CASE REPORT

Diagnosis and Management of Juvenile Systemic Sclerosis in a Resource-limited Setting: A Case Report from Zambia

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ABSTRACT

A 15-year-old female adolescent with juvenile systemic sclerosis (JSSc), an uncommon variant of scleroderma marked by multiorgan fibrosis and inflammation, is described. The patient had skin, musculoskeletal, lung, and gastrointestinal symptoms. The skin on the fingers and other parts of the body was hard and the joints had a limited range of motion. Juvenile systemic sclerosis was diagnosed using the 2013 American College of Rheumatology and European League Against Rheumatism (ACR-EULAR) classification criteria for systemic sclerosis, supported by the examination, and investigations which included histopathology and strongly positive Antinuclear Antibody (ANA) titres. With a multidisciplinary approach, the patient was treated with drugs that reduced inflammation, eased symptoms, and slowed disease progression. The patient's management faced difficulties due to delayed presentation and diagnosis, travel distances for scheduled reviews, and budgetary limitations. At follow-up, the patient reported fewer gastrointestinal, musculoskeletal and skin symptoms, and had softer skin. In rare disorders like JSSc, early detection, interdisciplinary management, and removing obstacles to care are critical for better outcomes as the report illustrates. The diagnosis requires high index of suspicion and management must be commenced early to slow disease progression as well as prevent complications. To monitor skin progression and possible drug side effects, regular reviews are needed.

INTRODUCTION

Scleroderma is a systemic autoimmune connective tissue disorder characterized by inflammation and fibrosis of multiple organs such as the skin, blood vessels, kidneys, heart, and lungs (8,14). The term is

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derived from the Greek words, “skleros” which is translated as “hard” and “dermis” which is translated as “skin” (17). It is more common in females and is classified as juvenile scleroderma if it develops before the age of 16 years. However, as there is no consensus on the cut-off age for juvenile scleroderma some authors use 16 years (8,14) whereas others use 18 years (17). The disorder has 2 clinical subtypes according to the extent of skin involvement: juvenile localized scleroderma (JLS) and juvenile systemic sclerosis (JSSc) (15,17). The disease is uncommon, with an incidence of 1-3 per 100, 000 children and 1 per 1, 000, 000 children for JLS and JSSc, respectively (1). JSSc has a worldwide distribution and affects all races, factors such as age, sex, genetic background, and environmental exposure may influence its susceptibility (14). This report describes a case of JSSc, a rare condition in a female adolescent with multi-organ involvement and showed improvement to standard therapy.

JLS was initially thought to be confined to the skin only but multi-systemic extracutaneous involvement (ECI) of the disease has been reported in 46-74% of patients, in prospective paediatric rheumatology studies, these include; neurologic (headache, seizure), ophthalmologic (uveitis), musculoskeletal (arthritis) and odontostomatologic (temporomandibular joint abnormalities) and it is associated with prolonged disease activity (11). JSScs also affects multiple internal organs with musculoskeletal and gastrointestinal systems being more frequently involved (17). There are 3 major clinical subtypes of juvenile systemic sclerosis which are; diffuse cutaneous, limited cutaneous, and overlap juvenile systemic sclerosis. Diffuse cutaneous juvenile systemic sclerosis (dcJSSc) – characterized by truncal and acral skin involvement as well as early and significant visceral involvement. Limited cutaneous(lcJSSc) – characterized by skin sclerosis distal to the wrist and ankles, over the face and neck, and has late visceral involvement. Overlap systemic sclerosis – meets the classification criteria for SSc but with overlap features of other connective tissue diseases such as dermatomyositis (4,13,17). The pathophysiology of JSSc is complex and poorly understood, it is associated with endothelial cell, fibroblastic, and immune system dysfunction.

