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Serum periostin levels in mycosis fungoides: associations with clinical subtype and disease stage

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Contributions: Ramazan Çetin: conception and design of the study, data collection, data analysis and interpretation, statistical analysis, drafting of the manuscript, critical revision of the manuscript for important intellectual content; Müge Güler Özden: conception and design of the study, contribution to data analysis and interpretation, critical revision of the manuscript for important intellectual content, overall supervision of the study. Both authors made substantial contributions to the work, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Abstract

Serum biomarkers with diagnostic and staging relevance in mycosis fungoides (MF) remain limited. In this prospective case-control study, we evaluated serum periostin levels in 40 patients with MF and 40 matched healthy controls, and assessed their associations with clinical subtype and disease stage. Serum periostin was measured by enzyme-linked immunosorbent assay (ELISA), and comparisons were performed using non-parametric tests. Serum periostin levels were significantly higher in patients with MF than in controls ($p<0.0001$). Receiver operating characteristic (ROC) analysis demonstrated moderate discrimination for MF, with an area under the curve (AUC) of 0.77 (95% confidence interval [CI], 0.67-0.88); the optimal cut-off was 7.50 ng/mL, yielding 74.36% sensitivity and 70.00% specificity. Periostin levels also differed significantly across clinical subtypes (Kruskal-Wallis, $p<0.0001$), with higher levels in patch and plaque disease than in tumor-stage disease. In addition, serum periostin was significantly higher in early-stage MF (IA-IIA) than in advanced-stage disease (IIB and above) ($p=0.035$). These findings support serum periostin as a supportive biomarker reflecting clinical subtype and stage in MF, warranting further validation.

Introduction

Mycosis fungoides (MF) is the most common subtype of primary cutaneous T-cell lymphoma and is characterized by a heterogeneous clinical course progressing from patch to plaque and tumor stages. Early stage MF frequently mimics benign inflammatory dermatoses, resulting in diagnostic delay, while advanced disease is associated with increased morbidity. Despite advances in histopathological and molecular techniques, accurate diagnosis and clinical stratification, particularly in early disease, remain challenging, highlighting the need for supportive, non-invasive biomarkers.[1]

Beyond malignant T cells, MF pathogenesis is strongly influenced by the cutaneous microenvironment. Disease progression is accompanied by a shift from a T helper (Th) 1 dominant immune response toward a Th2 skewed cytokine milieu, promoting immune evasion, fibroblast activation, and extracellular matrix remodeling. These microenvironmental changes may generate circulating signals that reflect disease activity and stage.[2-6]

Periostin is a matricellular protein secreted mainly by fibroblasts in response to Th2 cytokines such as interleukin-4 and interleukin-13. It plays a key role in tissue remodeling, angiogenesis, and immune stromal interactions and has been implicated in tumor stroma crosstalk in several malignancies.[7-9] In MF, periostin expression has been demonstrated in lesional skin, particularly within fibrotic stroma and tumor-associated macrophage rich areas, with stage dependent expression patterns.[10]

However, interpretation of circulating periostin in MF requires nuance. In a broader cutaneous T-cell lymphoma (CTCL) cohort, Takahashi *et al.* reported increased serum periostin levels compared with healthy controls and variation across clinical phenotypes and stages.[11] Nevertheless, MF-specific data derived from a dedicated case-control cohort remain limited, and the diagnostic performance of serum periostin specifically for MF has not been well characterized.

Accordingly, this study aimed to evaluate serum periostin levels in patients with MF compared with age- and sex-matched healthy controls and to explore their associations with MF clinical subtypes and tumor-node-metastasis-blood (TNMB) stage groupings. Rather than proposing the first observation of circulating periostin in CTCL, we sought to provide MF-focused clinical validation and quantify its potential supportive value as a non-invasive biomarker reflecting disease-associated microenvironmental activity.

Materials and Methods

This prospective case-control study included 40 adult patients with MF and 40 age- and sex-matched healthy controls. Controls had no allergic, chronic inflammatory, neoplastic, or autoimmune diseases affecting periostin levels. MF patients were classified as patch (n=24), plaque (n=8), or tumor clinical subtype (n=8), and grouped as early stage (IA-IIA) or advanced stage (IIB and above) according to TNMB criteria. Patients with conditions known to influence periostin expression were excluded. MF diagnosis was based on clinical, histopathological, and immunohistochemical findings following World Health Organization-European Organisation for Research and Treatment of Cancer (WHO-EORTC) guidelines.

