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Juvenile Systemic Sclerosis: About 9 Cases

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Abstract

Scleroderma is a rare disease with two primary forms: localized scleroderma (LS) and systemic sclerosis (SSc). Both are chronic conditions that can manifest in various patterns (subtypes) and are linked to extracutaneous involvement in pediatric patients. Juvenile SSc poses a higher risk of morbidity and mortality, with patients facing life-threatening complications such as lung, heart, and visceral organ fibrosis, and vasculopathy. In contrast, mortality is extremely rare in juvenile LS, but patients are susceptible to significant morbidity, leading to severe disfigurement and functional impairment. Treatment for scleroderma aims to control inflammation and address specific issues. An early diagnosis significantly enhances the overall outcome. This study conducts a retrospective descriptive analysis aiming to document the clinical manifestations, management approaches, and outcomes of systemic sclerosis in a cohort of nine children receiving treatment for juvenile systemic sclerosis at Pediatric B department of Mohammed VI University, Hospital Center in Marrakech, Morocco.

Keywords

Scleroderma, Systemic Sclerosis, Children, Pediatric

1. Introduction

Scleroderma is a rare disease characterized by two primary forms: localized scleroderma (LS) and systemic sclerosis (SSc). Both forms are chronic conditions, displaying various patterns (subtypes) and involving extracutaneous manifestations in pediatric patients. In juvenile SSc, morbidity and mortality are notably severe, with patients facing life-threatening complications such as lung, heart, and visceral organ fibrosis, and vasculopathy [1]. While mortality is exceptionally rare in juvenile LS, morbidity is common, posing a risk of significant disfi-

gurement and functional impairment. Treatment for scleroderma focuses on inflammation control and addressing specific issues. Early diagnosis plays a crucial role in improving outcomes.

We conducted a retrospective descriptive study with the aim of documenting the clinical manifestations, management approaches, and outcomes of systemic sclerosis for nine children receiving treatment for juvenile systemic sclerosis at the Pediatric B department of Mohammed VI University Hospital Center in Marrakech, Morocco.

2. Results

All of our patients were female. The mean age at onset was 10 years, ranging from 6 to 14 years. The average interval between disease onset and diagnosis was 9 months (Figure 1).

Prominent symptoms of systemic sclerosis included skin tightening in all cases (Figure 2), prolonged arthritis in six cases, functional impairment , edema of both hands in two patients, dysphagia in one patient, and prolonged fever in two patients (Figure 3).

Skin biopsy was performed in all cases, and the diagnosis was based on the ACR-EULAR classification criteria for systemic sclerosis.

Laboratory investigations revealed elevated acute phase reactants (ESR, CRP) in all patients. Additionally, three children exhibited microcytic anemia. An electromyogram identified peripheral neuropathy in one case. On the other hand, esogastroduodenal fibroscopy revealed significant thickening of the walls of the upper gastrointestinal tract in one patient.

Regarding immunological assessment, the antinuclear antibody test was positive in two patients, the anti-double-stranded DNA test was positive in one patient, and the anti-Scl-70 antibody was present in one case. Systemic lupus erythematosus was concomitant with systemic sclerosis in one girl. Finally, one patient exhibited proteinuria exceeding 500 mg/24h, leading to a kidney biopsy that revealed focal segmental glomerulosclerosis.

Management involved the use of steroids combined with methotrexate as a first-line treatment for a minimum duration of 24 months in all cases. In one

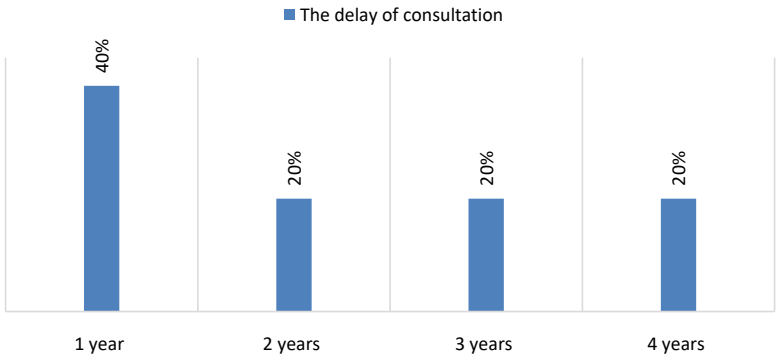

Figure 1. Delay of consultation.