Several sets of classification criteria have been developed due to the absence of a diagnostic test. The first proposed classification of JSSc was the provisional 2007 JSSc criteria, which was only preliminary validated in paediatric cohorts. It mirrored the initial 1980 preliminary criteria for the classification of SSc by the American Rheumatology Association (ARA), however, it has been replaced by the American College of Rheumatology and the European League Against Rheumatism (ACR-EULAR) a new classification criterion, due to insufficient sensitivity, especially in patients with early SSc and limited cutaneous SSc as well as an increase in advanced knowledge about SSc (5,16). According to the ACR-EULAR classification criteria, skin thickening of the fingers extending proximal to the metacarpophalangeal joints (MCP) is sufficient to classify a patient as having SSc, if not present the following seven additive items apply with varying weights for each: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nail fold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon and SSc related antibodies (3,16). This point-based SSc criterion has been validated in adults and validation is underway in JSSc, with preliminary data from 2 paediatric cohorts recognizing the limitation of the 2007 pediatric criteria and the international inception cohort modified its inclusion criteria to the 2013 ACR/EULAR adult classification (5).

Scleroderma management requires a multidisciplinary approach, with the healthcare team's makeup being customized to each patient's unique organ involvement. According to SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) recommendations, the goal is to provide a standardized comprehensive approach that is both multidisciplinary and interdisciplinary (6), Treatment seeks to lessen symptoms, halt spread of the disease, and prevent complications (16).

CASE PRESENTATION

A 15-year-old female adolescent presented to the outpatient department of the University Teaching Hospitals, Children's Hospital (UTHs-CH) after being referred from a district hospital, about 600km from Lusaka. She had a 2-year history of generalized hypopigmentation, hardening of the skin, and stiffening of joints. The hypopigmented lesions started from the anterior aspects of the lower limbs. The lesions started as areas of itchy swellings that healed by leaving hypopigmented spots. Over time the spots increased in size, coalesced, and spread to different parts of the body including both hands. These symptoms were associated with progressive hardening of the overlying skin and stiffening of joints. She further developed symptoms of discoloration of the skin of the fingers following exposure to the cold. There was a history of nausea, loss of appetite, weight loss, and occasional post-prandial emesis.

On clinical examination, she was undernourished with a body mass index (BMI) of 16.85kg/m², angular stomatitis, and pursed lips. She had generalized hypopigmentation of the skin which was more marked on the trunk both anteriorly and posteriorly. She had firm to hard skin, reduced range of motion of joints (fingers, wrists, knees, and elbows), and hardening of the skin of the fingers of both hands extending proximal to the metacarpophalangeal (MCP) joints **Figure 1**. The axillary temperature was 36.9°C, respiratory rate 24 bpm, pulse rate 88 bpm, and normal blood pressure of 101/58mmHg. The other systems were essentially normal. A working diagnosis of JSSc was made based on the history and examination using the ACR-EULAR classification criteria, (**Supplementary Table 1**).

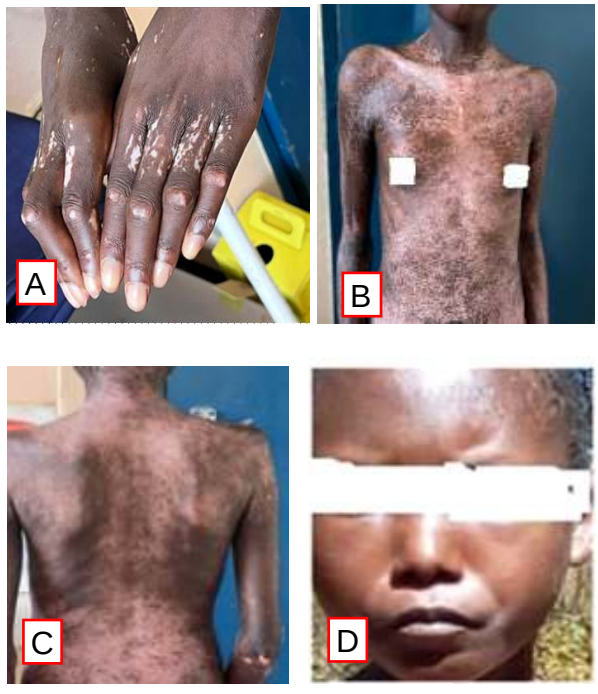

Figure 1: *shows the clinical manifestations of JSSc in the patient,* ***A*** *hardening and hypopigmentation of the skin of the fingers of both hands extending proximal to the metacarpophalangeal joints with semi-flexion deformities of the interphalangeal joints of the fingers.* ***B, C*** *generalized hypopigmentation of the skin on the trunk both anteriorly and posteriorly,* ***D*** *Characteristic scleroderma facies with pursed lips.*

The laboratory investigations are summarised in Table 1 below. Of note is the slight increase in CRP and ESR and a positive Anti-Nuclear Antibody (ANA) at the initial presentation to the hospital.