Data collection and clinical staging

Demographic and clinical data were recorded. Body surface area involvement was calculated using the Lund-Browder chart. Clinical staging was performed according to the International Society for Cutaneous Lymphomas (ISCL)/EORTC TNMB classification, supported by radiologic imaging when indicated.[12]

Serum periostin measurement

Venous blood samples were collected from all participants, allowed to clot at room temperature for 20 minutes, and centrifuged at 3000 rpm for 20 minutes. The resulting serum was aliquoted and stored at −80°C until analysis.

Serum periostin levels were measured using a commercial human periostin enzyme-linked immunosorbent assay (ELISA) kit (Catalog No: SG-10345, SinoGeneClon Biotech, China). Results

were expressed in ng/mL; assay sensitivity was 1.0 ng/mL, with a measurement range of 3-100 ng/mL.

Data integrity

Data were screened for extreme and potentially influential values prior to the primary biomarker analyses. One serum periostin value from a patient in the plaque clinical subtype was identified as an extreme influential observation and was excluded from the primary periostin analyses. Thus, 80 participants were enrolled in the study, whereas the primary periostin analyses were performed on 79 individuals. Sensitivity analysis was subsequently performed using the full 80-participant cohort.

Statistical analysis

Statistical analyses were performed using GraphPad Prism and IBM SPSS Statistics v26. Normality was assessed using the Shapiro-Wilk test, and non-parametric methods were applied accordingly. Continuous variables are presented as median (interquartile range [IQR]) or mean ± standard deviation (SD). Patients and healthy controls were matched for age and sex at the study design stage; therefore, additional multivariable adjustment for these variables was not considered necessary.

Comparisons between two groups were performed using the Mann-Whitney U test. Comparisons among multiple groups (plaque, patch, tumor, and control) were assessed using the Kruskal-Wallis test, followed by Dunn's *post-hoc* test with adjustment for multiple comparisons.

Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) analysis. Area under the curve (AUC), 95% confidence intervals (CIs), and the optimal cut-off value determined by Youden's index were reported.

Subgroup analyses were performed only when group sizes were sufficient for reliable inference. Because of the limited and imbalanced sample sizes in clinical subtype and stage-based subgroups, ROC analysis was not performed for these comparisons, and no cut-off values were derived. All tests were two-sided, and $p<0.05$ was considered statistically significant.[13] Sensitivity analysis was performed by repeating the main MF-*vs*.-control comparison after re-including the excluded extreme value.

Results

Baseline characteristics of the study population

A total of 80 participants were enrolled in the study, including 40 patients with MF and 40 age- and sex-matched healthy controls. After exclusion of one extreme serum periostin value from the MF group, the primary periostin analyses were performed on 79 individuals (39 MF and 40 controls).

The MF and control groups were comparable in terms of age and sex, with no statistically significant differences between groups ($p>0.05$). Among MF patients, the majority were classified as patch clinical subtype, followed by plaque and tumor clinical subtypes. According to TNMB staging, most patients had early-stage disease (IA-IIA), while a smaller proportion were categorized as advanced-stage disease (IIB and above). Descriptive analyses of serum periostin levels and clinical characteristics are summarized in Table 1. De-identified individual-level data for patients and controls are provided in *Supplementary Table 1*.

Serum periostin levels in MF patients and controls

Serum periostin levels were significantly higher in patients with MF compared with healthy controls. The median periostin concentration was 12.60 ng/mL (IQR: 6.60-18.20) in the MF group, whereas controls exhibited a median level of 5.05 ng/mL (IQR: 3.33-8.75). Non-parametric comparison using the Mann-Whitney U test confirmed a highly significant difference between the two groups ($p<0.0001$), illustrated in Figure 1.

Diagnostic performance of serum periostin in distinguishing MF patients from controls

ROC curve analysis was performed to evaluate the diagnostic performance of serum periostin in differentiating patients with MF from healthy controls. The analysis yielded an AUC of 0.773 (standard error of the mean [SEM]=0.052), indicating moderate discriminatory ability. The 95% CI for the AUC ranged from 0.670 to 0.876, and the overall ROC model was statistically significant ($p<0.0001$) (Figure 2).

