CASE REPORT

Pansclerotic Morphea with Features of Eosinophilic Fasciitis: Distinct Entities or Part of a Continuum?

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Abstract: Scleroderma is a highly complex disorder in its clinical manifestations and pathogenesis. It has a wide range of clinical manifestations due to varying degrees of vasculopathy, autoimmunity, altered endothelium function, and abnormal fibrosis. The most widely used classification system grouped eosinophilic fasciitis and disabling pansclerotic morphea of childhood into the category of deep morphea. This previous classification does not include a category for overlapping conditions. A proposed new classification includes a new mixed subtype in which a combination of two or more of the previous subtypes is present in the same individual, although eosinophilic fasciitis has been excluded. We present the case of a 4-year-old boy who presented with features of disabling pansclerotic morphea and eosinophilic fasciitis simultaneously, which to our knowledge has not been previously reported. This suggests that these diseases are part of a more closely related continuum rather than separate disorders, as currently classified.

Scleroderma is a rare spectrum of fibrosing disorders ranging from localized scleroderma (morphea) to systemic sclerosis. Within the most widely used classification of localized scleroderma, deep morphea encompasses morphea profundus, eosinophilic fasciitis (EF), and disabling pansclerotic morphea of children (DPM) (1,2). Typically, deep morphea extends from the deep dermis to muscle in a diffuse pattern, separating it from other forms of morphea (3). Each of these conditions has similarities in clinical presentation and laboratory and histologic findings, but they have different degrees of cutaneous involvement and response to treatment (3,4). Previous case reports have postulated a possible relationship between these subtypes of morphea because of simultaneous presentations in individual patients (3,4). A new classification for juvenile localized scleroderma has been recently proposed to include five subtypes: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea, and a mixed

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subtype (5). This new mixed subtype includes different types of lesions occurring in the same individual but intentionally excludes eosinophilic fasciitis. A recent multicenter study reported that this mixed subtype is more common than previously recognized, accounting for 15% of the whole group (6). Balat et al (7) reported a child with EF who progressed to linear scleroderma. Farrington et al (8) reported four pediatric patients who progressed from EF to localized scleroderma. He suggested that two-thirds of pediatric patients with EF progress to some form of scleroderma with cutaneous fibrosis (7,8). We report a 4-year-old with DPM and concurrent presentation of EF disease features, suggesting that these two entities may be related.

CASE REPORT

A previously healthy 4-year-old Caucasian boy presented with a 5-month history of progressive skin discoloration and thickening on his trunk and extremities. He had severe fatigue, generalized malaise, arthralgia, myalgia, decreased appetite, weight loss, and abdominal distention. On examination, the patient appeared ill, with periorbital swelling, oral and groin erosions, and massive matted, nontender cervical and inguinal lymphadenopathy. He had hypopigmented patches on the neck and trunk and atrophic, waxy-textured, bound-down, erythematous to yellow plaques on his chest, abdomen, and lower extremities. Joint examination revealed nontender swelling of the proximal interphalangeal joints, wrists, and knees, with fixed contractures of all peripheral joints. Digital tapering and pallor was noted (Figs. 1–3).

Extensive examination for malignancy (including imaging and bone marrow and lymph node biopsies) and infection was negative. He had high inflammatory markers, leukocytosis, eosinophilia (white blood cell [WBC] count of 6,800 and 11,000), and anemia. Liver and muscle enzymes were normal, with no evidence of internal organ involvement. At diagnosis, antinuclear antibody (ANA) titer was 1:160, but all other autoantibodies were negative, including anti-Smith antibody, anti-SSA antibody, anti-SSB antibody, anti-ribonucleoprotein antibody, anti-double-stranded deoxyribonucleic acid antibody, anti-SCL-70 antibody, anticentromere antibody, and anti-Jo1 antibody.

We performed a wedge biopsy that included tissue layers from the epidermis to muscle. The histopathologic evaluation revealed thinning of the epidermis and flattening of undulations between the rete ridges and dermal papillae. There were fewer subcutaneous adnexa and vessels, which were widely separated from

Figure 1. Hypopigmented patches on the neck and trunk and atrophic plaques on the chest, abdomen, and upper extremities.

