

Antinuclear antibody positivity as a marker of extracutaneous disease in juvenile localized scleroderma: A literature review

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Abstract

Juvenile Localized Scleroderma (jLS), or juvenile morphea, is a chronic inflammatory and fibrosing disorder that may extend beyond the skin into subcutaneous tissue, fascia, muscle, joints, and bone. Neurologic and ophthalmologic involvement may also occur, particularly in children with craniofacial disease. Antinuclear Antibodies (ANA) are frequently detected in patients with jLS, but their clinical significance remains uncertain. This focused review evaluates whether ANA positivity is associated with extracutaneous manifestations, particularly deeper musculoskeletal involvement. Large pediatric cohorts demonstrate that ANA positivity occurs in approximately one-third to one-half of tested patients. The strongest evidence for an association with disease severity comes from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry, in which ANA positivity was associated with joint contracture, muscle atrophy, and extremity shortening. In contrast, smaller cohorts have not consistently identified an association between ANA positivity and extracutaneous disease. Current evidence therefore suggests that ANA positivity may identify a subset of children with greater musculoskeletal or deep-tissue involvement but is insufficient to establish ANA as an independent prognostic biomarker. ANA status should be interpreted as an adjunct to clinical assessment rather than as a stand-alone predictor of extracutaneous disease.

Keywords: Juvenile localized scleroderma; Juvenile morphea; Antinuclear antibody; ANA; Extracutaneous manifestations; Musculoskeletal involvement; Pediatric rheumatology.

Introduction

Juvenile Localized Scleroderma (jLS) is an inflammatory and fibrosing disorder characterized by sclerosis of the skin and underlying connective tissues. Although traditionally considered a cutaneous disorder, jLS may involve the subcutaneous tissue, fascia, muscle, joints, and bone. In children, this deeper involvement is particularly consequential because fibrosis occurring during growth may lead to joint contractures, muscle atrophy, limb-length discrepancy, skeletal deformity, and permanent functional impairment [1,2]. Craniofacial subtypes, including linear scleroderma *en coup de sabre* and progressive

facial hemiatrophy, may additionally be associated with neurologic, ophthalmologic, and maxillofacial abnormalities [2,3].

The importance of extracutaneous disease was demonstrated in a multinational cohort of 750 children with localized scleroderma. Extracutaneous manifestations were identified in 22.4% of patients, with articular abnormalities accounting for nearly half of reported manifestations. Neurologic, vascular, ocular, gastrointestinal, pulmonary, cardiac, and renal abnormalities occurred less frequently [1]. Notably, some manifestations occurred at sites anatomically distant from the cutaneous lesion, emphasizing that skin examination alone may underestimate disease burden [1]. The ability to identify patients at increased risk for deeper disease could facilitate earlier investigation and closer longitudinal surveillance. Antinuclear antibodies are among the most frequently detected laboratory abnormalities in jLS [4]. However, ANA positivity is neither specific to localized scleroderma nor indicative of progression to systemic sclerosis [1,3]. Whether ANA instead functions as a marker of a clinically distinct jLS phenotype remains unresolved.

This review examines evidence supporting an association between ANA positivity and extracutaneous disease in children with localized scleroderma, with particular emphasis on musculoskeletal involvement and the potential clinical utility of ANA testing.

Methods

A focused narrative literature review was performed using PubMed/MEDLINE and reference screening. Search terms included combinations of *juvenile localized scleroderma*, *juvenile morphea*, *pediatric morphea*, *antinuclear antibody*, *ANA*, *extracutaneous manifestations*, *musculoskeletal involvement*, *joint contracture*, *muscle atrophy*, *limb shortening*, *neurologic involvement*, and *ophthalmologic involvement*.

Original pediatric cohort studies reporting ANA testing, extracutaneous manifestations, or both were prioritized. Consensus recommendations and contemporary reviews were used to provide clinical context. Adult-only studies and isolated case reports were not included in the primary evidence synthesis. Because available studies differed considerably in cohort composition, ANA testing practices, definitions of extracutaneous involvement, and outcome ascertainment, findings were synthesized narratively rather than quantitatively.