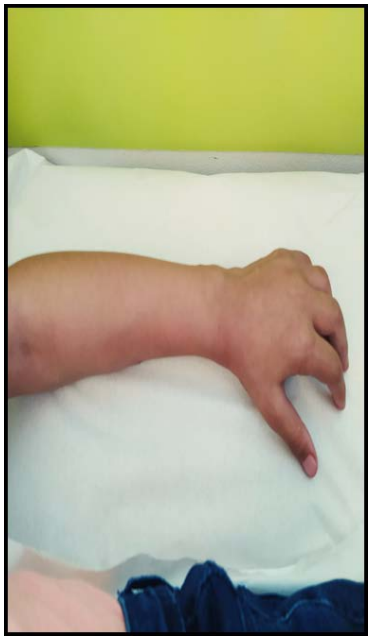

Figure 2. Patient in our series with cutaneous sclerosis and a claw-like appearance of the fingers.

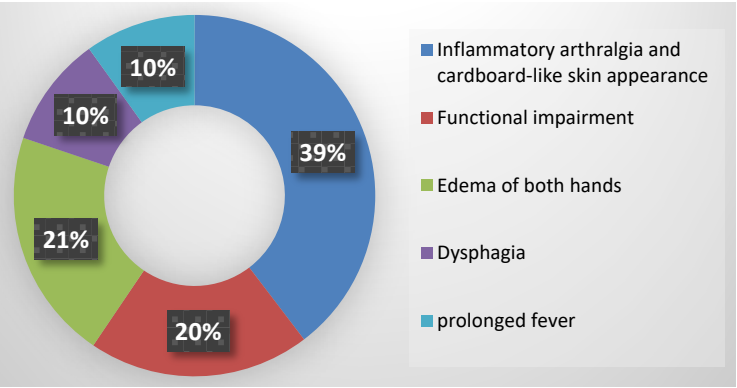

Figure 3. Prominent symptoms of systemic sclerosis in our series.

case, mycophenolate mofetil was later added to achieve remission. All patients received physiotherapy and psychological support.

The course of the disease resulted in complete remission in 5 patients and partial remission in 3 patients. Unfortunately, we mourn the loss of one patient due to septic shock.

3. Discussion

Juvenile systemic sclerosis (jSSc) is a rare and severe autoimmune disease characterized by life-threatening multiorgan inflammatory-driven fibrosis. The scarcity of cases in children has limited formal studies on the incidence and prevalence of jSSc, but estimates have been provided by a few investigations. A prospective study in the United Kingdom and Ireland found an incidence rate of 0.27 (95% CI 0.1 - 0.5) per million children per year for jSSc [2].

Another study using data from the US American Claim Database of the Truven MarketScan® reported an estimated annual prevalence ranging from 2.8 to 4.1 children per 1,000,000 [3]. In the 2018 international cohort, 5% of cases affected individuals of African race [4], while the North American cohort reported a 19% prevalence among African Americans [5].

The sole proposed classification of jSSc, established 14 years ago (2007), resulted from a case-based consensus involving expert opinions from pediatric and adult rheumatology and dermatology providers [6]. This classification includes one major criterion—sclerodermatous skin changes proximal to the metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joints—and two of 20 minor criteria representing various organ involvements and associated autoantibody profiles. The provisional 2007 jSSc criteria were initially validated in pediatric cohorts, mirroring the adult SSc criteria developed by the American College of Rheumatology (ACR) in 1980 [7]. However, it was acknowledged that these criteria lacked sensitivity for identifying patients with early or milder disease who could benefit from treatment.

In 2013, new adult classification criteria were introduced by the ACR and European League against Rheumatism (EULAR) to capture early-onset SSc using a points-based system [8]. This metric, validated in adult SSc, is currently undergoing validation in jSSc. Preliminary data from two jSSc cohorts show 81% and 84% of patients meeting the 2013 ACR/EULAR criteria, compared to 42% and 68% meeting the 2007 proposed pediatric criteria, respectively [9].

Recognizing the limitations of the pediatric 2007 criteria, the international Inceptions Cohort modified its inclusion criteria in October 2017 to use the 2013 ACR/EULAR adult classification.

Table 1 and **Table 2** [10] summarize the recommendations for JSSc, the corresponding level of evidence, recommendation strength and percentage of agreement between experts. Of note, one recommendation derived from a controlled study without randomization (strength of recommendation B and level of evidence 2 A, modified adding evidences from another controlled study published after the literature search) (**Table 2**). The remaining recommendations derive from descriptive or case-control studies (strength of recommendation C-D, level of evidence 3) or from the expert committee opinion (strength of recommendation D, level of evidence 4) [10].

