Single Case

Juvenile Localized Scleroderma with Hyaline Deposits in the Renal Arteriole

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Abstract
We report a 10-year-old boy with localized scleroderma of the linear and plaque type, who showed proteinuria and hematuria. In this patient, skin, articular, and renal manifestations appeared successively and then began to resolve in the same order. A renal biopsy specimen demonstrated mild mesangial cell proliferation, exudate of immunoglobulin in the glomerular capillary, and large electron-dense deposits in the afferent arteriole. We consider that there were some transient factors that had caused the skin and articular manifestations, which also induced renal vascular inflammatory responses.

Introduction
Juvenile localized scleroderma (JLS), unlike systemic sclerosis, is typically confined to the skin and subcutaneous tissue and includes several subtypes: circumscribed, generalized, linear, pansclerotic, and mixed (defined by the presence of more than one subtype in the same patient) [1]. Linear lesions may involve the skin, subcutaneous tissue, muscle, and underlying bone. However, several studies have demonstrated that children with JLS might
also have multiple organ involvement. A large study showed that extracutaneous manifestations occur in approximately one-quarter of all patients with JLS [2]. Renal manifestation has been regarded as one of the rarest manifestations and has not been well assessed. To our knowledge, our patient is the second reported case of JLS who had a renal biopsy.

Case Report

Our patient was a 10-year-old boy with a 6-month history of stiffness and a change in the color of skin on his right leg. Examination revealed confluent hyper- or hypo-pigmented plaques that extended from the right thigh to the ankle without non-pitting edema (Fig. 1a, b) and a 4-cm diameter hypo-pigmented plaque on the left lower abdomen. Motion of the flexion contracture was not observed. His medical and family history was unremarkable, but he had many untreated dental caries with apical periodontitis. Routine laboratory investigations produced findings within the normal limits. Anti-nuclear, anti-double-stranded DNA and anti-single-stranded DNA antibodies, and rheumatoid factor were all negative. A skin biopsy specimen showed vacuolization of the basement membrane, perivascular inflammatory infiltration, and fibrosis with thickened collagen bundles in the dermis and superficial subcutis (Fig. 2a). Alcian blue stain revealed no deposition of mucin between the collagen fibers.

Initially, the patient was treated with topical steroids. Ten months after his first visit, he developed swelling in the right knee with slight flexion contracture. Magnetic resonance imaging delineated a small exudation in the right knee joint. His parents did not consent for him to receive systemic immunosuppressive therapies, because he had no trouble with activities of daily life. One year after his first visit, he was noted to have slight proteinuria and hematuria in a school medical check-up. These findings continued intermittently during the following 3 years. At the age of 14 years, he was admitted for close examination of renal manifestation. Urinalysis laboratory investigation revealed +1 proteinuria (0.3 g/g creatinine, normal range: ≤0.15 g/g creatinine), +3 hematuria with dipstick, and an increased β2-microglobulin level of 352 μg/L (normal range: ≤230 μg/L). Hematological laboratory results were in the normal range including white blood cell counts, hemoglobin, hematocrit, platelet counts, blood urea nitrogen, serum creatinine, total protein, albumin, C3, C4, erythrocyte sedimentation rate, and C-reactive protein. Tests for anti-Scl-70, anti-SSA antibodies, anti-neutrophil cytoplasmic antibodies targeting proteinase-3, and myeloperoxidase were all negative.

Renal biopsy was performed for evaluation of his proteinuria and hematuria. Light microscopy examination revealed mild mesangial cell proliferation with mild increased mesangial matrix in 11 of 22 observed glomeruli. Large hyaline deposits were seen in the afferent arteriole of the vascular poles in 3 glomeruli (Fig. 2b). Immunofluorescence microscopy documented linear staining along the glomerular capillary walls for immunoglobulin (Ig)G (2+), IgM (2+), C3 (2+), and IgA (1+) (Fig. 2c). However, electron microscopy (EM) did not show immune deposits either in mesangial areas or capillary walls, and revealed large electron-dense deposits (EDD) in the afferent arteriole, which corresponded to the hyaline deposits observed by light microscopy (Fig. 2d, e). To reduce the proteinuria, we began to treat the patient with angiotensin-converting enzyme inhibitor [3] and continued to do so for 16 months.

In his clinical course, the skin manifestations began to resolve 22 months after their appearance. The flexion contracture slowly remitted without serious functional impairment,
following a 2-year continuation. At 14 years of age, atrophic macules with mild subcutaneous tissue reduction remained on his right leg (Fig. 1c). The urinary findings disappeared approximately 5 years after the first observed manifestation (Fig. 3). The articular and renal manifestations have not relapsed during 7 years of follow-up.