Table 1: Selected studies evaluating ANA positivity and extracutaneous manifestations in juvenile localized scleroderma.

Study	Population	ANA findings	Extracutaneous findings	Relationship with ANA
Wu et al., 2019	n=381	ANA available in 296; approximately 48% positive	Muscle atrophy, joint contracture, extremity shortening, functional limitation	ANA positivity associated with joint contracture, muscle atrophy, and extremity shortening
Zulian et al., 2005	n=750	ANA more frequent in patients with extracutaneous disease	ECM in 22.4%; articular 47.2%, neurologic 17.1%, ocular 8.3% of reported ECM	ANA prevalence significantly higher in patients with ECM than in skin-limited disease
Jindal et al., 2023	n=84	ANA tested in 25; 8 positive (32%)	ECM in 14 patients (16.6%)	No significant association between ANA positivity and ECM
Branton et al., 2024/2025	n=341	ANA-stratified predictive analysis not primary objective	High burden of extracutaneous and multisystem involvement	Supports clinical importance of extracutaneous disease but does not establish ANA as an independent predictor
Herrick et al., 2010	Pediatric UK/Ireland cohort	ANA testing reported in a subset	Demonstrated burden of childhood localized disease and complications	Limited ANA-stratified outcome data

ANA positivity in juvenile localized scleroderma

ANA positivity is common in jLS, although its reported prevalence varies among studies.

One of the largest pediatric datasets is the CARRA Legacy Registry. Wu and colleagues analyzed 381 children with jLS enrolled across 49 pediatric rheumatology centers. Of 296 patients who underwent ANA testing, 48% were ANA positive. ANA positivity was not significantly associated with disease subtype or age at onset [4].

Lower rates have been observed in smaller cohorts. Jindal and colleagues evaluated 84 children with jLS at a tertiary referral center in India. Only 25 underwent ANA testing, of whom eight were positive, corresponding to 32% of tested patients [5].

Differences in prevalence likely reflect variation in referral populations, assay methodology, laboratory thresholds, disease subtype, and patient selection for testing. The proportion of ANA-positive patients should therefore be interpreted as a proportion of tested children rather than as a definitive population prevalence.

Extracutaneous disease in jLS

Extracutaneous involvement is a major contributor to morbidity in juvenile localized scleroderma.

In the multinational study by Zulian and colleagues, 168 of 750 children had at least one extracutaneous manifestation. Articular abnormalities accounted for 47.2% of these manifestations, followed by neurologic involvement in 17.1%, vascular involvement in 9.3%, ocular disease in 8.3%, gastrointestinal disease in 6.2%, and respiratory disease in 2.6% [1]. Importantly, more than one-quarter of articular, neurologic, and ocular abnormalities occurred at sites unrelated to the location of cutaneous disease. ANA and rheumatoid factor positivity were also more frequent among children with extracutaneous manifestations than among those with skin-limited disease [1].

The CARRA Legacy Registry demonstrated a similarly substantial burden of noncutaneous abnormalities. Forty-six percent of children had at least one extracutaneous manifestation and 31% had evidence of noncutaneous damage. Muscle atrophy occurred in 23%, joint contracture in 18%, extremity shortening in 9%, hemifacial atrophy in approximately 9%, and arthritis in 5% [4].

These abnormalities are particularly consequential in children because fibrosis involving muscle, joints, and growing bone may result in permanent functional impairment and altered growth even after inflammatory activity has subsided [7,8].

These findings reinforce an important clinical distinction: localized scleroderma is localized relative to systemic sclerosis, but it is not necessarily confined to the epidermis or dermis.

Association between ANA positivity and musculoskeletal disease

The strongest evidence linking ANA positivity to deeper tissue involvement comes from the CARRA Legacy Registry.

