

Mycosis Fungoides

Report of the 2011 Society for Hematopathology/European Association for Haematopathology Workshop

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Upon completion of this activity you will be able to:

- summarize approaches recommended for making a confident diagnosis of mycosis fungoides.
- apply ancillary studies in diagnosing mycosis fungoides in the context of clinicopathologic correlations.
- distinguish Sézary syndrome from mycosis fungoides.

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Abstract

Session 1 of the 2011 Workshop of the Society for Hematopathology and European Association for Haematopathology focused on mycosis fungoides (MF), the most common cutaneous lymphoma. The 62 cases in this case group demonstrated a wide spectrum of clinicopathologic features, including those seen in typical cases as well as those, by contrast, with atypical clinical history, morphology, immunophenotype, and/or genotype. Of the 62 cases, 27 (44%) were presented at the workshop and highlighted diagnostic challenges plus related issues. This report summarizes the approach recommended for making a confident diagnosis of MF and its clinically significant variants; emphasizes pitfalls in evaluating early MF, assessing nodal involvement, and diagnosing transformed MF; and discusses the relationship between MF and primary cutaneous CD30+ T-cell lymphoproliferative disorders. Last, Sézary syndrome is discussed, with concentration on those features distinct from MF.

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and represents nearly 50% of all primary cutaneous lymphomas.¹ It occurs mostly in elderly adults (age ≥ 55 years) but can also be seen in children and young adults. The male-to-female ratio is about 2:1. There is usually a prolonged clinical course with evolution of patches and plaques to tumor stage in some patients.¹⁻³ Less than one-third of patients develop advanced disease involving lymph nodes, blood, and visceral organs.^{4,5} Morphologically, the neoplastic lymphoid infiltrate is epidermotropic and composed predominantly of small- to intermediate-sized atypical lymphocytes with enlarged hyperchromatic, cerebriform nuclei and clear cytoplasm (haloed cells). These atypical lymphocytes often colonize the basal layer of epidermis singly or in a linear fashion, forming a “string of pearls.” Pautrier microabscesses, which consist of small aggregates of atypical lymphocytes often in association with Langerhans cells, can be helpful in the diagnosis but are seen in less than 25% of cases.^{6,7} MF is a clonal disorder of memory T-helper cells, in which progressive immunodeficiency of the hosts occurs, and consequently, patients may develop severe infections in the advanced stages. Immunodeficiency results not only from expansion of the dysfunctional and malignant T cells but also from the immunosuppressive role that the neoplastic T cells play in conjunction with regulatory T cells and other complex factors and pathways.⁸⁻¹³

Ancillary studies may be useful in aiding the diagnosis of MF. The neoplastic T cells in MF are usually CD4+ mature T cells, expressing T-cell receptor (TCR) β and variable T-cell-associated antigens such as CD2, CD3, CD5, and CD7.^{14,15} Loss of 1 or more of these pan-T-cell markers (most often

CD7, followed by CD5) is common. In evaluating immunohistochemical stains, it is helpful to consider the epidermal and dermal components independently because the dermal component may contain numerous inflammatory or reactive lymphocytes. As many as 20% of cases of early MF display a CD8+ phenotype,¹⁶ which occurs more frequently in pediatric cases and is more commonly associated with hypopigmented and hyperpigmented lesions.^{6,17-21} The clinical behavior of CD8+ MF is similar to that of the CD4 type.^{6,16-21} Molecular studies may reveal clonal T-cell gene rearrangements by polymerase chain reaction (PCR) analysis. Gene rearrangement studies are not required for diagnosis and may be misleading because clonal T cells are frequently found in inflammatory skin conditions. To increase the specificity and diagnostic value of the T-cell clonality evaluation by molecular analysis, some investigators suggest using 2 sets of primers for detecting both the TCR β and γ genes,^{22,23} as well as detecting identical clones from 2 different skin sites.²⁴ In skin biopsy samples in which the percentage of suspected neoplastic T cells is low, it is recommended to assess the PCR target in duplicate to demonstrate reproducibility of the signals.²³

The objective of this report is to summarize practical issues and common diagnostic challenges that were raised in session 1 during the panel review as well as case presentations at the 2011 Workshop of the Society for Hematopathology and European Association for Haematopathology. The discussions concentrate on (1) pitfalls in diagnosing early MF; (2) assessment of nodal involvement; (3) definition, prognosis, and differential of transformed MF; (4) relationship of MF with primary cutaneous CD30+ T-cell lymphoproliferative disorders (LPDs); (5) clinically significant MF variants; and (6) Sézary syndrome.

