Histopathologic spectrum of morphea: a single-center retrospective study

Özben Yalçın,[1] Mine İlayda Şengör Aygün,[1] Elif Moustafa,[2] Ezgi Aktaş[2]

[1]Department of Pathology, and [2]Department of Dermatology, Prof Dr. Cemil Taşcıoğlu City Hospital, Istanbul, Turkey

Abstract

Morphea is a rare autoimmune disease that often affects skin and subcutaneous tissues. The aim of this study was to determine the association between patient demographic parameters, lesion site, clinical subtype of morphea, and histological findings. Between 2016 and 2022, we investigated 78 patients with morphea at the Department of Pathology, Prof. Dr. Cemil Taşcıoğlu City Hospital in Turkey. Case-specific hematoxylin and eosin stain slides were obtained from the pathology archive and assessed blindly by two pathologists. Flattening of rete ridges, location of inflammatory infiltrate, grade of inflammatory infiltrate, presence of plasma cells, presence of eosinophils, homogenization of dermal collagen, decrease of skin appendages, basal pigmentation and melanin incontinence were evaluated. Statistical analyses were performed using SPSS Statistics v.20 (IBM, Armonk, NY, USA). The most common clinical presentation was plaque type (87.5%), while histopathological findings included homogenization of dermal collagen (100%) and decrease of skin appendages (98.7%). Flattening of the rete ridges was observed in 46.2% of patients. Severity of the inflammatory infiltrate was found to be higher in these patients (p=0.028). Basal pigmentation was observed in 59% of patients. *Line* sign was more common in lower extremity lesions among all localizations (p=0.015). The histopathologic features of morphea are variable and confusing. Particularly, in cases with collagen homogenization, morphea should be considered in differential diagnosis with clinical correlation. In addition, the *line* sign could be helpful for identifying lesions located in the lower extremities.

Correspondence: Mine İlayda Şengör Aygün, Kaptanpasa mah. No: 27 Prof. Dr. Cemil Tascioglu Sehir Hastanesi Sisli İstanbul, Turkey.
E-mail: ilaydasengor@gmail.com

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Introduction

Morphea (localized scleroderma) is a rare autoimmune connective tissue disease that often affects the skin and subcutaneous tissue lesions.[1,2] It is predominantly seen in Caucasians and females.[3,4] Although its pathogenesis is not clearly understood, it is thought to develop as a result of a combination of genetic predisposition and environmental factors, similar to other autoimmune diseases.[5] It is distinguished from systemic scleroderma by the absence of internal organ involvement.[6] Its clinical presentation is highly variable. According to the most widely accepted classification system, there are 5 subtypes: plaque, linear, generalized, pansclerotic, and mixed.[7] Sometimes, histopathological distinction between systemic sclerosis and morphea is not possible.[5]

Objectives

There are limited number of studies in the literature investigating the clinicopathological relationship.[2,6-9] In this retrospective study, we aimed to evaluate the histopathological spectrum of morphea.

Materials and Methods

Compliance with ethical standards

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All procedures applied in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Istanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (IRB No. 2023-325).

Study population

We studied 78 patients diagnosed with morphea between 2016 and 2022 at the Department of Pathology Prof. Dr. Cemil Taşcıoğlu City Hospital. Clinical information was gathered using the institute's database records.

Pathological examination

Hematoxylin and eosin stained (H&E) slides of cases were retrieved from the pathology archive and were independently evaluated by two pathologists (OY and MISA) under blinded conditions. The diagnosis was based on morphology in H&E, periodic acid-Schiff (PAS), Alcian blue stained sections. Flattening of rete ridges, location of inflammatory infiltrate (superficial, deep, superficial+deep), grade of inflammatory infiltrate (absent, mild, moderate, dense), presence of plasma cells, presence of eosinophils, homogenization of dermal collagen, decrease of skin appendages (mild, moderate, complete loss), basal pigmentation and melanin incontinence were evaluated based on prior criteria by Walker *et al.*[2] and Chiu *et al.*[7]

Clinical examination

Clinical data of patients included in the study were analyzed retrospectively from electronic medical records. The clinical features obtained from the records included demographic characteristics of the patients, location of the lesion, clinical subtype of morphea (plaque, linear, generalized, pansclerotic, mixed), patient's age at onset of lesion, age at biopsy, and time from lesion onset to biopsy.