Table 1: Laboratory Investigations.

Parameter	At initial Presentation	Review at 6 months	Review at 24 months	Normal values
White Cell Count	8.01 x 10^9/L	8.50 x 10^9/L	7.80 x 10^9/L	4-10 x 10^9/L
Red cell count	5.81 x 10^{12}/l	6.00 x 10^{12}/l	6.00 x 10^{12}/l	3.80 – 4.80 x 10^9/L
Haemoglobin	13.9g/dl	14.0g/dl	14.5g/dl	12.0-15.0 g/dl
Haematocrit	46.5%	46.7%	47.2%	36.0-46.0%
Mean corpuscular volume	80.0 fl	75.4 fl	75.0 fl	83.0-101.0 fl
Mean corpuscular haemoglobin	23.9pg	23.2pg	23.2pg	27.0-32.0pg
Platelets	206 x 10^9/L	270 x 10^9/L	270 x 10^9/L	150-410 x 10^9/L
C-reactive protein (CRP)	**18.9mg/l**	-	-	<5.0mg/l
Erythrocyte sedimentation rate (ESR)	**27mm/hr**	-	-	0-24mm/hr
Anti-Nuclear Antibody (ANA)	**Positive 1:3200**	-	-	0.0 –40 (negative)
Urea	2.58 mmol/l	3.0 mmol/	2.60 mmol/l	1.40-5.40mmol/l
Creatinine	16.0µmol/l	15.0 µmol/l	17.0 µmol/l	23.0-68.0 µmol/l
Sodium	139mmol/l	138mmol/l	139mmol/l	138-145mmol/l
Potassium	3.60mmol/l	4.42mmol/l	4.20mmol/l	3.50-5.10mmol/l

***The bold figures in Table 1 denote abnormal laboratory values found in the patient.**

A 3mm punch biopsy was obtained by a dermatologist from the anterior aspect of the thigh. Histology showed unremarkable epidermis, subcutaneous tissue, and adipose tissue with preservation of adnexa structures (hair follicles), and scanty mononuclear infiltration. The dermis was remarkable for dense collagen deposition and this was consistent with JSSc.

To investigate the extent of organ involvement, a CT scan of the chest and abdomen was done showed left basal lung segment fibrotic changes, segmental dilatation of the oesophagus, and significant duodenal dilatation, respectively **Figure 2**. Echocardiography did not show any signs of increased pulmonary artery pressures.

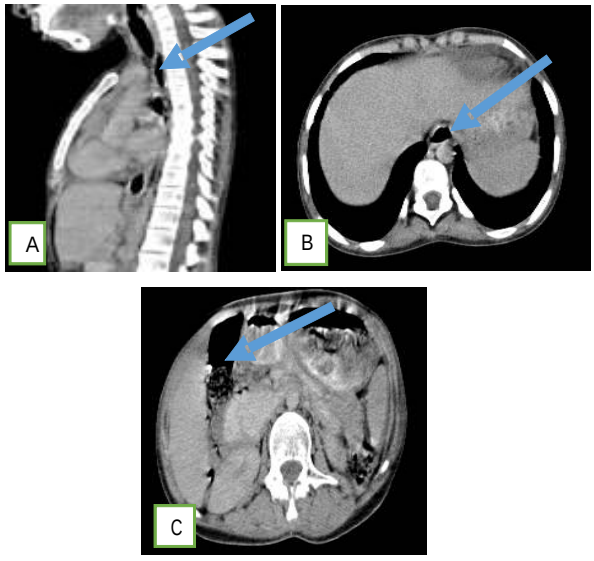

***Figure 2**, Contrast-enhanced CT scan images demonstrating **A:** Dilatation of the oesophagus in sagittal section **B:** Patulous dilatation of the oesophagus in cross-section of the lower abdomen **C:** Dilatation of the second part of the duodenum in cross-section of the abdomen*