Table 1
Algorithm for Diagnosis of Early Mycosis Fungoides (MF)^a

Criteria	Scoring System (Points) by Criteria
1. Clinical Basic Persistent and/or progressive patches/thin plaques Additional 1) Non-sun-exposed location 2) Size/shape variation 3) Poikiloderma	2 (basic plus 2 additional); 1 (basic plus 1 additional)
2. Histopathologic Basic Superficial lymphoid infiltrate Additional 1) Epidermotropism without spongiosis 2) Lymphoid atypia	2 (basic plus 2 additional); 1 (basic plus 1 additional)
3. Molecular Clonal T-cell receptor gene rearrangement	1 (clonality)
4. Immunophenotypic 1) <50% CD2+, CD3+, and/or CD5+ T cells 2) <10% CD7+ T cells 3) T-cell antigen loss confined to epidermis	1 (1 or more criteria)

Adapted and modified from Pimpinelli et al.²⁵

^a A total of 4 points is required for the diagnosis of MF based on any combination of points from the clinical, histopathologic, molecular, and immunophenotypic criteria.

Pitfalls in Diagnosing Early MF

Accurate diagnosis of early MF is essential for staging, prognostic stratification, and determining therapeutic options. In practice, however, the diagnosis of patch and early plaque stage MF can be very challenging because of its overlapping clinicopathologic findings with various reactive dermatoses as well as conflicting clinical presentations and pathologic features. In 2005, the International Society for Cutaneous Lymphoma (ISCL) developed an algorithm for diagnosing early MF based on a combined approach of using both clinical and pathologic criteria from diverse methodologies (Table 1).²⁵ The algorithm was subsequently validated on a large scale in practice,²⁶ leading to the conclusion that utilization of the combined clinical and pathologic criteria should be considered for evaluating early MF. For cases that are clinically concerning for early MF but do not display clear-cut diagnostic features, rebiopsy is recommended.²⁶

Case 165 was a 70-year-old man who had a characteristic clinical presentation of early MF with a 6-year history of erythematous patches of variable size and shape in the sun-protected areas on his thighs, buttocks, and lower abdomen. He was initially diagnosed and treated for eczema. A more recent clinical photograph demonstrated erythematous patches on the left thigh (Image 1A). Pathologic findings (Image 1B) and (Image 1C) were also typical for early MF lesions. Punch biopsy specimen of the left thigh showed lichenoid lymphoid infiltrate within the superficial and upper dermis, which was composed predominantly of small- to intermediate-sized lymphocytes with cerebriform nuclei. Epidermotropism was focal and mild without spongiosis. There were no Pautrier microabscesses. Immunohistochemical studies (Image 1D),