All centers affiliated with the EULAR Scleroderma Trials and Research group were invited to participate in a Delphi approach to submit and select clinical questions pertaining to the treatment of Systemic Sclerosis (SSc). Subsequently, a total of 46 clinical questions related to 26 different interventions were chosen for a systematic literature review. The formulation of new recommendations ensued, grounded in the available evidence, and crafted through a consensus meeting involving clinical experts and patients. The outcome of this process yielded 16 recommendations, an increase from the 14 recommendations in 2009. These recommendations specifically address the treatment of various SSc-related organ

Table 1. JSSc—recommendations regarding assessment.

		L	S	Agreement %
1	*Overarching principle* All children with suspected JSSc should be referred to a specialized paediatric rheumatology centre for multi-disciplinary care.	4	D	100
2	*Vascular involvement* All patients with isolated RP should have a nailfold capillary assessment and ANA testing. If capillaroscopy is abnormal and/or ANA are positive, then regular follow-up is recommended.	3	C	80
3	*Cutaneous involvement* A standardized skin score tool should be used for clinical assessment in JSSc. The modified Rodnan skin score is suitable, but needs to be adapted and validated for use in childhood.	4	D	100
4	*Internal organ involvement* The Juvenile Systemic Sclerosis Severity Score (J4S) can be used as a severity assessment tool in JSSC, but needs to be validated.	4	D	100
5	Pulmonary function tests, including DLCO, and HRCT in children with JSSc are sensitive tools to detect presence and severity of interstitial lung disease. Pulmonary function tests are also indicated for the respiratory function monitoring.	3	C	100
6	Patients with JSSc should have assessment of pulmonary function tests with DLCO, cardiac echo, renal function and modified Rodnan skin score at least every 6 months.	4	D	90

DLCO: diffusing capacity for carbon monoxide; HRCT: high resolution computed tomography; JSSc: juvenile systemic sclerosis; L: level of evidence; S: strength of recommendation.

Table 2. JSSc—recommendations regarding treatment.

		L	S	Agreement %
1	*Skin involvement* Systemic corticosteroids, in combination with a DMARD, are useful in the active inflammatory phase of JSSc.	4	D	100
2	At the time of diagnosis of JSSc, a systemic immunomodulatory treatment, like methotrexate, should be considered.	4	D	100
3	In case of non-response to methotrexate an additional immunomodulatory agent (*i.e.* MMF) should be considered.	3	D	90
4	*Pulmonary involvement* Cyclophosphamide may be used to treat cardiac and/or pulmonary involvement.	4	D	100
5	*Vascular involvement* Iloprost may be used to treat ischaemic digits and digital ulcerations.	3	C	90
6	In New York stage II pulmonary hypertension, and/or digital ulcerations refractory to other therapies, bosentan should be considered.	3	D	100
7	*Experimental treatment* Biological agents, in particular tocilizumab or rituximab, should be considered in severe or refractory cases.	4	D	100
8	Autologous stem cell transplantation may be an option to treat patients with JSSc with progressive disease refractory to immunosuppressive therapy.	2a 2b	B	100

JSSc: juvenile systemic sclerosis; L: level of evidence; S: strength of recommendation.

complications, including Raynaud's phenomenon (RP), digital ulcers (DUs), pulmonary arterial hypertension (PAH), skin and lung disease, scleroderma renal crisis, and gastrointestinal involvement [11].

Comparing the 2016 recommendations to those of 2009, notable additions include the incorporation of phosphodiesterase type 5 (PDE-5) inhibitors for treating SSc-related RP and DUs, as well as considerations for riociguat, new aspects related to endothelin receptor antagonists, prostacyclin analogues, and PDE-5 inhibitors in the context of SSc-related PAH. Furthermore, new recommendations have been introduced, such as the use of fluoxetine for SSc-related RP and the consideration of hematopoietic stem cell transplantation for selected patients exhibiting rapidly progressive SSc. The update also includes additional comments on other treatments addressed in clinical questions and suggestions for the research agenda in the field of SSc [11].

As of now, no medications are licensed specifically for jSSc, and all treatments are off-label. Treatment recommendations are primarily based on adult studies, with pediatric dosing adjustments made for juvenile patients. The SHARE recommendations for jSSc, general EULAR adult SSc treatment guidelines, and a treatment algorithm by Fernadez-Codina *et al.* [12] are used, with pediatric dosing adjustments where appropriate.

Our study has two significant limitations that could be addressed in future research. Firstly, the study centered on certain subjective opinions of patients, potentially complicating the drawing of conclusions. Secondly, generalizing the findings from the study may be challenging due to the small sample size. Additionally, it's important to note that descriptive research does not permit the drawing of conclusions about cause and effect.

4. Conclusion

The delay in the diagnosis and management of systemic sclerosis in children can result in permanent sequelae and significantly impact their quality of life. Increased awareness among pediatricians is crucial for improving outcomes in children affected by this disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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