The patient was commenced on prednisolone, 0.5 mg/kg/day for a 2 weeks to dampen the inflammation before methotrexate could be sourced – low dose was used so as to avoid triggering renal crisis; nifedipine a calcium channel blocker was prescribed at 5mg twice daily for Raynaud's phenomenon, methotrexate a Disease Modifying Anti-Rheumatic Drug (DMARD) was commenced at 5mg weekly subcutaneously to suppress disease progression; folic acid 5mg once weekly to prevent the side effects of methotrexate; omeprazole a proton-pump inhibitor was started at 1.5 mg/kg/day for treatment of gastro-oesophageal reflux; skin moisturizers to prevent the skin from excessive dryness and high energy protein supplements for nutritional rehabilitation. Physiotherapy was started to improve the mobility of joints.

She was reviewed 6 months later and reported to have an improvement in the symptoms other than experiencing generalized abdominal discomfort which occurred occasionally. There was no progression of the skin lesions and the range of motion of the joints had improved. Repeat tests at 6 months were all normal, **Table 1**. The challenge identified at this hospital review was that the patient was not consistent with medication, especially the injectable methotrexate, because of its lack of availability at the local hospital, and to overcome this, oral methotrexate at a dose of 10mg weekly was prescribed which was more readily available and affordable, the patient was scheduled for reviews every 3 months.

The next hospital scheduled review was at 24 months, the patient was however unable to come for review due to a lack of funds for transport from her hometown to the hospital. Despite the transport challenges, the patient had shown remarkable signs of improvement in the skin, gastrointestinal and musculoskeletal manifestations. Repeat CT scan done at this review showed improvement with only patulous irregular dilatation of the oesophagus and subtle basal atelectasis, with resolved lung changes, the other features seen on the previous CT had resolved, spirometry was done at this review, FVC was 2.05, 79%, FEV1 was 1.97, 89%, the FEV1/FVC ratio was 96.13%, indicating normal lung function test. During the same review, marked reduction in symptoms as well as obvious reduction in hypopigmentation and thickness of the skin was noted, **Fig 3.** She was compliant with her medication despite the family still facing challenges in accessing medication. The UTH-Children's Hospital via the Social Welfare Department has been helping the patient in acquiring drugs. Taking into account the financial constraints and distance between the town of origin and our hospital, the patient is scheduled to be reviewed at least every 6 months to monitor the progression of the disease.

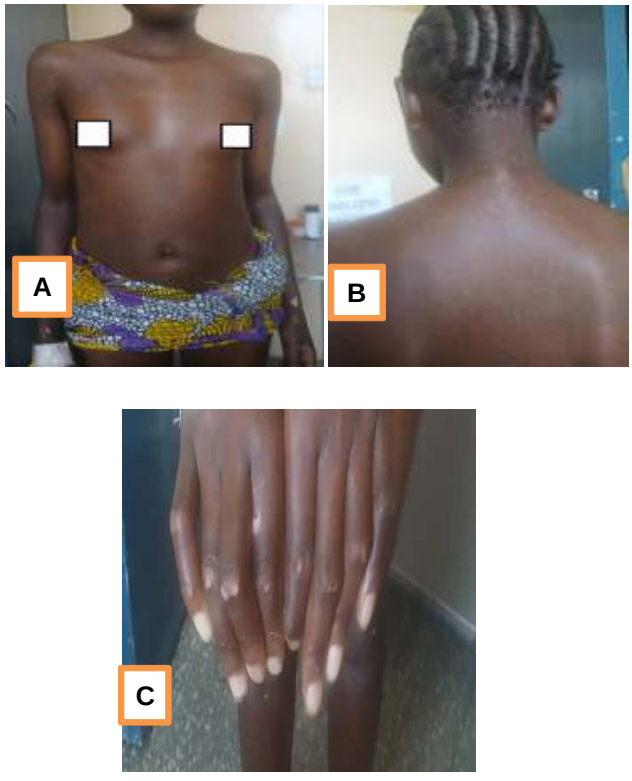

Figure 3: *shows the improvements in clinical manifestations 24 after initiation of treatment.* ***A, B*** *reduction in skin hypopigmentation* ***C*** *reduced hypopigmentation of the skin on the fingers and no change in flexion deformities.*

DISCUSSION

The case described here demonstrates how Juvenile systemic sclerosis (JSSc), an uncommon variant of scleroderma marked by organ fibrosis and inflammation can present and the challenges that are faced in managing such a rare condition in a low-resource setting.