**Figure 2.** Hyperpigmented sclerotic plaques on the back.

each other. The dermis and underlying fascia were thick, with extensive deposition of collagen fibers infiltrated by extensive inflammatory infiltrate com-

Figure 3. Inflammatory changes with periorbital swelling and hypopigmented and hyperpigmented patches on the face.

posed of mononuclear inflammatory cells, plasma cells, lymphocytes, histiocytes, and abundant eosinophils. The inflammatory infiltrate extended into and in between the underlying muscle fibers, focally surrounding fragmented myocytes (myocytes necrosis; Fig. 4), consistent with DPM and EF with associated myopathy.

The patient was initially treated with intravenous (IV) methylprednisolone and IV immunoglobulin (IVIG). Outpatient therapy included daily oral steroids, weekly subcutaneous methotrexate, and monthly IVIG and IV methylprednisolone. Over the next 2 years the patient had slow but gradual improvement in his skin and joint range of motion on combination immune modulation with prednisolone, methotrexate, mycophenolate mofetil, imatinib, and monthly IVIG. Increased disease activity was always marked by worsening peripheral eosinophilia and increased erythrocyte sedimentation rate, both of which responded robustly to increased steroid therapy. More recently, the disease recurred, and autologous stem cell transplantation was performed. Although the patient tolerated stem cell transplant without serious complications, his disease relapsed
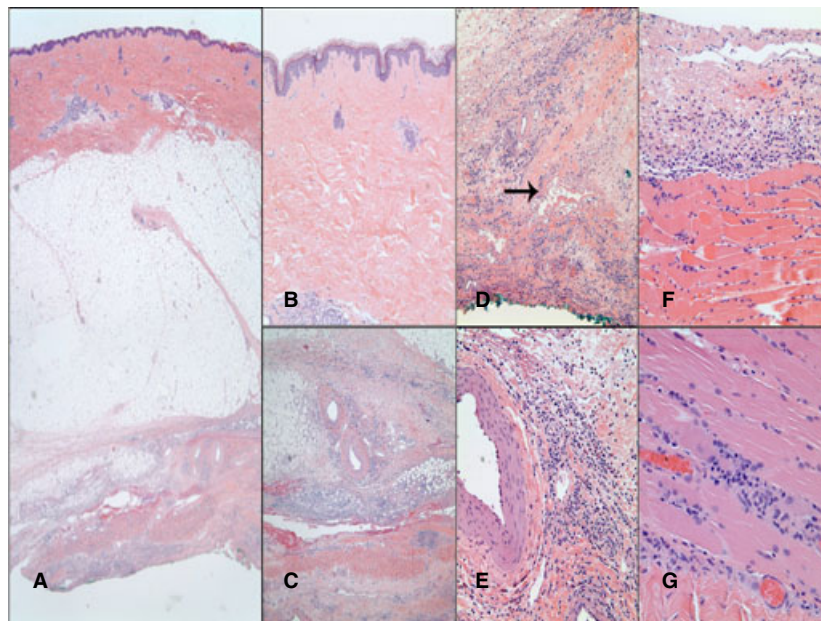
Figure 4. Histopathologic evaluation of the skin, fascia, and muscle: (**A**) full-thickness skin, panniculus adiposus, and fascia biopsy; (**B**) thinning of the epidermis and significantly widened dermis with extensive deposition of collagen fibers parallel to the surface and a decrease in the number of cutaneous adnexa units and blood vessels; (**C** and **D**) the septa of panniculus adiposus and thickened fascia involvement by mixed inflammatory cell infiltrate composed of lymphocytes, plasma cells and eosinophils, and focal necrobiosis (arrow); (**E**) perivascular inflammatory infiltrates; (**F**) fascia with inflammatory infiltrate extension into and in between the underlying muscle fibers; and (**G**) focal myocytes necrosis.

with peripheral eosinophilia and new skin lesions on his abdomen within 3 months after transplantation while taking no immunosuppressive medications. His disease has stabilized on systemic steroids, and he is currently receiving abatacept infusions in an attempt to mitigate steroid exposure.

