Fibrous Arthropathy Associated With Morphea: A New Cause of Diffuse Acquired Joint Contractures

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Etiologies for childhood-onset diffuse joint contractures encompass a large group of inherited disorders and acquired diseases, in particular a subtype of juvenile idiopathic arthritis called "dry polyarthritis," dermatomyositis, and systemic sclerosis. We report on 2 boys, aged 5 and 8 years, who developed acquired symmetric painless joint contractures preceding the development of superficial plaques of morphea by 7 to 13 months. There was no other clinical involvement, biological inflammation, or autoantibodies. No urinary mucopolysaccharidosis was seen. In both patients, wrist MRI showed no joint effusion, no bone erosion, and no or mild synovial thickening with slight enhancement after gadolinium infusion. One patient underwent a synovial biopsy, which showed dense fibrosis with a sparse inflammatory infiltrate, similar to the pathologic pattern observed in the skin biopsy. With methotrexate and systemic steroids, joint contractures slowly improved in the first patient and remained stable in the second. These 2 cases suggest that fibrous synovitis should be considered in children with acquired diffuse, symmetric, painless contractures and without elevation of acute-phase reactants, even in the absence of cutaneous manifestations. Articular MRI with gadolinium and careful cutaneous examination at onset and during follow-up should provide clues for diagnosing this entity.

Etiologies of childhood-onset diffuse joint contractures encompass a large group of inherited disorders and acquired diseases, in particular, subgroups of patients within connective tissue diseases that demonstrate a "dry synovitis," which is the presence of joint contractures or stiffness without obvious effusion or warmth of the joint. These include juvenile idiopathic arthritis (JIA), dermatomyositis, systemic sclerosis, and localized scleroderma (LS), typically the deep morphea and linear morphea subtypes of LS affecting the extremity. In LS and systemic sclerosis, the dry synovitis is associated with deep subcutis, fascial, tendon, and joint capsule fibrosis. The skin and subcutis in these patients is described as hard and indurated and feels "tacked down." At times, involvement of deep connective tissue below the skin may affect joint functioning slightly distal to the area. For example, an indurated linear patch of LS of the upper arm may affect the functioning of the elbow, wrist, and fingers if the deeper tendons are involved, causing a "pulley effect." The forearm and hand will otherwise appear normal without cutaneous findings in these instances.

Here we describe for the first time the cases of 2 patients who presented with diffuse acquired joint contractures preceding distant superficial

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circumscribed morphea, without associated deep morphea. This report emphasizes that fibrosing synovitis should be considered in children with acquired contractures, even in the absence of cutaneous manifestations.

CLINICAL REPORTS

Two Caucasian boys, aged 5 and 8 years, were referred to a pediatric rheumatologist for the evaluation of diffuse joint contracture that had developed some months earlier. Their medical history was negative (Table 1). There was no noteworthy family history or consanguinity. Joint limitation was graduated from 1 to 3, as mild (1), moderate (2), or severe (3).

Patient 1

An 8-year-old boy had diffuse painless mild joint limitation of motion that had developed 5 months earlier, involving the proximal and distal interphalangeal joints, wrists, hips, knees, and ankles. The severity of joint limitations was mild with no functional impact. Seven months after the onset of joint involvement, 3 hyperpigmented superficial cutaneous plaques suggestive of morphea had appeared on the pubis, back, and leg. Laboratory tests found normal complete blood cell count with differential and C-reactive protein level. Rheumatoid factor and antinuclear antibody were negative (single-strand DNA and histone antibodies were not tested). Joint x-rays (hips, knees, ankles, wrists, and spine), echocardiography, eye examination, and pulmonary function tests were normal. Ultrasonography and MRI showed no joint effusion or bone erosions, but a mild synovial thickening slightly enhanced after gadolinium infusion with no subcutis or fascial edema (Fig 1). Skin biopsy was consistent with the diagnosis of morphea (Table 1 and Fig 2). Four months of physiotherapy provided no valuable benefit, and the patient began treatment with methotrexate (10 mg/m^2/week) combined with corticosteroids (1 mg/kg/day prednisone for 1 month then tapered to 5 mg/day) for 6 months. In the absence of any articular improvement, a wrist synovial biopsy was performed, which showed dense fibrosis with a sparse inflammatory infiltrate (Fig 2). Methotrexate and steroids were stopped after 6 months, and physiotherapy was pursued. Morphea remitted within the next 4 months, leaving residual hyperpigmentation without induration. One year after the treatment discontinuation, the patient was well with stable mild joint limitations.