Statistical analysis

Descriptive statistics, including median (range) for continuous variables and percentages for categorical data, were used to explore baseline and patient characteristics. The Mann Whitney test was used to compare continuous variables between groups. The X^2 test was used to examine differences in categorical variables between groups. A p-value ≤0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics v.20 (IBM, Armonk, NY, USA).

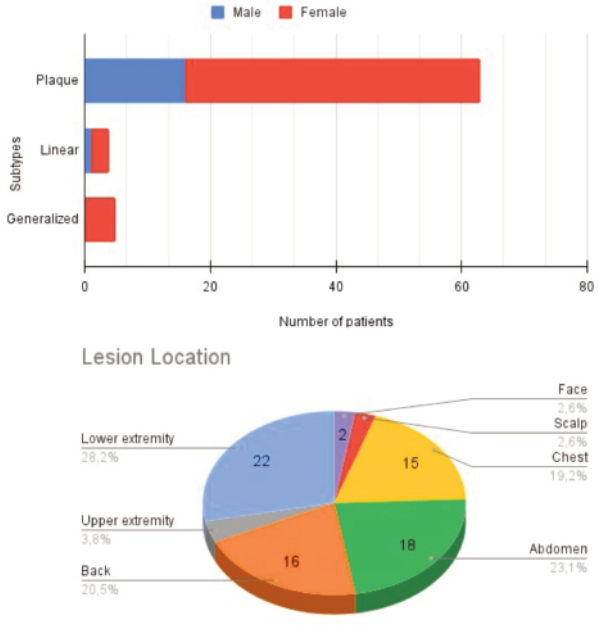

Figure 1. Number of patients: subtypes and location of lesions.

Results

Seventy-eight patients were included in the study. The clinical records of 6 patients could not be accessed. 79.5% (n=62) of the patients were women. The mean age at disease onset was 39.5±20.8 years, the age at biopsy was 42.4±19.7 years, and the time from baseline to biopsy was 1.8±2.8 years. At the time of biopsy, the mean age at female patients (42.6) was higher than that of male patients (39.5). The frequency of clinical subtypes was plaque (n=63, 87.5%), linear (n=4, 4.6%), and generalized (n=5, 7.9%), respectively. There was no patient presenting as pansclerotic. The most common localization of the lesions was the lower extremity (n=22, 28.2%), followed by abdomen (n=18, 23.1%), back (n=16, 20.5%), chest (n=15, 19.2%), the upper extremity (n=3, 3.8%), scalp (n=2, 2.6%), and face (n=2, 2.6%) (Figure 1). The most common histopathological finding was homogenization of dermal collagen in all cases (Figure 2). Flattening of rete ridges were found in 36 patients (46.2%) (Figure 3).

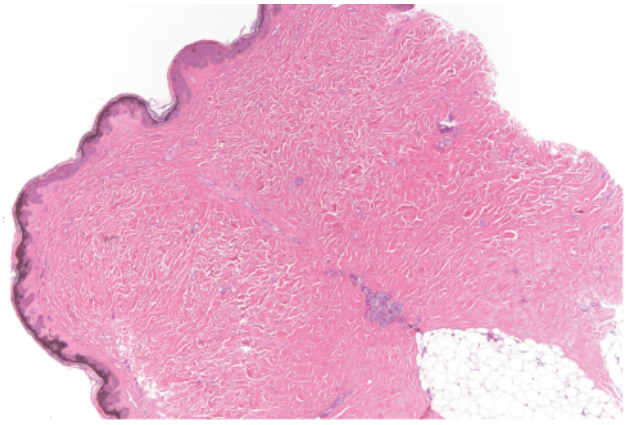

Figure 2. Homogenization of dermal collagen. Hematoxylin and Eosin 40×.

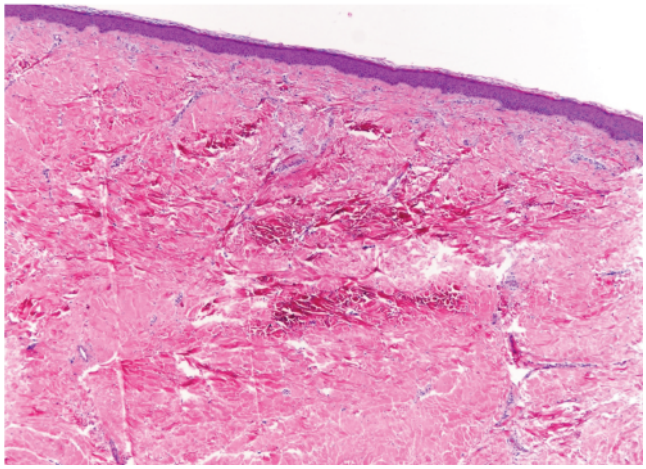

Figure 3. Flattening of the rete rideges. Hematoxylin and Eosin 40×.