DISCUSSION

Shulman first described a new sclerodermatous syndrome with diffuse fasciitis, hypergammaglobulinemia, and peripheral eosinophilia (9), which Rodnan et al (10) later named "eosinophilic fasciitis." Bielsa et al (3) stated that Díaz-Perez et al first reported children with a mutilating form of cutaneous scleroderma and named it DPM. Peterson et al (1) grouped EF and DPM under deep morphea. These two types of deep morphea differ in the depth of the disease.

These diseases are rare in children, with only 53 EF cases and 24 DPM cases previously reported. Eosinophilic fasciitis has been reported in combination with linear or localized morphea (3) and with features of scleredema adultorum in two cases (11,12). This case highlights a pediatric patient with concurrent DPM and EF.

Disabling pansclerotic morphea is rapidly progressing pansclerosis extending to all the layers of the skin from the dermis to the subcutaneous tissue, fascia, muscle, and bone (13). It is an aggressive mutilating form of deep morphea, reported most commonly in girls ages 1 to 14 years old, although adult onset has been reported (3,14). DPM initially begins on the extremities and spreads to the trunk, scalp, and face, resulting in contractures and atrophy (3).

Disabling pansclerotic morphea typically presents with sclerotic plaques on the extensor surface and trunk, which can progress to the entire skin. The sclerotic lesions are usually superficial and ill defined and appear bound to the underlying fascia (13,15). Joint contractures, nonhealing ulcers, and soft tissue calcifications are common; fingertip and toe involvement is rare (3,13).

Hypergammaglobulinemia is a common finding, although hypogammaglobulinemia has been reported (13). Mild peripheral eosinophilia, high inflammatory markers, and an intermittent positive ANA are typically seen (3), although eosinophilia as a biomarker of disease activity has not been previously reported in DPM. Visceral involvement in DPM can include lymph nodes, lungs, muscles, and esophagus, and in rare cases, hepatic and cardiac involvement have been reported (3,13,16). Pulmonary function tests, electromyography, and barium swallow are often abnormal (3). Zulian et al (17) stated that patients with localized scleroderma with extracutaneous manifestations represent a new subset of patients with mild, non-life-threatening organ involvement, suggesting that localized scleroderma and systemic sclerosis represent the ends of a continuous disease spectrum.

Histologic changes depend on the depth of skin involvement. In DPM, diffuse inflammation of the entire dermis and panniculus is noted, including lymphocytes, plasma cells, and eosinophils. This progresses to sclerosis and thickening affecting the entire dermis and panniculus (3).

Disabling pansclerotic morphea is a disabling disease and has a poor prognosis, with severe orthopedic, cosmetic, and psychological complications (1). Disabling pansclerotic morphea has a chronic, progressive disease course and is often refractory to treatment (3). Some success has occurred with a combination of steroids and immunosuppressive agents.

In contrast, EF mostly affects the fascia and panniculus and may affect the dermis and muscle. It is rare in children, affecting girls more than boys (9). It is a rapidly spreading disease that occurs in the extremities, trunk, and neck, sparing the hands and face. The etiology of deep morphea is unknown but is postulated to be multifactorial, involving genetic and environmental factors (1,3). The process initially involves an inflammatory stage followed by excess accumulation of collagen and dermal fibrosis (3). Early manifestations of EF involve symmetric diffuse tenderness, warmth, and stiffness of the extremities. It is often associated with erythema, early induration, edema, alopecia, and scaling of the skin. Pitting edema, dimpling of the skin (cobblestoning or peau d'orange), and furrows along superficial veins develop as the disease progresses (1,3,9,18,19). With increasing fibrosis, the skin becomes hypopigmented, appears tight and indurated, and is often tender (3). Joint contractures, inflammatory arthritis, carpal tunnel, and constitutional symptoms are common. Raynaud's phenomenon and nail capillary involvements are rare (20). Underlying skeletal muscle can be affected (9).

Findings in EF include hypergammaglobulinemia, high peripheral eosinophilia, and high inflammatory markers and muscle enzymes (creatine phosphokinase, aldolase). A positive ANA is rare. It can be associated with hematologic disorders, including cytopenia (9). It is uncommon for EF to have visceral involvement (4), although some reports have stated that EF may be seen with mild lung, muscle,

esophageal, hepatosplenic, and cardiac abnormalities (3,20).

