Skin mapping for the classification of generalized morphea

Noelle Teske, MD, MSc,[a] Joseph Welser, MD,[b] and Heidi Jacobe, MD, MSCS[a]
Dallas, Texas, and Memphis, Tennessee

Background: Generalized morphea lacks cohesive clinical features, limiting its clinical and investigative utility.

Objective: We sought to use computerized lesion mapping to objectively subtype morphea.

Methods: We conducted a 2-part cross-sectional study. In part 1, we created a discovery cohort of patients with generalized morphea of whom lesion maps were created to characterize subsets. Clinical and demographic features were compared between proposed subsets to determine if they identified clinically relevant differences. In part 2, we created a validation cohort to determine if proposed criteria were applicable to different individuals.

Results: A total of 123 patients with generalized morphea were included. Mapping produced 2 distribution patterns that encompassed the majority in both cohorts: isomorphic (areas of skin friction) and symmetric (symmetrically distributed on trunk/extremities). In the discovery cohort, the isomorphic subset was older (55.6 ± 12.7 vs 42.2 ± 20.1 years, $P < .001$), all female (30/30 vs 38/43, $P = .05$), and more often had lichen sclerosus changes (12/43 vs 8/43, $P = .02$); involvement of the reticular dermis, subcutaneous fat, and/or fascia was more common in symmetric (10/43 vs 1/30) ($P = .02$). These features persisted in the validation cohort.

Limitations: Single cohort was a limitation.

Conclusions: Symmetric and isomorphic subsets possess distinctive demographic and clinical features, suggesting they more accurately define the phenotype of generalized morphea. Consideration should be given to revising classification. (J Am Acad Dermatol 2018;78:351-7.)

Key words: clinical research; cohort study; cross-sectional study; disease registry; localized scleroderma; morphea; skin mapping.

Generalized morphea is one of the most severe subtypes of morphea, characterized by widespread skin involvement,[1] and extension to the subcutaneous tissue and fascia in some cases.[2]

Although linear morphea is identified by specific demographic and clinical features, criteria for generalized morphea differ across classification schemes. This is because current classifications for morphea are largely based on expert opinion rather than prospective, systematic efforts. The most commonly used system classifies generalized morphea by the presence of 4 or more lesions larger than 3 cm in diameter in at least 2 of 7 anatomical sites.[3-5]

From the Department of Dermatology, University of Texas Southwestern Medical Center,[a] and Department of Urology, University of Tennessee Health Science Center at Memphis.[b]

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Correspondence to: Heidi Jacobe, MD, MSCS, Department of Dermatology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9069. E-mail: heidi.jacobe@utsouthwestern.edu.

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However, it is unclear whether patients with multiple linear lesions who meet these criteria are included in the generalized morphea subtype,[3,5] and aside from widely distributed cutaneous lesions, demographic and clinical features of the generalized subtype are not well defined.

Our observation of patients in the prospective Morphea in Adults and Children (MAC) cohort suggested that the generalized subtype, as currently defined, represents not 1 but a conglomeration of phenotypes. This jeopardizes the results of ongoing studies in morphea, which require a consistently defined population to build understanding of disease genetics and mechanisms.

We used computerized lesion mapping to identify distribution patterns of morphea lesions in patients who met criteria for the generalized subtype by 2 commonly used classification schemes[3,5] to determine the cutaneous distribution of lesions in an objective manner, and to determine whether these patterns reflected unique demographic and clinical features.

CAPSULE SUMMARY

- Generalized morphea is a poorly described disease subtype with unclear inclusion criteria.
- Computerized lesion mapping helps define meaningful subsets of generalized morphea.
- Patients with generalized isomorphic morphea more frequently have lichen sclerosus and uncommonly have deep involvement whereas those with symmetric lesions are at risk for deep involvement.

METHODS

This is a 2-part cross-sectional study of participants of the prospective MAC cohort at the time of their enrollment. First, computerized lesion mapping was used to characterize lesion distribution patterns (discovery cohort) in generalized morphea, which created 2 proposed subsets of generalized morphea. Secondly, these distribution patterns were applied to an independent set of participants at their enrollment into the MAC cohort (validation cohort).

To create the discovery cohort, a cross-sectional analysis was performed of patients in the prospective MAC cohort at the University of Texas Southwestern Medical Center between 2007 and 2010 (criteria for enrollment and cohort characteristics previously described).[6] Patients were included who had generalized morphea based on criteria described by Laxer and Zulian[5] and Peterson et al,[3] as identified by a single investigator (H. J.), had clinical photographs of sufficient quality for lesion mapping, and completed case report forms for variables of interest. Patients with multiple linear lesions who met aforementioned criteria for generalized morphea were also initially included. Patients with pansclerotic and indeterminate subtypes were excluded.

Graphical lesion maps were created for each patient using methods described by Weibel and Harper,[7] using common body outlines as a basis for clinical illustration. Based on clinical photographs taken at the time of cohort enrollment, areas of involvement, including both active and inactive lesions, were shaded black on lesion maps using a computer paint program (GNU Image Manipulation Program, MIT, Cambridge, MA). Independent raters without knowledge of proposed subtypes triple-checked these maps against clinical photographs. Assigning distinct numeric value to black-and-white pixels resulted in matrices that could be analyzed with standard statistical techniques using MATLAB (Mathworks, Natick, MA). Individual lesion maps were superimposed and the result was plotted as a heat map (Fig 1, *A*). Because the resulting composite map contained many areas present only in a few patients, a statistical filter developed for brain imaging studies[8,9] was used to identify statistically significant regions ($P > .025$) and to correlate lesions that occurred frequently together, creating 2 patterns of distribution. The resultant black-and-white image was examined and statistically significant areas of lesion distribution (black) were noted as suggesting characteristic lesion patterns for the new proposed subsets (Fig 1, *B*). Areas of involvement common to both subsets, identified by the intersection of these data sets, were subtracted from composite maps, generating maps of unique areas of involvement (Fig 1, *C*). Patients who had lesions distributed in areas of chronic friction (waistband and brassiere-band area) were classified as isomorphic, as previously described by our group,[10-12] whereas those with largely symmetric lesions about the midline distributed on the trunk, limbs, or both were called symmetric.

Demographics (age at onset, adult vs pediatric [<18 years] onset, gender, and race) and clinical features (overlying lichen sclerosus [LSA] change or deep involvement) were compared between patients of the 2 proposed subsets. Deep involvement was defined as involvement of the