Inflammatory infiltrate in the dermis was not found in 8 patients (10.3%). Inflammatory infiltrate was mild in 54 patients (69.2%), moderate in 14 patients (17.9%), and severe in 2 patients (2.6%). Inflammatory infiltrate was observed superficially in 41 patients (57.7%), deeply in 5 patients (7%) and superficial and deep dermis infiltration were observed in 25 patients (n=35.3). Other histopathological findings are summarized in Table 1. Among the parameters in Table 1, rete ridge flattening, basal pigmentation, and the 'line' sign' are the parameters that can be detected more quickly at first glance. For this reason, they were evaluated in terms of their effectiveness as a quick diagnostic clue in daily practice. Relationships with other histological parameters were also analyzed.

Flattening of the rete ridges was observed in 46.2% of the patients in our study. Severity of the inflammatory infiltrate was found to be higher in patients with flattening of the rete ridges (p=0.028). In addition, the age at disease onset and the mean age at the time of biopsy were also found to be more advanced in patients with flattened rete ridges (p=0.024; p=0.010) (Table 2).

Basal pigmentation was observed in 59% of the patients in our study. The severity of the inflammatory infiltrate was milder, and the plasma cell count was lower in these patients (p=0,030, p=0,024) (Table 3). In our series, *line* sign was found in 46.2% of the cases, and inflammation was found to be more deeply located in these cases (p=0.011). Among all localizations, *line* sign was more common in lower extremity lesions (p=0.015). The age at disease onset and age at biopsy were lower in these patients (p=0.026, p=0.022) (Table 4).

Discussion

Morphea, or localized scleroderma, is an autoimmune skin disorder characterized by inflammation and sclerosis of the skin and underlying tissues. The estimated incidence of morphea is 0.4-2.7 per 100,000 people.[10] Although different classification schemes exist, the most accepted morphea subtypes include plaque (circumscribed), linear, generalized, pansclerotic and mixed. Plaque is the most frequently encountered subtype in adult-onset morphea, while linear is the predominant in pediatric-onset subtype.[11] A female predominance of 2.4 to 4.2:1 has been reported.[5] In our study, female predominance was remarkable with a rate of 79.5% in line with the literature. Consistent with the results of epidemiological studies, the most common subtype in our study was plaque type with a rate of 87.5%.[2,4,7,9,12] Plaque subtype is known to be a common morphea type. In a study conducted among morphea patients in our country, plaque type was observed in 62% of the patients as the most common type.[12] In another study plaque morphea was observed in 78.8% of the study population.[13] Prasad *et al.* found that only 15% of subjects had plaque subtype.[14] There is a wide variety in the frequency of the morphea subtypes. In our study 85% of the patients had plaque subtype which is relatively high. The differences in sample sizes of the studies may be an explanation of the variations in frequencies. Further research may reveal whether there are genetic and racial factors contributing to development of different subtypes.

There are few studies in the literature that evaluate the histopathological findings of morphea.[2,4,6,7,9] In most case series,

Table 1. Histopathological findings.

	N.	%
Flattening of rete ridges	36	46.2
Inflammatory infiltrate		
Absent	8	10.3
Mild	54	69.2
Moderate	14	17.9
Dense	2	2.6
Location of inflammatory infiltrate		
Superficial	41	57.7
Deep	5	7.0
Superficial and deep	25	35.3
Plasma cells		
Absent	36	46.2
Mild	35	44.9
Moderate	7	9.0
Dense	0	0
Eosinophils	4	5.1
Homogenization in dermal collagen	78	100
Decrease in skin appendages		
Absent	1	1.3
Mild	17	21.8
Moderate	59	75.6
Complete loss	1	1.3
Keratinocyte necrosis	10	12.8
Basal pigmentation	46	59.0
Melanin incontinence	20	25.6
Line sign	36	46.2