The optimal cut-off value for serum periostin was determined using the Youden index (sensitivity + specificity −1). The highest combined sensitivity and specificity were observed at a threshold of 7.50 ng/mL (see *Supplementary Table 2* for the complete list of sensitivity and specificity values at various cut-off points). At this cut-off, serum periostin demonstrated a sensitivity of 74.36% and a specificity of 70.00% for distinguishing MF patients from healthy controls.

These findings indicate that serum periostin provides moderate discrimination between MF patients and healthy controls in this case-control setting, supporting its potential role as an adjunctive rather than standalone biomarker. A sensitivity analysis based on the full 40-patient MF cohort showed that inclusion of the excluded extreme value did not materially alter the main MF-*vs.*-control comparison; the association remained statistically significant, and discriminatory performance was similar to that observed in the primary analysis (*Supplementary Table 3*).

Serum periostin levels across MF clinical subtypes and TNMB stage groupings

Serum periostin levels differed significantly across MF clinical subtypes and healthy controls. Overall group comparison using the Kruskal-Wallis test demonstrated a statistically significant difference among the four groups (patch, plaque, tumor, and control; $p<0.0001$) (Figure 3).

Post hoc pairwise comparisons were performed using Dunn's multiple comparisons test with adjustment for multiple testing. Compared with healthy controls, serum periostin levels were significantly higher in the patch subtype (adjusted $p=0.0003$) and the plaque subtype (adjusted $p=0.0063$), whereas no significant difference was observed between the tumor subtype and healthy controls ($p>0.05$).

Within MF clinical subtypes, periostin levels were significantly higher in the plaque subtype than in the tumor subtype (adjusted $p=0.0258$) and in the patch subtype than in the tumor subtype (adjusted $p=0.0258$). No statistically significant difference was observed between the patch and plaque subtypes ($p>0.05$). These findings indicate that serum periostin varies across MF clinical subtypes, with higher concentrations in patch and plaque disease and lower levels in tumor clinical subtype.

Separately, based on TNMB stage grouping, serum periostin levels were significantly higher in patients with early-stage MF (IA-IIA) than in those with advanced-stage disease (IIB and above), with median values of 13.10 ng/mL and 5.05 ng/mL, respectively ($p=0.035$). Given the limited and markedly imbalanced subgroup sizes, particularly in the advanced-stage group, ROC analysis was not performed for this comparison and no cut-off value was derived.

Discussion

Reliable, non-invasive biomarkers for the diagnosis and clinical stratification of MF remain limited.[4,6,14] In this context, the present findings demonstrate that serum periostin levels are significantly elevated in MF patients compared with healthy controls and provide moderate diagnostic discrimination. These results are directionally consistent with the broader CTCL study by Takahashi *et al.*, who also reported increased serum periostin levels and stage-related variation.[11] Our study builds on that work by focusing specifically on MF in a prospectively collected, age- and sex-matched case-control cohort and by quantifying diagnostic performance using ROC analysis. Non-parametric analyses showed clear separation between patients and controls, and ROC analysis identified an optimal cut-off value using Youden's index, supporting serum periostin as an adjunctive biomarker rather than a standalone diagnostic test. Specifically, the optimal cut-off value of 7.50 ng/mL identified in our study may provide a preliminary reference point for future validation studies in supportive MF assessment.

Serum periostin levels also varied according to MF clinical subtype and TNMB stage grouping in our cohort. The patch and plaque clinical subtypes showed significantly higher periostin levels than

the tumor clinical subtype, whereas no significant difference was observed between the patch and plaque clinical subtypes. Notably, periostin levels in tumor-stage disease did not differ significantly from those in healthy controls. This pattern suggests that circulating periostin may be more closely associated with earlier phases of MF than with increasing tumor burden and may provide supportive information regarding disease-associated microenvironmental activity across MF clinical subtypes and TNMB stage groupings.[6,9,15]