Discussion

JLS often remits spontaneously after 3–5 years. It has been estimated that 50% of localized scleroderma (LS) patients undergo spontaneous remission [4]. However, because the residual damage may be severe, systemic immunosuppressive therapy is recommended for deep involvement of the subcutis, fascia, and muscle, and for rapidly progressive or widespread active disease [5]. We did not treat our case with systemic therapy because he had no rapidly progressive lesions or functional impairment, his laboratory findings did not indicate active autoimmune disease, and his parents’ disagreed with systemic immunosuppressive therapy.

To our knowledge, only 4 patients with JLS and renal involvement have been reported to date [2, 6, 7]. One patient with linear JLS underwent a renal biopsy for renal involvement concurrent with pneumonia, when she was 7 years old [7]. Light microscopy examination demonstrated mesangial cell proliferation with mesangial immunofluorescence staining for IgM, IgA, and C3. EDD, suggestive of immune complexes, were identified in mesangial areas by EM. The other 3 patients presented with proteinuria and hematuria, and were clinically diagnosed as having glomerulonephritis.

In our JLS patient, light and immunofluorescence microscopy examination of the renal specimen showed mild mesangial cell proliferation and linear staining for immunoglobulins along the glomerular capillary walls. However, EM did not demonstrate the deposition of immune complexes in mesangial areas, and EDD, which was suggestive of an exudation of serum protein, was revealed at afferent arterioles. Based on these findings, we suggest that the renal pathological changes in our patient were caused by increased vascular permeability.

The underlying pathogenesis of JLS remains unknown, but upregulation of transforming growth factor-β (TGF-β) production is thought to play a prominent role in excessive collagen deposition [8]. Previous studies gave variable results as to the serum levels of TGF-β in patients with LS [9], but highly elevated serum levels were reported in children with linear and generalized types of LS [10]. Furthermore, a recent report demonstrated that ectopic TGF-β induced vascular endothelial growth factor (VEGF) synthesis in normal fibroblasts, and that overexpression of VEGF was seen in activated systemic sclerosis fibroblasts which acquired autocrine TGF-β signaling following chronic inflammation [11]. VEGF is known as a vascular permeability factor because it possesses potent vascular permeability-enhancing activity [12]. Thus, it seems likely that TGF-β and VEGF played important roles in the appearance of skin, articular, and renal involvements in our patient, and there may be some factor that caused the overproduction of these cytokines, which acted for only a limited time.

In recent studies, it has been assumed that TGF-β and VEGF are involved in the evolution of the immune response in periodontal disease and caries [13, 14]. Our patient had many untreated dental caries with apical periodontitis at the onset of JLS, and healthy permanent teeth gradually replaced them. The chronic oral bacterial infection may contribute to the development of JLS in receptive individuals. Unfortunately, we do not have further information on the clinical course of our patient’s dental condition. Clarifying why JLS often remits spontaneously may also provide further clues to understanding the pathogenesis of JLS.
Renal manifestation has been regarded as one of the rarest manifestations of JLS. However, JLS patients with renal involvement may be detected more often if periodic urinalysis was undertaken. We found an instance of a renal vascular lesion in a JLS patient by renal biopsy. We hope that further clinical and laboratory investigations will provide new clues to understanding the pathogenesis of JLS.

Statement of Ethics

The parents of the subject of this case report gave their informed consent.

Disclosure Statement

The authors report no conflicts of interest.

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Fig. 1. Clinical features. a, b At 10 years of age. Hyper- or hypo-pigmented plaques around the right thigh (a) and shin (b). c At 14 years of age. Atrophic macules and pigmentations with slight subcutaneous tissue reduction around the right knee.
Fig. 2. Histopathological findings. a Skin biopsy. Fibrosis with thickened collagen bundles in the dermis and superficial subcutis (hematoxylin and eosin stain; original magnification ×40). b Light microscopy examination of kidney biopsy. Mild mesangial hypercellularity and large blue-stained hyaline deposits in the afferent arteriole (arrow) (Mallory-Azan stain; original magnification ×400). c Immunofluorescence microscopy examination of kidney biopsy. Diffuse linear capillary wall deposits (immunofluorescence stain using antiserum to IgG; original magnification ×200). d, e Electron microscopy examination of renal glomeruli. Large electron-dense deposits in the afferent arteriole at the vascular pole (original magnification ×500 in d and ×1,500 in e).
Fig. 3. The clinical course. Skin, articular, and renal manifestations appeared successively. Skin and articular manifestations improved before the renal findings disappeared.