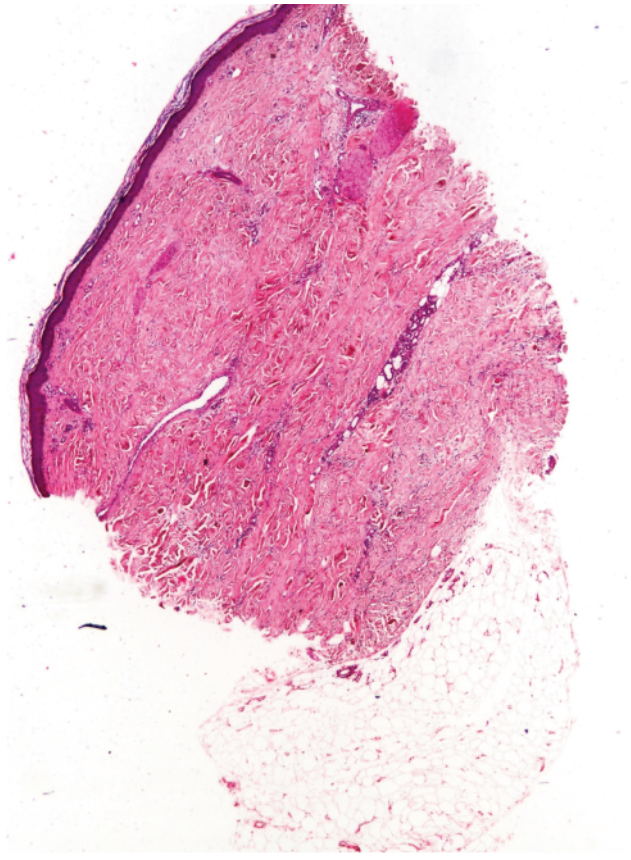

Figure 4. The line sign. Hematoxylin and Eosin 20×.

inflammatory infiltrate is reported to be present in more than 80% of cases,[2,4,7,9] whereas it was found to be in 45% of the patients in the case series conducted among by Hong *et al.*[6] They thought that inflammatory cells disappeared due to increasing fibrosis as the disease stage progressed, but they could not find a statistically significant difference between plasma cell count and stage of the disease. In our study, 89.7% of the cases had inflammatory infiltrate consistent with the literature [2,4,7,9] and there was not a significant relationship between biopsy time and the degree of inflammatory infiltrate (p=0.055).

In our study, flattening of the rete ridges was found in 36 patients. Inflammation was found more severe in these patients (p=0.028). Also in these patients, the mean age at the time of biopsies were found more advanced (p=0.010). Inflammation induces fibrosis by causing the release of cytokines. Fibrosis may cause scar tissue formation, resulting in flattening of the rete ridges. Due to this scar formation, patients may have a longer subclinical course and consequently the biopsy age may be more advanced.

Plasma cells were found at a rate of 75-100% in different case series.[2,4,7,9] Chiu *et al.*[7] suggested using plasma cells as a diagnostic clue. In our study, it was 53.9%, lower than the literature. Walker *et al.*[2] evaluated the presence of increased plasma cells accompanying lymphocytes, consistent with the mechanism of fibrosis, which indicates an immune response dominated by T helper cell 2. The low plasma cells in our study may have been the result of patients' late admission to the clinic. Also, the eosinophil

Table 2. Comparative analysis of flattening of rete ridges and other histopathological findings.

	Flattening of rete ridges, n (%)		p
	Absent (n=42)	Present (n=36)	
Sex			
Male	10 (23.8)	6 (16.7)	0.436[a]
Female	32 (76.2)	30 (83.3)	
Subtype			
Plaque	34 (87.2)	29 (87.9)	0.952[a]
Linear	2 (5.1)	2 (6.1)	
Generalized	3 (7.7)	2 (6.1)	
Inflammatory infiltrate			
Absent	1 (2.4)	7 (19.4)	0.028*[a]
Mild	32 (76.2)	22 (61.1)	
Moderate	9 (21.4)	5 (13.9)	
Severe	-	2 (5.6)	
Location of inflammatory infiltrate			
Superficial	24 (58.5)	17 (56.7)	0.506[a]
Deep	4 (9.8)	1 (3.3)	
Superficial+deep	13 (31.7)	12 (40.0)	
Plasma cell			
Absent	19 (45.2)	17 (47.2)	0.975[a]
Mild	19 (45.2)	16 (44.4)	
Moderate	4 (9.5)	3 (8.3)	
Eosinophils	3 (7.1)	1 (2.8)	0.384[a]
Homogenization of dermal collagen	42 (100)	35 (97.2)	0.277[a]
Decrease of skin appendages			
Absent	-	1 (2.8)	0.090[a]
Mild	13 (31.0)	4 (11.1)	
Moderate	28 (66.7)	31 (86.1)	
Complete loss	1 (2.4)	-	
Keratinocyte necrosis	4 (9.5)	6 (16.7)	0.347[a]
Basal pigmentation	25 (59.5)	21 (58.3)	0.915[a]
Melanin incontinence	8 (19)	12 (33.3)	0.150[a]
Line sign	22 (52.4)	14 (38.9)	0.233[a]
Face	-	1 (3)	0.274[a]
Scalp	1 (2.6	1 (3)	0.905[a]
Chest	12 (30.8)	5 (15.2)	0.120[a]
Abdomen	7 (17.9)	12 (36.4)	0.077[a]
Back	8 (20.5)	10 (30.3)	0.339[a]
Upper extremity	4 (10.3)	1 (3)	0.229[a]
Lower extremity	14 (35.9)	9 (27.3)	0.434[a]
Age at biopsy, avg±ss	37.7±19.9	47.9±18.4	0.024**[b]
Age at onset of lesion, avg±ss	33.9±20.3	46.7±9.4	0.010**[b]
Time from lesion onset to biopsy, avg±ss	2.5±3.4	0.93±1.2	0.063[b]

