; focal, pebbly thickened skin; joint stiffness</td>
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<td>Lysosomal storage diseases</td>
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<tr>
<td>Neonatal mucolipidosis II (I-cell disease)</td>
<td>Newborn onset; restricted joint mobility; tight, thickened skin</td>
<td>Abnormal facies; psychomotor retardation; organomegaly multiple skeletal dysplasias</td>
<td>Elevated serum level and low fibroblast lysosomal enzyme activities; genetic sequence analysis available for mutations in N-acetylgalactosamine-1 (GlcNAc)-phosphotransferase α/β-subunits precursor gene</td>
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<td>Farber lipogranulomatosis</td>
<td>Contractures of the limbs; subcutaneous nodules and plaques</td>
<td>Joint swelling; hoarseness; nutritional failure; neurologic abnormalities visceral involvement</td>
<td>Biopsy specimen shows large cells with foamy cytoplasm in the dermis; defective lysosomal acid ceramidase activity in cultures of skin fibroblasts</td>
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<td>Other conditions with known genetic mutations</td>
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<td>Infantile systemic hyalinosis</td>
<td>Neonatal onset; diffusely thickened skin; flexion contractures</td>
<td>Perioral papules; gingival hyperplasia; perirectal nodules; diarrhea; failure to thrive; death in early childhood; caused by mutations in the capillary morphogenesis factor-2 gene (CMG2)</td>
<td>Skin biopsy specimen demonstrates areas of pale, hypocellular “hyaline” and absent elastic fibers within the papillary dermis</td>
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<td>Juvenile hyaline fibromatosis</td>
<td>Presents in infancy or early childhood; flexion contractures; discrete, large subcutaneous nodules</td>
<td>Gingival hyperplasia; osteolytic bone lesions; caused by mutations in the capillary morphogenesis factor-2 gene (CMG2)</td>
<td>Skin biopsy specimen demonstrates deposition of amorphous hyaline material in the papillary and reticular dermis</td>
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<td>Restrictive dermopathy</td>
<td>Newborn onset; abnormally tight skin; joint contractures</td>
<td>Dysmorphic facies with a fixed open mouth in an “O” position; universally fatal in the neonatal period; polyhydramnios; pulmonary hypoplasia; biopsy showing thick epidermis and thin dermis</td>
<td>Diagnosis made by clinical findings and course; genetic sequence analysis available; mutation in the LMNA gene encoding A-type lamins; mutation in the ZMPSTE24 gene encoding a metalloproteinase essential for posttranslational processing of lamin A</td>
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<td>Hutchinson-Gilford progeria</td>
<td>Sclerodermalike thick skin; onset in infancy</td>
<td>Loss of subcutaneous tissue; prominent veins; pigmentary changes; alopecia; midfacial cyanosis; abnormal birdlike facies; short stature; skeletal hypoplasia and dysplasia</td>
<td>Diagnosis made by clinical findings; genetic sequence analysis available; mutation in the LMNA gene, typically in codon 608</td>
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(continued)
ties between SSS and an infantile form of deep morphea, the clinical and histopathologic differences suggest that they are distinct entities.

Early cases of SSS may resemble smooth muscle hamartomas or connective tissue nevi, both of which can present as an indurated plaque on the trunk or extremity. Histologic findings of a marked increase in smooth muscle fibers in the dermis distinguish smooth muscle hamartoma from SSS.31 Biopsy results of connective tissue nevi can demonstrate a hamartomatous proliferation of collagen or elastin or may appear as normal skin,32,33 but facial sclerosis, sclerotic collagen bundles in the deep reticular dermis, increased interstitial mucin, or increased cellularity are not found.