TABLE 1 Characteristics of the Patients

	Patient 1	Patient 2
Age at onset of contractures/sex	8 y/male	5 y/male
Joints involved	Mild limitations of PIP, DIP, wrists, elbows, hips, knees, ankles	Moderate limitations of PIP, DIP, wrists, hips, knees, ankles, cervical spine
Time from onset of polyarthritis and onset of morphea	7 mo	13 mo
Type of morphea	3 superficial plaques (pubis, back, leg)	5 superficial plaques (neck, axilla, pubis, groin)
ESR/CRP	Normal	Normal
Eosinophilia/elevated CPK	No/no	No/no
Autoantibodies	ANA, anti-SSA, anti-SSB, anti-RNP, anti-Scl70: negative	ANA and RF: negative
Wrist MRI with gadolinium infusion	Mild synovial thickening with slight enhancement of synovial membrane after gadolinium infusion No joint effusion, sparse intraosseous edema without bone erosion	No synovial thickening, slight enhancement of synovial membrane after gadolinium infusion No joint effusion, no bone abnormalities
Skin biopsy	Dermal fibrosis, mild lymphocytic infiltrate, horizontalization of elastic fibers and adnexa rarefaction	Dermal fibrosis, sparse inflammatory infiltrate
Synovial biopsy	Dense fibrosis with very sparse inflammatory infiltrates	Not done

ANA, antinuclear antibodies; CPK, creatinine phosphokinase; CRP, C reactive protein; DIP, distal interphalangeal joint; ESR, erythrocyte sedimentation rate; NSAID, nonsteroidal antiinflammatory drug; PIP, proximal interphalangeal joint; RF, rheumatoid factor; RNP, ribonucleoprotein; SSA and SSB, Sjögren syndrome A and B.

Patient 2

A 5-year-old boy had symmetric diffuse painless moderate joint limitations identified 10 months earlier (Table 1). His parents reported morning stiffness lasting <15 minutes. No other clinical abnormalities were noted. Wrist x-rays, ophthalmologic examination (including slit-lamp examination), and echocardiography were normal, along with acute phase reactants. Wrist MRI showed no joint effusion, no bone abnormalities, no synovial thickening, no subcutis/fascial edema, but mild enhancement of the carpal synovium after gadolinium infusion. Laboratory results are given in Table 1. Nonsteroidal antiinflammatory drugs provided a mild subjective improvement, and methotrexate (15 mg/m^2/week) combined with steroids (10 mg/day prednisolone 6 weeks, then 7.5 mg/day 6 weeks, then 5 mg/day 8 weeks, then 2.5 mg/day) and physiotherapy was started. Three months later, the parents noted 4 new small pigmented macules on the neck, pubis, and leg, suggestive of superficial plaque morphea. Biopsy of 1 of these lesions was consistent with the diagnosis of