*p<0.05. **p<0.001. [a]X^2-test and Fisher exact; [b]Mann Whitney.

count was found to be 5.1%, lower than the literature (10-21%).[4,7,9] A significant correlation was found between the presence of eosinophils and generalized morphea in a series of 137 patients by Kim *et al*. (p=0.050).[15] The reason for the low eosinophils in our study may be related to the rare occurrence of generalized morphea (7.9%).

Basal pigmentation was found in 46 patients in our study (56%). In these patients, the inflammatory response was found to be milder, and the plasma cell count was found lower. (p=0,030, p=0,024). This may be because as the chronic inflammatory process progresses, the increased plasma cell number may cause basal cell damage and cause lichenoid inflammation resulting in loss of basal pigmentation and increased melanophage formation.

The most common findings in our case series are homogenization of dermal collagen (100%) and decrease in skin appendages (98.7%). These can be used as diagnostic clues. The *line* sign, a newly defined finding, is used to describe the sharp transition between dermal collagen and subcutaneous adipose tissue (Figure 4).[16] The *line* sign was found in 36 patients (46.2%). Inflammation was found to be deeper and more diffuse in these patients (p=0.011). The probability of detecting a *line sign* increases as the inflammation deepens and spreads to the subcutaneous tissue. In biopsy samples containing subcutaneous tissue, the 'line' sign may be a diagnostic finding.

There are studies in the literature that consider changes in elastic fibers, loss of CD34+ dermal dendritic cells, and the presence of CD123+ and BDCA-2+ plasmacytoid dendritic cells as diagnostic methods.[17,18] To our knowledge, there is no clear histopathological parameter indicating a poor prognosis in morphea. Kim *et al.*[15] found the presence of eosinophils and the presence of basal pigmentation to be associated with poor treatment response. When some studies in the literature are examined, it has been observed that plaque subtype and linear subtype can transform into generalized morphea. In addition, cases showing the

Table 3. Comparative analysis of basal pigmentation and other histopathological findings.

	Basal pigmentation, n (%)		p
	Absent (n=32)	Present (n=46)	
Sex			
Male	7 (21.9)	9 (19.6)	0.804[a]
Female	25 (78.1)	37 (80.4)	
Subtype			
Plaque	28 (87.5)	35 (87.5)	0.576[a]
Linear	1 (3.1)	3 (7.5)	
Generalized	3 (9.4)	2 (5)	
Inflammatory infiltrate			
Absent	-	8 (17.4)	0.030*a
Mild	23 (71.9)	31 (67.4)	
Moderate	7 (21.9)	7 (15.2)	
Severe	2 (6.3)	-	
Location of inflammatory infiltrate			
Superficial	17 (53.1)	24 (61.5)	0.687[a]
Deep	2 (6.3)	3 (7.7)	
Superficial+deep	13 (40.6)	12 (30.8)	
Plasma cell			
Absent	11 (34.4)	25 (54.3)	0.024*[a]
Mild	15 (46.9)	20 (43.5)	
Moderate	6 (18.8)	1 (2.2)	
Eosinophils	2 (6.3)	2 (4.3)	0.708[a]
Homogenization of dermal collagen	32 (100)	45 (97.8)	0.401[a]
Decrease of skin appendages			
Absent	-	1 (2.2)	0.409[a]
Mild	5 (15.6)	12 (26.1)	
Moderate	27 (84.4)	32 (69.6)	
Complete loss	-	1 (2.2)	
Basal pigmentation	2 (6.3)	18 (39.1)	0.001**[a]
Line sign	-	1 (2.5)	0.368[a]
Face	1 (3.1)	1 (2.5)	0.873[a]
Scalp	7 (21.9)	10 (25)	0.756[a]
Chest	10 (31.3)	9 (22.5)	0.403[a]
Abdomen	8 (25)	10 (25)	1.000[a]
Back	2 (6.3)	3 (7.5)	0.836[a]
Upper extremity	10 (31.3)	13 (32.5)	0.910[a]
Age at biopsy, avg±ss	44.1±21.6	41.3±18.5	0.493[b]
Age at onset of lesion, avg±ss	41.9±21.5	37.5±20.3	0.452[b]
Time from lesion onset to biopsy, avg±ss	2.0±2.7	1.6±2.9	0.510[b]