Stage-related variation in our cohort warrants comparison with previous literature. Takahashi *et al.* reported increased serum periostin levels in CTCL compared with healthy controls and variation across CTCL clinical phenotypes, including patch, plaque, tumor, and erythrodermic presentations.[11] However, that study addressed a broader CTCL population. In contrast, our study focused specifically on MF and demonstrated differences not only between MF patients and healthy controls but also across MF clinical subtypes and TNMB stage groupings. In addition, Furudate *et al.*, demonstrated periostin expression within the stromal compartment of MF lesions, particularly in earlier-stage disease.[10] Taken together, these findings suggest that periostin may reflect stromal and microenvironmental activity in MF, particularly in earlier disease phases. As a matricellular protein linked to Th2 signaling, fibroblast activation, and extracellular matrix remodeling,[7,16] periostin may be elevated in patch and plaque disease because of more active stromal remodeling in earlier MF. Unlike many solid tumors, in which periostin tends to increase with progression,[17,18] the lower levels observed in tumor-stage MF in our cohort suggest that periostin may follow a distinct stage-related pattern in MF, or that serum periostin in MF differs from patterns observed across the broader CTCL spectrum. However, this interpretation remains exploratory because the study was based solely on serum measurements and did not include paired tissue-level or functional analyses.

Mechanistic interpretation should remain cautious, as the present study was limited to serum periostin measurements. Gordon *et al.* proposed that periostin can enhance transforming growth factor-β1 secretion and promote expansion of Foxp3+ regulatory T cells.[19] This may be relevant to MF, as Gjerdrum *et al.* associated higher regulatory T-cell counts in early-stage disease with more favorable outcomes.[20] This differs from the pattern seen in many solid tumors, where increasing regulatory T-cell density is more often associated with immune evasion and poor prognosis.[21,22] In this context, higher periostin levels in early-stage MF may reflect a more active stromal and immune-regulatory milieu, whereas lower levels in tumor-stage disease may accompany progression-related remodeling. This interpretation is supported by Gaydosik *et al.*, who described loss of specific periostin-producing fibroblast subsets in advanced disease.[23] Nevertheless, these observations remain exploratory, and further longitudinal studies integrating paired tissue-serum

analyses and spatially resolved methods are needed to determine whether periostin is functionally involved in this process or primarily reflects stromal remodeling.

Several limitations should be acknowledged. While the comparable number of MF patients and controls enabled reliable ROC analysis, subgroup analyses were constrained by small and imbalanced sample sizes, particularly in advanced-stage MF. This precluded robust stage-specific cut-off derivation; thus, subgroup findings should be interpreted descriptively. Additionally, this was a single-center study, and external validation in larger cohorts is required. Furthermore, future studies should evaluate the comparative diagnostic utility of serum periostin between MF and benign inflammatory mimics, such as psoriasis or atopic dermatitis, rather than healthy controls alone. Accordingly, the present findings should be interpreted as evidence of supportive biomarker potential rather than disease-specific diagnostic accuracy in routine differential diagnosis.

Conclusions

In conclusion, serum periostin is elevated in MF and varies according to MF clinical subtype and TNMB stage grouping, with higher levels observed in early-stage disease and lower levels in the tumor clinical subtype within this cohort. Taken together with prior CTCL literature, these findings support serum periostin as a non-invasive, supportive biomarker reflecting microenvironmental activity rather than tumor burden. Larger, multicenter studies incorporating longitudinal sampling and clinically relevant inflammatory comparator groups are warranted to further clarify its adjunctive role in evaluation of MF.

Reference

1. Zinzani PL, Ferreri AJ, Cerroni L. Mycosis fungoides. Crit Rev Oncol Hematol 2008;65:172-82.

2. Larocca C, Kupper T. Mycosis fungoides and Sézary syndrome: an update. Hematol Oncol Clin North Am 2019;33:103-20.

3. Alberti-Violetti S, Talpur R, Schlichte M, et al. Advanced-stage mycosis fungoides and Sézary syndrome: survival and response to treatment. Clin Lymphoma Myeloma Leuk 2015;15:e105-12.

4. Johnson VE, Vonderheid EC, Hess AD, et al. Genetic markers associated with progression in early mycosis fungoides. J Eur Acad Dermatol Venereol 2014;28:1431-5.