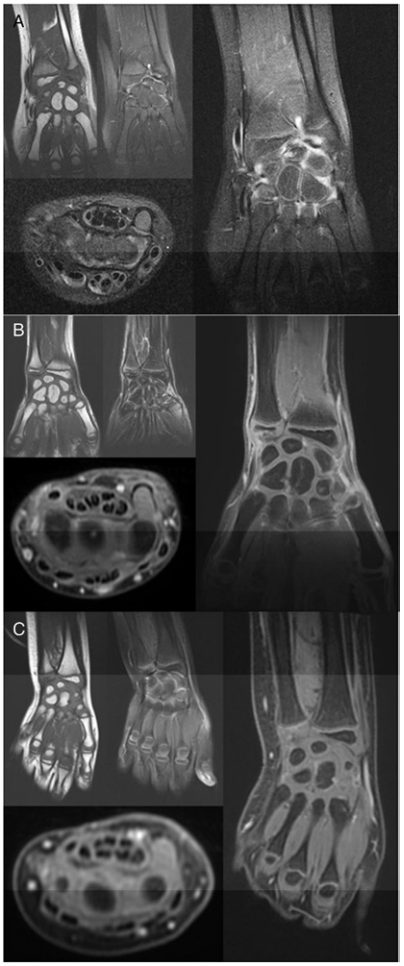

FIGURE 1

MRI patterns of inflammatory dry synovitis for comparison (A) and fibrotic arthropathy in morphea (B and C). A, For comparison, a patient cared for at our center, a 3-year-old girl with inflammatory painful diffuse dry polyarthritis (left wrist: T1-weighted frontal view, T2 fat-saturated (FS)-weighted frontal and axial views and T1 gadolinium FS-weighted frontal view); B, patient 1 (right wrist, T1-weighted frontal view, T2 FS-weighted frontal view and T1 gadolinium FS-weighted frontal and axial views); C, patient 2 (right wrist, T1-weighted frontal view, T2 FS-weighted frontal view and T1 gadolinium FS-weighted frontal and axial views). Synovial thickening slightly enhanced after gadolinium administered; no subcutis, fascia, tendon, or muscle edema was noted on the upper extremity MRI in either case.

morphea. Six months after initiation of treatment, the articular motion had improved slightly; after 12 months of therapy complete articular and active cutaneous remission was achieved. Macules turned hypochromic without induration.

DISCUSSION

We report here, to our knowledge for the first time, that childhood-onset diffuse joint contractures may result from fibrous arthropathy preceding the development of superficial morphea. These contractures presented the same clinical, biological, and radiologic characteristics. Our 2 patients had acquired painless, symmetrical polyarthritis of mild severity, involving both peripheral and axial joints and associated with normal acute phase reactants and no autoantibodies. Articular MRI provided clues for diagnosing this superficial morphea-associated fibrous arthropathy by showing absent or moderate thickening of synovium with mild enhancement after gadolinium infusion and no bone erosion or synovial effusion. A synovial pathology study evidenced that this arthropathy resulted from synovial fibrosis with minimal inflammatory infiltrate, which may be considered an "articular morphea."

Morphea, also referred to as LS, is a fibrotic autoimmune disease of the skin and underlying tissues that is equally frequent in children and adults.[1,2] The clinical subtypes (superficial circumscribed morphea, generalized morphea, deep morphea, and linear and mixed scleroderma)[3] share the same histologic features as systemic scleroderma: deep dermal infiltration by mononuclear cells with thickened collagen fibers, horizontalized fragmented elastic fibers, and adnexal rarefaction. Morphea is usually thought to be a self-limiting disease, but extracutaneous involvement is reported in ~22% of patients, especially in the linear and generalized subtypes in the series of Zulian et al.[4] Extracutaneous involvement was mainly articular[4,5] and presented as oligoarthritis or polyarthritis, related to the skin lesion site in three-quarters of patients. However, the remaining patients had arthritis completely unrelated to the site of the skin lesion, and 30% were positive for rheumatoid factors, raising the suspicion of a systemic, rather than local, pathologic process.[5,6] The clinical characteristics of polyarthritis associated with morphea were not described in this study, and extracutaneous manifestations occurred at the same time or after the diagnosis of morphea.

Although it is not uncommon to find joint contractures in the linear and generalized morphea subtypes, such involvement seems infrequent in superficial subtypes. Our patients had no subcutis induration, and proximal MRI of the forearm and upper arm showed no subcutis