*p<0.05. **p<0.001. [a]X²-test and Fisher exact; [b]Mann Whitney.

Table 4. Comparative analysis of *Line* sign and other histopathological findings..

	Line sign, n (%)		p
	Absent (n=42)	Present (n=36)	
Sex			
Male	11 (26.2)	5 (13.9)	0.180[a]
Female	31 (73.8)	31 (86.1)	
Subtype			
Plaque	33 (84.6)	30 (90.9)	0.654[a]
Linear	3 (7.7)	1 (3.0)	
Generalized	3 (7.7)	2 (6.1)	
Inflammatory infiltrate			
Absent	5 (11.9)	3 (8.3)	0.451[a]
Mild	29 (69)	25 (69.4)	
Moderate	8 (19)	6 (16.7)	
Severe	-	2 (5.6)	
Location of inflammatory infiltrate			
Superficial	28 (73.7)	13 (39.4)	0.011*[a]
Deep	1 (2.6)	4 (12.1)	
Superficial+deep	9 (23.7)	16 (48.5)	
Plasma cell			
Absent	21 (50)	15 (41.7)	0.700[a]
Mild	18 (42.9)	17 (47.2)	
Moderate	3 (7.1)	4 (11.1)	
Eosinophils	1 (2.4)	3 (8.3)	0.235[a]
Homogenization of dermal collagen	42 (100)	35 (97.2)	0.277[a]
Decrease of skin appendages			
Absent	-	1 (2.8)	0.116[a]
Mild	6 (14.3)	11 (30.6)	
Moderate	36 (85.7)	23 (63.9)	
Complete loss	-	1 (2.8)	
Basal pigmentation	1 (2.5)	-	0.368[a]
Line sign	12 (30)	5 (15.6)	0.154[a]
Face	12 (30)	7 (21.9)	0.437[a]
Scalp	9 (22.5)	9 (28.1)	0.584[a]
Chest	2 (5)	3 (9.4)	0.468[a]
Abdomen	8 (20)	15 (46.9)	0.015*
Age at biopsy, avg±ss	47.2±19.3	36.9±19.1	0.026*[b]
Age at onset of lesion, avg±ss	45.1±20.0	32.9±20.0	0.022*[b]
Time from lesion onset to biopsy, avg±ss	1.32±1.8	2.39±3.5	0.186[b]

*p<0.05. **p<0.001. [a]X^2-test and Fisher exact; [b]Mann Whitney.

development of squamous cell carcinoma from the pansclerotic subtype have been reported.[19-21] For this reason, close follow-up is crucial.

The limitation of our study is that the activity of the lesions could not be evaluated due to its retrospective nature. Due to the small number of cases, lack of clinical data and treatment method, a clear prognostic factor could not be revealed.

Conclusions

In conclusion, we describe the histopathological features of morphea in our patients. We emphasize the critical role of skin biopsy for diagnosis and treatment modalities. Our data suggest that homogenization in dermal collagen and decrease in skin appendages could be used as histopathological clues in the diagnosis. In addition, the *line* sign could be helpful for identifying lesions located in the lower extremities. In the pathology report, specifying the degree of inflammation and the localization of the inflammatory infiltrate may be helpful for new treatment methods and predict prognosis. Our study is one of the largest clinicopathological data analysis study conducted in Turkey.

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