The diagnosis of JSSc is made with a suggestive history, physical examination, and relevant investigations (9). Our patient fulfilled the adult 2013 Classification Criteria for Systemic Sclerosis in which, skin thickening or hardening of the fingers extending proximal to the MCP is sufficient to classify someone as having SSc, which our patient had. If not present seven additive items apply with varying weights for each: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon, and SSc-related antibodies. Patients with a score of $\geq$9 are classified as having definite SSc (22). Aside from having satisfied the major criteria, our patient also had Raynaud's phenomenon and evidence of pulmonary involvement, giving a score of 14. However, this is a classification and not a diagnostic criterionwhich can therefore miss some patients, is yet to be validated in children, and recent studies have found lower sensitivity of the 2013 adult criteria for JSSc in a current cohort (19).

The clinical manifestations of scleroderma are broad, ranging from fatigue to more serious and debilitating ones such as pulmonary fibrosis (1) Although any organ can be affected in JSSc, the musculoskeletal and gastrointestinal systems are more frequently involved (22). The salient skin and musculoskeletal features present in our patient on physical examination were a puffy face with pursed lips, generalized hypopigmentation, thickness and hardness of the skin, reduced range of motion of the joints, and semi-flexion deformities of the interphalangeal joints of the fingers. The characteristic scleroderma facies have the appearance of a pinched nose, thin pursed lips, small mouth opening with thickened and adherent skin on the face (9) was also present in our patient. It is important to note that our patient had diffuse cutaneous JSSc characterized by widespread and rapidly progressive skin thickening (spreading proximal to elbow and knees) associated with early visceral disease.

The gastrointestinal symptoms are among the earliest to manifest and depend on the site and extent of involvement. Oesophageal involvement occurs in as many as 70-90% of patients (3,9). The underlying pathology of the symptoms involves progressive atrophy and fibrosis of the circular smooth muscle layer resulting in dysmotility. Our patient presented with a history of loss of appetite, abdominal discomfort and loss of weight. The symptoms of nausea, postprandial emesis, and heartburn were due to gastroparesis. Typically, gastrointestinal involvement is identified radiographically as dilatation of the oesophagus and sometimes shortening of the oesophagus resulting from fibrosis. Radiographic evidence of small bowel involvement includes dilatation of the lumen (2,7). Our patient had significant dilatation of the duodenum and segmental dilatation of the oesophagus.

Pulmonary involvement in our patient was suspected based on the findings on the initial CT chest which showed left basal lung segment fibrotic changes. Pulmonary involvement indicates a poor prognosis and is a common cause of death in patients with SSc. Pulmonary involvement although frequently asymptomatic, can present as a dry, hacking cough to dyspnoea on exertion and radiological features include basilar interstitial fibrosis on chest radiograph or high-resolution computed tomography (21). The repeat CT scan done at 24 months showed subtle bilateral basal atelectasis, with resolved lung changes and lung function tests were normal. This improvement is attributed to the disease modifying therapy that the patient was on. Some improvements are summarized in table 2.

The vascular manifestation present in our patient was Raynaud's phenomenon. She developed symptoms of discolouration of the skin of the fingers associated with some pain following

exposure to the cold. Raynaud's phenomenon is usually the earliest manifestation of SSc and is associated with nailfold capillary changes (7). In our patient, however, it was not the first sign and we were not able to ascertain nailfold capillary changes.

The laboratory findings in our patient were normal except for a slight increase in inflammatory markers CRP and ESR and a strong positive ANA at initial presentation to the hospital. Laboratory findings in patients with JSSc vary. High titers of antinuclear antibodies (ANAs) are commonly found with a frequency of 80% in children with JSSc, this was true for our patient who had very high titers of 1:3200. But the presence of both anti topoisomerase I (ScI-70) and anticentromere antibodies is lower in children compared with the adults (21). General markers of inflammation including erythrocyte sedimentation rate (ESR) and serum immunoglobulin levels may be useful markers of disease progression in selected patients (15). Due to limited resources, we were unable to do, SSc-related autoantibodies and inflammatory markers CRP and ESR were only done at initial presentation and were not repeated in the subsequent reviews to monitor disease progression.