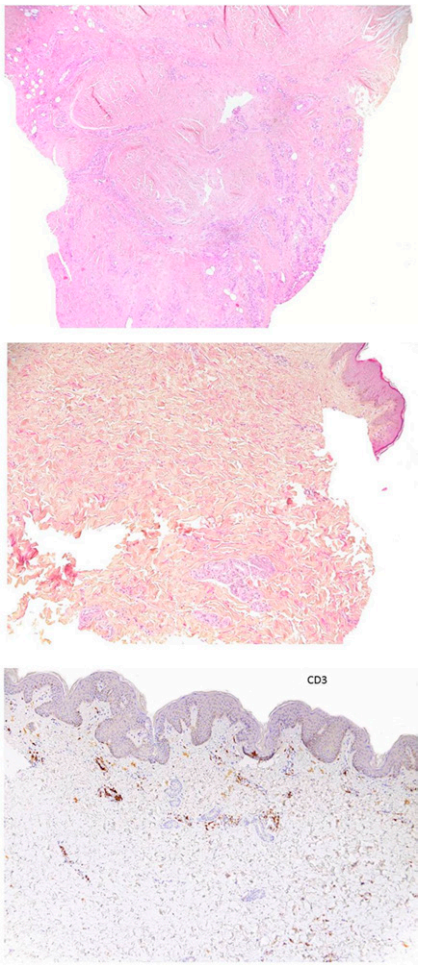

FIGURE 2

Articular (A) and cutaneous (B and C) histologic features of patient 1. A, Hematoxyline Eosine Safran coloration ×200 wrist synovial biopsy: dense fibrosis with few inflammatory cells, mostly located around the capillaries (black arrow: fibrosis and white arrow lymphocytes). B, Hematoxyline Eosine Safran coloration ×100 cutaneous biopsy showing clear dermal fibrosis associated with horizontalization of elastic fibers (black arrow) and scarce perivascular lymphocytes (white arrow). C, Same cutaneous biopsy. Immunostaining with anti-CD3 emphasizes this perivascular infiltrate (×100).

edema. This suggests that their contractures resulted not from deep hidden fibrosis but rather from primary synovial fibrosis preceding cutaneous morphea. The present findings thus argue for including "articular morphea" among the causes of childhood-onset diffuse contractures, even in the absence of cutaneous manifestations. Because morphea is usually asymptomatic and the development of lesions is typically insidious, a careful cutaneous examination is warranted at onset and during follow-up of patients who present with acquired symmetric contractures of unknown cause. This examination will search for superficial plaque morphea associated with this newer "articular morphea," in addition to being on the lookout for the more "typical" "dry synovitis" in deep/linear scleroderma.

Articular MRI provides clues for diagnosing this superficial morphea-associated fibrous arthropathy. It showed mild synovial enhancement after gadolinium infusion with no joint effusion, and a mild bone edema predominant in perivascular regions. This radiologic feature should be distinguished from those observed in deep morphea. In patients with deep morphea, musculoskeletal involvement is frequently detected with MRI, but it is adjacent to the area of morphea and frequently associated with fascial thickening and increased fascial enhancement. Moreover, tenosynovitis, perifascial enhancement, myositis, enthesitis, and bone marrow involvement are detected in addition to articular synovitis.[7]

A careful evaluation of family history and clinical, biological, and radiologic features should allow exclusion of most differential diagnoses for childhood contractures. Causes of diffuse evolving contractures not present at birth include many conditions, both inherited (connective tissue disorders, neuromuscular diseases, mucopolysaccharidosis type I [MPS I]) and acquired (JIA, dermatomyositis, systemic sclerosis).[8] Most of these are associated with extra-articular manifestations, which promptly lead the physician to suspect the cause of contractures. The more relevant differential diagnoses are attenuated MPS I and "dry arthritis." Attenuated MPS I, unlike the severe Hurler form of the disease, is often revealed by painless joint contractures and no clinical or biological signs of inflammation or obvious physical abnormalities.[8] However, almost all forms of MPS show dysplastic carpal and tarsal bones, which are hypoplastic and irregularly shaped, a sign that should prompt the physician to perform a urinary glycosaminoglycan analysis (both quantitative and qualitative) at a reputable laboratory. Joint imaging shows prominent dysostosis associated with thickening of soft tissues.[9] Dry polyarthritis is considered an uncommon variant of rheumatoid factor–negative JIA characterized by an absence of joint effusions and synovial

hypertrophy.[10] It thus also presents as joint contractures but differs from fibrosing synovitis by the occurrence of joint pain and stiffness, associated with laboratory indicators of inflammation. In addition, the articular MRI pattern of dry JIA also differs from that observed in our patients in showing a higher intensity of synovial enhancement, a more prominent synovial thickening, and sometimes the presence of bone erosions and tenosynovitis (Fig 1A).