5. Jawed SI, Myskowski PL, Horwitz S, et al. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 2014;70:205.e1-16.

6. Rubio Gonzalez B, Zain J, Rosen ST, et al. Tumor microenvironment in mycosis fungoides and Sézary syndrome. Curr Opin Oncol 2016;28:88-96.
7. Izuhara K, Nunomura S, Nanri Y, et al. Periostin: an emerging biomarker for allergic diseases. Allergy 2019;74:2116-28.
8. Kudo Y, Siriwardena BS, Hatano H, et al. Periostin: novel diagnostic and therapeutic target for cancer. Histol Histopathol 2007;22:1167-74.
9. Ruan K, Bao S, Ouyang G. The multifaceted role of periostin in tumorigenesis. Cell Mol Life Sci 2009;66:2219-30.
10. Furudate S, Fujimura T, Kakizaki A, et al. The possible interaction between periostin expressed by cancer stroma and tumor-associated macrophages in developing mycosis fungoides. Exp Dermatol 2016;25:107-12.
11. Takahashi N, Sugaya M, Suga H, et al. Thymic stromal lymphopoietin acts through Th2 cytokine production to induce cutaneous T-cell lymphoma. Cancer Res 2016;76:6241-52.
12. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-22.
13. Panos GD, Boeckler FM. Statistical analysis in clinical and experimental medical research: simplified guidance for authors and reviewers. Drug Des Devel Ther 2023;17:1959-61.
14. Ion A, Popa IM, Papagheorghe LM, et al. Proteomic approaches to biomarker discovery in cutaneous T-cell lymphoma. Dis Markers 2016;2016:9602472.
15. González-González L, Alonso J. Periostin: a matricellular protein with multiple functions in cancer development and progression. Front Oncol 2018;8:225.
16. Sahai E, Astsaturov I, Cukierman E, et al. A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer 2020;20:174-86.
17. Zhu M, Fejzo MS, Anderson L, et al. Periostin promotes ovarian cancer angiogenesis and metastasis. Gynecol Oncol 2010;119:337-44.
18. Kotobuki Y, Yang L, Serada S, et al. Periostin accelerates human malignant melanoma progression by modifying the melanoma microenvironment. Pigment Cell Melanoma Res 2014;27:630-9.
19. Gordon ED, Sidhu SS, Wang ZE, et al. A protective role for periostin and TGF-beta in IgE-mediated allergy and airway hyperresponsiveness. Clin Exp Allergy 2012;42:144-55.
20. Gjerdrum LM, Woetmann A, Odum N, et al. FOXP3+ regulatory T cells in cutaneous T-cell lymphomas: association with disease stage and survival. Leukemia 2007;21:2512-8.

21. Beyer M, Schultze JL. Regulatory T cells in cancer. Blood 2006;108:804-11.

22. Woo EY, Yeh H, Chu CS, et al. Cutting edge: regulatory T cells from lung cancer patients directly inhibit autologous T-cell proliferation. J Immunol 2002;168:4272-6.

23. Gaydosik AM, Stonesifer CJ, Tabib T, et al. The mycosis fungoides cutaneous microenvironment shapes dysfunctional cell trafficking, antitumor immunity, matrix interactions, and angiogenesis. JCI Insight 2023;8:e170682.

Figure 1. Serum periostin levels in patients with MF and healthy controls. Violin plots show the distribution of serum periostin concentrations (ng/mL) in controls (n=40) and patients (n=39). Horizontal lines indicate medians and IQR (p<0.0001).

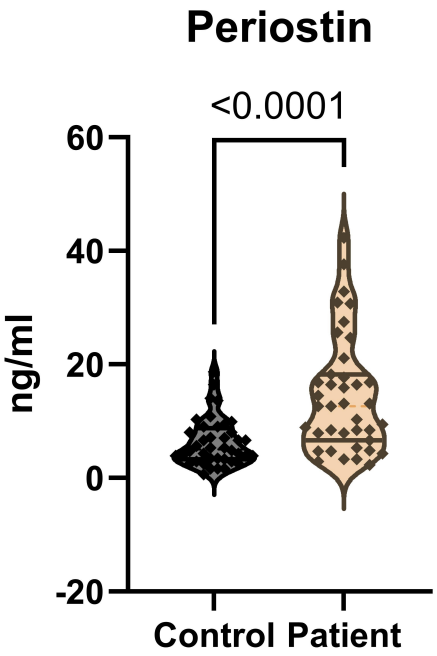

Figure 2. ROC curve of serum periostin for distinguishing patients with MF from healthy controls (AUC: 0.773, 95% CI: 0.670-0.876). The red dashed line indicates the line of no discrimination.