Management of JSSc requires a multidisciplinary approach. The composition of the team is dependent on the organs involved, but general measures such as antacid medication for gastroesophageal reflux disease, vasodilators for Raynaud's phenomenon, and DMARD like methotrexate can be used (15). Our patient was commenced on prednisolone, for a few weeks to dampen the inflammation; nifedipine a calcium channel blocker for Raynaud's phenomenon, omeprazole a proton-pump inhibitor for the treatment of gastro-oesophageal reflux and Methotrexate was prescribed to suppress disease progression. Pulmonary involvement is an indicator of poor prognosis and is a common cause of death in patients with SSc. Treatment options for ILD in juvenile scleroderma include mycophenolate mofetil which can be used if methotrexate is ineffective, disease relapse can occur following clinical remission or if intolerance to methotrexate sets in (18,20) tocilizumab is indicated when active disease exists even on maximum doses of methotrexate and one other DMARD (12) cyclophosphamide which is equally effective as methotrexate except it is not as well tolerated (10) and rituximab which is also an excellent choice in the setting of early-onset diffuse skin involvement in addition to ILD 2 (18) . The patient had some features suggestive of pulmonary involvement, but due to the unavailability of the above treatment options in our setting, methotrexate was the only viable choice to which by the time of writing the she had responded well.

The multidisciplinary team that is currently managing our patient includes; general paediatricians, dermatologists, rheumatologists, gastroenterologists, nutritionists, and physiotherapists. Treatment is not curative but aims to slow down the progression of the disease, prevent complications, and relieve symptoms. The general consensus on the need for periodic follow-up of JSSc patients includes at least musculoskeletal and internal organ assessment with pulmonary, cardiac, and renal function tests, the time interval for these checks depends upon the disease status (3). Taking into account the financial constraints and distance between the town of origin and our hospital, the patient will be reviewed at least every 6 months.

The challenges faced in the management of our patient included; a delayed initial presentation and diagnosis, long distance of about 600 km, making it difficult for the scheduled reviews, the cost of the and limited access to rheumatological and imaging investigations and specific drugs that were not part of the National Health Insurance Management Authority (NHIMA) scheme and inadequate numbers of specialists to look after patients with such conditions. As for other rare conditions, the referral system should be streamlined and a register developed at the higher facilities like the UTHs-CH as this will make collaboration with centres in the developed world relatively well organized.

Table 2: Summary of some improvements

	Sign	Improvement noted on examination	Time after initiation of treatment (months)
1.	Skin hypopigmentation	Halted progression	6
		Reduction	24
2.	Skin thickness	Reduction	24
3.	Left basal lung segment fibrotic changes	Resolved	24
	Subtle basal atelectasis	Persisted	24
4.	Segmental dilatation of the oesophagus, and significant duodenal dilatation	Improved	24

Patient Perspective

Although the patient's mother and herself have gained better understanding of the condition, and have reported improvement in symptoms commencement of treatment including her resumption of schooling; their particular challenges regarding drugs especially those not covered on the NHIMA scheme and costly travel for review have continued.

CONCLUSION

JSSc is an uncommon autoimmune condition marked by multi-organ involvement and both early symptom identification and referral to specialized care are essential for a speedy diagnosis and treatment. The purpose of treatment is to lessen inflammation, avoid complications, and enhance the quality of life. Our patient presented with advanced disease due to delayed diagnosis, treatment, and long distance to a higher facility. For uncommon diseases like JSSc, efforts should be made to raise awareness, improve referral processes, and expand access to reasonably priced healthcare resources.

DECLARATIONS

Ethics approval and consent to participate: Not applicable.

Consent for publication: written informed consent was obtained from the patient's legal guardian

Author's contribution: BC, HM, VS, and CS were responsible for the diagnosis and clinical management of the patient. BC and HM drafted the manuscript. EM, ON, and VS participated in the analysis, supervision, writing of the original draft, reviewing, and editing of the manuscript for intellectual content. All authors read and approved the final manuscript.

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