ANA-positive patients demonstrated significantly greater odds of several clinically important forms of noncutaneous damage. ANA positivity was associated with joint contracture, with an Odds Ratio (OR) of 1.79 (95% Confidence Interval [CI], 1.03–3.13; $p=0.04$), muscle atrophy (OR, 2.02; 95% CI, 1.15–3.56; $p=0.014$), and extremity shortening (OR, 3.19; 95% CI, 1.36–7.47; $p=0.007$) [3].

These associations are clinically relevant because each abnormality represents extension beyond superficial cutaneous sclerosis. Joint contracture may reflect fibrosis affecting structures surrounding a joint, whereas muscle atrophy and extremity shortening suggest involvement of deeper soft tissues and developing skeletal structures.

Additional laboratory findings in the same cohort strengthen the concept of a deeper-tissue phenotype. Elevated aldolase was associated with joint contracture, while elevated creatine kinase was associated with muscle atrophy and extremity shortening [4].

Together, these observations suggest that ANA positivity may be one component of a phenotype characterized by greater immune activation and increased musculoskeletal involvement. Importantly, however, the association should not be interpreted as causal. There is insufficient evidence that ANA directly contributes to fibrosis or tissue damage. ANA positivity is more plausibly a marker of underlying immune dysregulation accompanying a more extensive disease phenotype.

Conflicting evidence across cohorts

The association between ANA positivity and extracutaneous disease has not been consistently reproduced.

In the single-center cohort reported by Jindal and colleagues, 14 of 84 patients had extracutaneous manifestations, including arthritis, brain parenchymal abnormalities, and pulmonary involvement. ANA was positive in eight of 25 tested patients. No significant association was identified between ANA positivity and extracutaneous manifestations ($p=1.000$) [5].

Several methodological factors may explain the discrepancy between this study and the CARRA registry. First, only 25 children underwent ANA testing, substantially limiting statistical power. Second, extracutaneous manifestations were analyzed as a composite outcome rather than separating specific musculoskeletal manifestations. Third, referral patterns, ethnicity, disease duration, lesion subtype, treatment exposure, and testing practices differed between cohorts.

The existing evidence therefore appears stronger for an association between ANA positivity and specific musculoskeletal manifestations than for a generalized relationship between ANA and all forms of extracutaneous disease.

Neurologic and ophthalmologic involvement

Neurologic and ophthalmologic complications are among the most clinically significant manifestations of jLS, particularly in patients with craniofacial involvement. Reported neurologic abnormalities include seizures, headaches, peripheral neuropathy, vascular abnormalities, central nervous system inflammation, and abnormal neuroimaging findings. Ocular manifestations include uveitis, episcleritis, glaucoma, papilledema, and structural abnormalities [1,3].

At present, evidence does not demonstrate a consistent relationship between ANA status and neurologic or ophthalmologic disease specifically. These complications appear more strongly related to anatomical distribution and clinical phenotype.

This distinction has practical implications. Consensus recommendations advise brain magnetic resonance imaging in children with jLS involving the face or head, regardless of whether neurologic symptoms are present, and recommend ophthalmologic assessment particularly in patients with facial or scalp lesions. Comprehensive joint examination is likewise recommended at diagnosis and during follow-up [6].

Thus, ANA status should not be used to determine whether these evaluations are necessary when the clinical phenotype already indicates increased risk.

ANA positivity does not imply systemic sclerosis

Detection of ANA may generate concern about progression from localized scleroderma to systemic sclerosis. Available evidence indicates that such progression is uncommon.

Among the 750 children studied by Zulian and colleagues, only one developed systemic sclerosis. Furthermore, systemic sclerosis-associated antibodies, including anti-topoisomerase I and anticentromere antibodies, were not significantly increased in children with extracutaneous involvement [1].

ANA positivity in a child with localized scleroderma should therefore be interpreted primarily within the context of the patient's localized disease phenotype and should not, in isolation, be considered evidence of impending systemic sclerosis.

Clinical implications

Current evidence supports a limited but potentially useful role for ANA testing in jLS.

An ANA-positive result may reasonably increase awareness of possible deeper musculoskeletal disease, particularly when accompanied by linear extremity lesions, reduced joint range of motion, asymmetry, muscle wasting, or impaired growth. In such patients, examination should specifically assess joint mobility, muscle bulk, limb circumference and length, functional limitation, and evidence of deeper lesion extension [4,6].