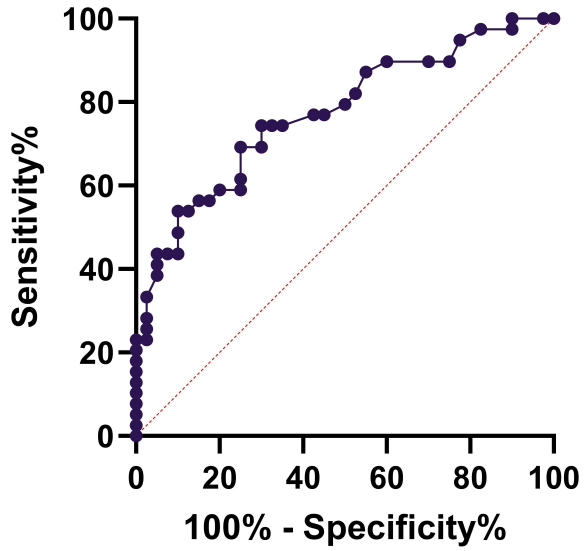

Figure 3. Serum periostin levels across MF clinical subtypes and healthy controls. Horizontal lines indicate medians and IQR. Brackets denote significant pairwise differences identified by Dunn's post hoc test after Kruskal-Wallis analysis. One extreme value in the plaque subgroup was excluded from the primary periostin analyses.

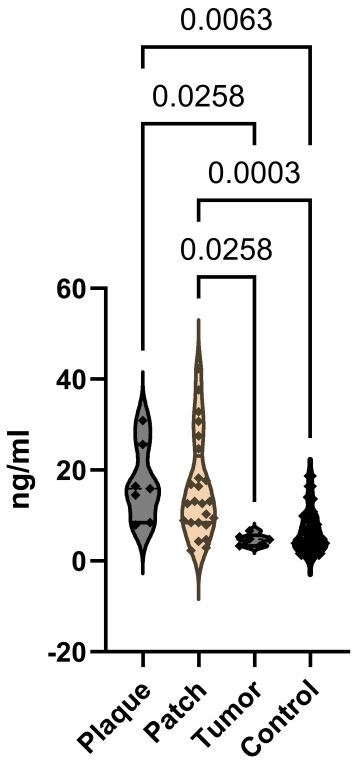

Table 1. Clinical characteristics and serum periostin levels of the study groups.

Variable†	**Patients (overall)**	**Patch**	**Plaque**	**Tumor**	**Advanced stage¶**	**Early stage¶**	**Controls**
Participants, n	39‡	24	7	8	8	31	40
Age (years), mean ± SD	54.4±16.2	55.9±16.3	49.4±15.4	54.0±17.7	54.0±17.7	54.5±16.1	52.0±13.8
Gender, M/F	25/14	14/10	5/2	6/2	6/2	19/12	26/14
Periostin (ng/mL), median (IQR)	12.6 (6.6-18.2)	12.8 (8.4-19.8)	15.9 (11.4-21.0)	5.05 (4.3-9.1)	5.05 (4.3-9.1)	13.1 (8.4-21.4)	5.05 (3.3-8.7)

SD, standard deviation; IQR, interquartile range.

†Values are presented as mean ± SD, median (IQR), or number, as appropriate. ‡One extreme serum periostin value in the plaque clinical subtype was excluded from the primary periostin analyses because it behaved as an influential observation within a small subgroup; sensitivity analysis including this value did not materially alter the overall findings. Because tumor-stage disease was concentrated in the advanced-stage group, the similarity of values between these columns reflects the underlying overlap in patient distribution. Early stage disease was defined as stages IA-IIA, and advanced stage disease as stages IIB and above.

Online supplementary material:

Supplementary Table 1. *Demographic, clinical, and laboratory characteristics of patients with MF and healthy controls.*

Supplementary Table 2. *Sensitivity and specificity values of serum periostin at different cut-off points for determining the optimal threshold by Youden index.*

Supplementary Table 3. *Sensitivity analysis of the main MF* vs. *control comparison*.