The criterion standard for diagnosing EF requires a wedge biopsy including skin, muscle, and fascia (1,9). With EF, early changes are seen in interlobular fibrous septa of the subcutis and deep fascia with edema and infiltration of lymphocytes, histiocytes, plasma cells, and eosinophils (3,10). Eventually it progresses to diffuse inflammation in the fascia and subcutis with eosinophilia and thickening and sclerosis of the dermis extending into the underlying muscle (3,9), although the presence of eosinophils is not necessary to make the diagnosis (13).

Eosinophilic fasciitis usually has a good outcome, especially with early diagnosis and treatment (8); poor prognosis is associated with young age of onset, truncal involvement, and morphea lesions (9). Farrington et al (8) found risk factors for progression to include age younger than 7 years and extensive disease at time of diagnosis. Unlike DPM, EF is often responsive to corticosteroids, immunosuppressive agents (methotrexate, mycophenolate), and biological agents (infliximab) (9).

Our patient presented with severe disease with features of DPM and EF at a very young age. He had constitutional symptoms, joint contractures, lymphadenopathy, sclerotic skin changes with hypopigmentation, erythema, edema, and ulceration. He had sclerodactyly but no Raynaud's phenomenon. His gamma globulin, liver, and muscle enzyme levels were within normal limits. He had a positive ANA, high inflammatory markers, leukocytosis, and anemia. He had no visceral involvement other than lymphadenopathy. All of these features can be seen in DPM. He had other findings indicating EF, including high peripheral eosinophilia and changes in his eosinophil count that corresponded directly with disease activity. In a review of the literature, six cases did not report the level of eosinophilia, nine cases reported eosinophilia but did not specify levels, two cases reported high eosinophilia (30% with 13,000 WBC count and 9.5% with no WBC count provided), and the remaining seven cases of childhood DPM had normal to mild peripheral eosinophil counts (13,14,16,21). All EF cases had high eosinophil counts. Histologic findings in our patient also showed abundant eosinophils and thickened fascia. In a review of the literature, only one of the DPM cases mentioned eosinophils on biopsy (21), whereas all except three EF cases showed eosinophils on biopsy (22–24). Lastly, although peripheral eosinophil count has been reported to be a surrogate marker for disease activity in EF, it has never been reported in DPM. The robust response of this patient's peripheral

TABLE 1. *Clinical and Laboratory Features in Disabling Pansclerotic Morphea (DPM), Eosinophilic Fasciitis (EF), and Our Patient*

Feature	DPM	EF	Our patient
High blood eosinophil count	−	+	+
Inflammatory markers	+	+	+
Hypergammaglobulinemia	±	+	−
Raynaud's phenomenon	−	−	−
Visceral involvement	+	−	+
Resistant to therapy	+	−	+
Tissue eosinophilia on histology	−	+	+
Inflammation in all layers of skin on histology	+	−	+
Fingertips and toes spared	+	−	−
Face and trunk spared	−	+	−
Painful symmetric, diffuse swelling of extremities	−	+	−
Evolving over years	+	−	+
Peau d'orange or cobblestoning	−	+	−

eosinophilia to steroids is also a classic feature of EF. The presence of steroid-responsive peripheral eosinophilia as a disease marker also supports our contention that EF and DPM may be on a continuum of disease with similar pathophysiology, although it is important to remember that DPM is rare, with only a few case reports in the literature, and that DPM may have some features that overlap with EF that may not have been previously reported. This child may not represent an overlap of two diseases but rather may be presenting as DPM with novel features of EF. In spite of treatment with high-dose steroids, various immunosuppressive therapies, and autologous stem cell transplantation, the patient's disease has recurred, and he is currently being treated with abatacept and steroids (Table 1).

Our patient presented with clinical and histopathologic features of two subtypes of deep morphea: EF and DPM. The simultaneous presentation indicates that EF and DPM are closely related and may be disease entities that fall along a continuum that includes other forms of localized scleroderma, a concept that is not currently recognized in currently published classification systems for localized juvenile scleroderma. It is hoped that further understanding of the pathogenesis of scleroderma and the complex interplay of these various damaging processes will change the current organ-based approach to more effective targeted therapy.

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