Morphea involves autoimmune lesions that follow an initial inflammatory pattern and subsequent fibrosis.[1] The primary lymphocytic infiltrate is mainly composed of T lymphocytes, the cytokine secretion of which stimulates fibroblasts and endothelial cells to produce profibrotic factors such as tumor growth factor β.[11]

A distinct interleukin-17 isoform expression identifying a profibrotic motif was recently described.[12] Skin dysregulation of regulatory T-cell function has also been shown to be involved in the triggering of fibrosis.[13] Thus, the imbalance between Th1/Th2/Th17-cell subsets should drive inflammation in the early stages of disease and fibrosis in the later stages of scleroderma.[11] Our observations prompt us to hypothesize that joint involvement follows the same evolution as morphea, with a first mild inflammatory phase followed by a fibrotic process.

Current recommendations for treating morphea include methotrexate combined with oral prednisone.[14] Methotrexate's mechanism of action in morphea is still unclear but probably combines immunosuppressive and antifibrotic effects.[15] It therefore appears adequate in patients with diffuse fibrosing synovitis associated with morphea.

In light of these findings, physicians should consider the diagnosis of fibrosing synovitis in children with acquired diffuse, symmetrical, painless contractures and no elevation of acute phase reactants. Articular MRI with gadolinium and careful cutaneous examination at onset and during follow-up are clues for diagnosis.

ABBREVIATIONS

JIA: juvenile idiopathic arthritis
LS: localized scleroderma
MPS I: mucopolysaccharidosis type I

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REFERENCES

1. Torok KS. Pediatric scleroderma: systemic or localized forms. *Pediatr Clin North Am*. 2012;59(2):381–405
2. Fett N, Werth VP. Update on morphea: part I. Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol*. 2011;64(2):217–228, quiz 229–230
3. Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol*. 2006;18(6):606–613
4. Zulian F, Vallongo C, Woo P, et al; Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PRES). Localized scleroderma in childhood is not just a skin disease. *Arthritis Rheum*. 2005;52(9):2873–2881
5. Pequet MS, Holland KE, Zhao S, et al. Risk factors for morphoea disease severity: a retrospective review of 114 paediatric patients. *Br J Dermatol*. 2014;170(4):895–900
6. Zulian F, Athreya BH, Laxer R, et al; Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PRES). Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology (Oxford)*. 2006;45(5):614–620
7. Schanz S, Fierlbeck G, Ulmer A, et al. Localized scleroderma: MR findings and clinical features. *Radiology*. 2011;260(3):817–824
8. Cimaz R, Coppa GV, Koné-Paut I, et al. Joint contractures in the absence of inflammation may indicate mucopolysaccharidosis. *Pediatr Rheumatol Online J*. 2009;7(1):18
9. Palmucci S, Attinà G, Lanza ML, et al. Imaging findings of mucopolysaccharidoses: a pictorial review. *Insights Imaging*. 2013;4(4):443–459
10. Ostrov BE. What is the significance of dry synovitis? *Pediatr Rheumatol Online J*. 2004;2:114–118
11. Kurzinski K, Torok KS. Cytokine profiles in localized scleroderma and relationship to clinical features. *Cytokine*. 2011;55(2):157–164
12. Lonati PA, Brembilla NC, Montanari E, et al. High IL-17E and low IL-17C dermal expression identifies a fibrosis-specific motif common to morphea and systemic sclerosis. *PLoS One*. 2014;9(8):e105008
13. MacDonald KG, Dawson NAJ, Huang Q, Dunne JV, Levings MK, Broady R. Regulatory T cells produce profibrotic cytokines in the skin of patients with systemic sclerosis. *J Allergy Clin Immunol*. 2015;135(4):946-.e9
14. Li SC, Torok KS, Pope E, et al; Childhood Arthritis and Rheumatology Research Alliance (CARRA) Localized Scleroderma Workgroup. Development of consensus treatment plans for

juvenile localized scleroderma: a roadmap toward comparative effectiveness studies in juvenile localized scleroderma. *Arthritis Care Res (Hoboken)*. 2012;64(8):1175–1185

15. Nabai L, Kilani RT, Aminuddin F, Li Y, Ghahary A. Methotrexate modulates the expression of MMP-1 and type 1 collagen in dermal fibroblast. *Mol Cell Biochem*. 2015;409(1–2):213–224

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