When musculoskeletal involvement is suspected, imaging may provide additional information. Consensus recommendations support magnetic resonance imaging for evaluating deeper musculoskeletal disease, particularly when lesions cross a joint [6].

ANA positivity should not, however, independently determine imaging, therapy, or prognosis. Existing studies have not established adequate sensitivity, specificity, or predictive value for ANA as a stand-alone prognostic test. Conversely, a negative ANA does not exclude clinically important extracutaneous disease.

The most appropriate interpretation is therefore probabilistic rather than diagnostic: ANA positivity may contribute additional risk information when integrated with lesion subtype, anatomical location, depth, disease activity, physical examination, and longitudinal growth and functional assessment.

Limitations of the available evidence

Several limitations prevent definitive characterization of ANA as a prognostic biomarker.

Most available studies are observational, retrospective, or cross-sectional. Such designs establish associations but cannot determine whether ANA positivity precedes the development of musculoskeletal damage.

ANA testing is also incomplete in several cohorts. Selective testing creates potential ascertainment bias if patients with more extensive or atypical disease are more likely to undergo serologic evaluation [4,5]. Differences in assay methodology, dilution thresholds, and laboratory definitions of ANA positivity further limit comparisons between studies.

Extracutaneous outcomes are heterogeneous. Composite endpoints may combine arthritis, joint contracture, muscle atrophy, neurologic disease, ophthalmologic abnormalities, and internal-organ findings despite likely differences in pathogenesis and relationship to cutaneous disease.

Most importantly, disease subtype and anatomical distribution are potential confounders. Linear disease involving an extremity intrinsically carries a greater risk of muscle, joint, and skeletal abnormalities, whereas craniofacial disease is associated with neurologic and ophthalmologic complications [1,6]. Demonstrating that ANA independently predicts outcomes therefore requires adjustment for these clinical characteristics.

Future directions

Prospective multicenter studies are needed to determine whether ANA provides clinically meaningful prognostic information beyond established clinical risk factors.

Future studies should perform ANA testing systematically at diagnosis and record antibody titer, staining pattern, assay methodology, and relevant autoantibody specificities. Longitudinal assessment should include standardized measures of lesion depth, disease activity, joint range of motion, muscle bulk, limb growth, functional status, neurologic disease, and ophthalmologic abnormalities.

Multivariable models should evaluate whether ANA retains an association with musculoskeletal damage after adjustment for disease subtype, lesion location, depth, duration, and treatment exposure. Combining ANA with laboratory markers such as creatine kinase and aldolase may also warrant investigation [4].

The development of standardized multidimensional assessment strategies in jLS is particularly important because skin-centered measures alone may fail to capture deeper musculoskeletal damage and other extracutaneous manifestations [5,8]. Future prospective registries incorporating standardized serologic and extracutaneous measurements may clarify whether ANA can meaningfully contribute to risk stratification.

Conclusion

Juvenile localized scleroderma is not exclusively a cutaneous disorder. Musculoskeletal and other extracutaneous manifestations represent important sources of morbidity, particularly when disease affects growing tissues.

ANA positivity is common in children with jLS. In the largest multicenter pediatric registry studied to date, ANA positivity was significantly associated with joint contracture, muscle atrophy, and extremity shortening, suggesting that it may identify a subgroup with greater deep-tissue involvement [4]. However, this association has not been consistently reproduced across cohorts [5].

Current evidence therefore does not support ANA as an independent prognostic biomarker. Instead, ANA positivity is best regarded as an adjunctive clinical finding that may increase suspicion for deeper musculoskeletal involvement but cannot replace comprehensive physical examination, phenotype-based screening, imaging when indicated, and longitudinal assessment.

Future prospective studies incorporating standardized ANA testing and detailed extracutaneous outcomes are needed to determine whether serologic status provides prognostic information beyond lesion subtype, anatomical distribution, and depth.

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