Nephrogenic systemic fibrosis, formerly called nephrogenic fibrosing dermopathy, is a scleromyxedemalike fibrosing skin condition found in patients with kidney disease. Pediatric cases have been reported.34 This condition presents as extensive thickening and hardening of the skin with a peau d’orange appearance typically located on the extremities, buttocks, and trunk. Occasionally, joint contractures occur as well. Histopathologic findings demonstrate an increase in dermal fibroblasts, thickened collagen bundles with surrounding clefts, and increased mucin and elastic fibers extending through the subcutis along the septa of fatty lobules, and typically, the degree of overall dermal and subcutaneous cellularity is strikingly different than that of SSS. While there is considerable clinical overlap, a history of renal insufficiency is universally present in this entity and differentiates it from SSS.34 Recent publications suggest an association between exposure to gadolinium-containing

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Eosinophilic fasciitis classically presents with rapidly appearing tender swelling on the arms and legs evolving into brawny induration, often following exercise.\(^{7,39}\) Localized morphea-like skin changes and joint contractures may be present, and the induration is often more distal than proximal. Hematologic abnormalities including peripheral blood eosinophilia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate are often present. Histopathologic findings demonstrate thickened fascia with a cellular inflammatory infiltrate of lymphocytes and plasma cells, with or without eosinophils. In an appropriate biopsy specimen, this entity can be readily distinguished from SSS.

Several other rare conditions can have presentations resembling SSS. The clinical and diagnostic features of these are summarized in Table 3.

### PATHOGENESIS

The pathogenesis of SSS is unclear, but proposed mechanisms include a primary fibroblast disorder resulting in increased acid mucopolysaccharide deposition in the dermis,\(^1,5\) a primary fascial dystrophy resulting in an increased accumulation of collagen,\(^2,6\) and an inflammatory process.\(^7\) It has recently been shown that the fascia in patients with SSS differs from normal fascia by an abundance of myofibroblasts and an overproduction of type VI collagen.\(^9\) Interestingly, myofibroblasts are thought to be the operative cells in extrabdominal desmoid tumors, and type VI collagen might be the material deposited in juvenile hyaline fibromatosis\(^45\) and is also overproduced in systemic scleroderma.\(^46\) Hence, there may be a cytological and biochemical overlap between some of these entities.

The tight-skin (TSK) mouse model has been advanced as an animal model for SSS.\(^6\) The TSK gene is transmitted in an autosomal dominant pattern and is located on the mouse chromosome 2.\(^2,7\) The heterozygous TSK mice (the homozygous state appears to be lethal) develop substantial hypertrophy of loose connective tissue, tendons, cartilage, and bone and have a tightness of the skin that makes it difficult to grasp a fold of skin on the back. Microscopically, there appears to be an abundance of acid mucopolysaccharide deposition in the dermis and hypodermis as well as a markedly thickened fascia.\(^7,2\) The defect appears to be an accelerated biosynthesis of collagen in the fibroblasts of TSK mice.\(^7\) Characterizing the defective gene product of the TSK mutation could well shed significant light on the pathogenesis of SSS, scleroderma, and perhaps some of the other conditions that lead to the stiff skin phenotype.

### CONCLUSIONS

Stiff skin syndrome is characterized by an early, insidious onset of stony-hard, sometimes even unindentation of the skin, centered on the pelvic and/or shoulder girdle usually with contracture-like joint restriction. Hypertrichosis and postural and thoracic wall abnormalities such as a pseu

dohypertrophic stance, thinned thorax, broad shoulders, barrel chest, and tiptoe gait occur variably. The diagnosis is supported by histopathologic findings consisting of either fascial sclerosis or an increased fibroblast cellularity with thickened, sclerotic, usually horizontally oriented collagen bundles in the deep reticular dermis and/or subcutaneous septa with no inflammation or distortion of adnexa and no increased spaces between the bundles. The findings of increased mucin with increased fibroblast cellularity are suggestive but not diagnostic of SSS.

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**Author Contributions:** Drs Liu and Gilliam had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Liu, Williams, Connolly, and Gilliam. **Acquisition of data:** Liu, Frieden, Williams, Connolly, and Gilliam. **Analysis and interpretation of data:** Liu, McCalmont, Frieden, Williams, and Connolly. **Drafting of the manuscript:** Liu. **Critical revision of the manuscript for important intellectual content:** Liu, McCalmont, Frieden, Williams, Connolly, and Gilliam. **Statistical analysis:** Liu. **Administrative, technical, and material support:** Liu. **Study supervision:** Liu, McCalmont, Frieden, Connolly, and Gilliam.

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