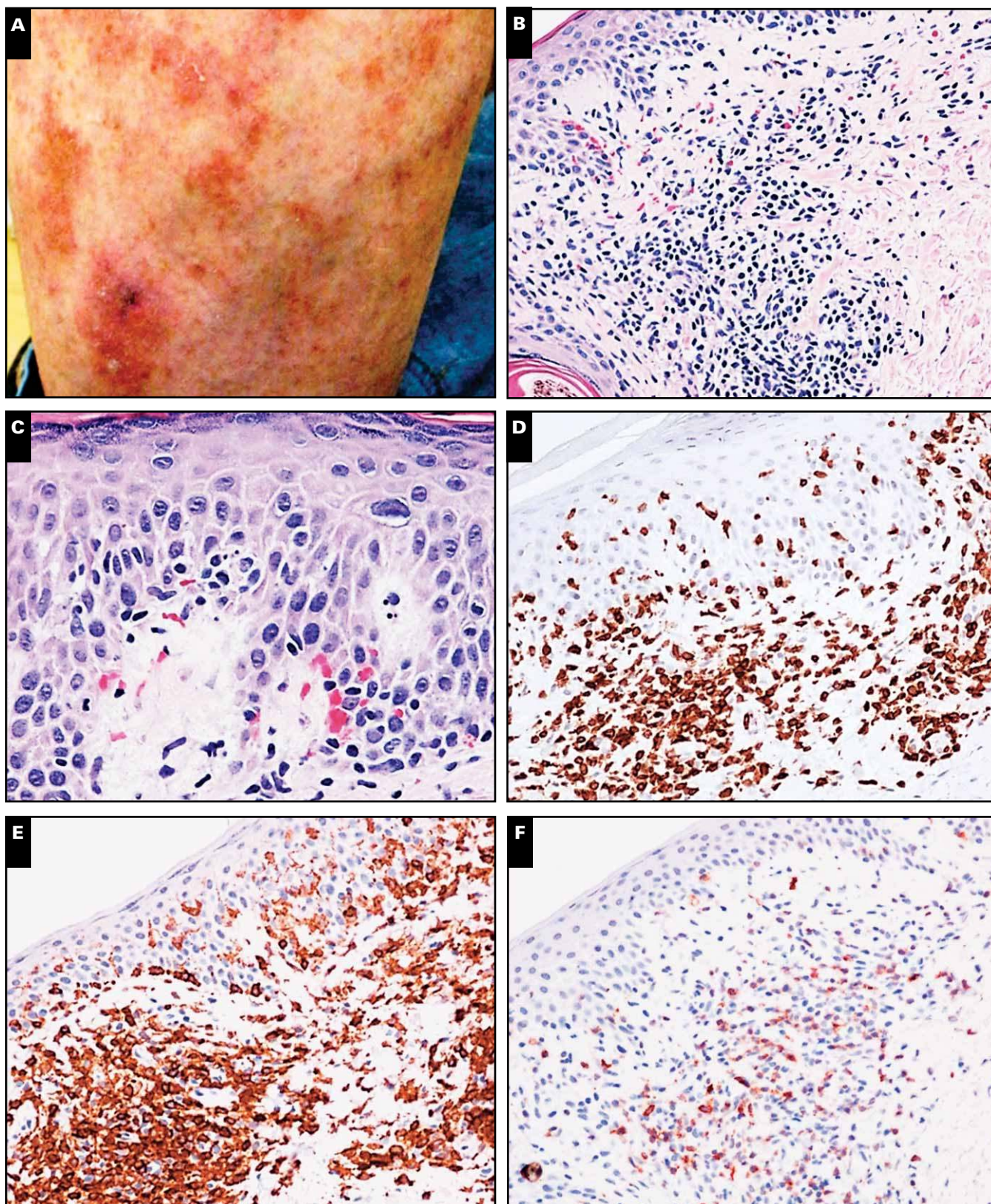


Image 1 Clinico-pathologic findings of early mycosis fungoides. **A**, Clinical photograph reveals erythematous patches of a left thigh that are variable in size and shape. **B** and **C**, Biopsy specimen of the lesion demonstrates an atypical lymphoid infiltrate involving the superficial and upper dermis, which was composed predominantly of small- to intermediate-sized cerebriform lymphocytes. Mild epidermotropism is present without spongiosis, focally lining up at the basal epidermis and forming a “string of pearls.” Pautrier microabscess was not seen (H&E). Immunohistochemical studies highlight CD3+ T cells (**D**) expressing CD4 (**E**) with significant loss of CD7 (**F**) within the epidermis. (Case 165, courtesy of Gerald M. Penn, MD, PhD, Amy Nutting, PA-C, and Brett Kockentiet, MD.)

Image 1E, and **Image 1F** demonstrated CD4+ T cells displaying significant loss of CD7 within the epidermis. Molecular studies were negative for both clonal TCR β and γ gene rearrangements. The panel diagnosis was early MF despite the negative clonal T-cell gene rearrangements. In contrast, case 271 showed positive clonal TCR γ gene rearrangement in a 29-year-old woman, who presented with a chest and abdominal skin rash with blanching and recent use of minocycline. The biopsy specimen showed a superficial dermal lymphoid infiltration with prominent spongiosis and a vase-shaped “pseudo-Pautrier microabscess,”²⁷ composed predominantly of Langerhans cells with only rare T cells **Image 2A**, **Image 2B**, **Image 2C**, and **Image 2D**. Despite the clonal T-cell gene rearrangements, the panel diagnosis was superficial spongiotic dermatitis. Similar to case 271, spongiosis was also a noticeable feature of case 82, which the submitter and the panel did diagnose as MF. However, unlike case 271, the spongiosis was only focal **Image 2E**, and the remaining clinicopathologic findings were typical of MF. Although “epidermotropism without spongiosis” was considered a histopathologic criterion in the ISCL algorithm for diagnosing early MF,²⁵ spongiosis can be seen in about 30% of MF cases.²⁸ When present, it is mostly mild or focal and should be concurrent with disproportionate epidermotropism.

Case 65 represented a case of pediatric MF in which the early diagnosis can be especially challenging because of the patient’s young age, frequent unusual CD8+ immunophenotype, and more variable clinical presentation. The patient was a 6-year-old boy with an 18-month history of recurrent erythematous papulonodules and white scaly patches. He was initially diagnosed with spongiotic and psoriasiform dermatitis, treated as pityriasis lichenoides with azithromycin and then narrow-band UV-B phototherapy plus methotrexate, but he had continued disease. His skin showed hypopigmented patches and pink-red papulonodules on the back **Image 3A**. The biopsy specimen of a hypopigmented patch showed a mild superficial dermal infiltrate of small atypical lymphocytes with sparse epidermotropism. In the biopsy specimen of a papulonodule **Image 3B**, the atypical lymphoid infiltrate was more visible with more prominent epidermotropism, including rare, small Pautrier microabscesses. Immunohistochemical studies highlighted CD8+ T cells **Image 3C**, and molecular studies demonstrated identical clonal TCR γ gene rearrangements in both specimens. Similar to case 65, case 313 **Image 3D**, **Image 3E**, **Image 3F**, **Image 3G**, **Image 3H**, and **Image 3I** was CD8+ hypopigmented MF with hypopigmented patches and erythematous plaques, but the patient was a 38-year-old African American man. The skin biopsy specimen revealed striking epidermotropism, and immunohistochemical studies showed prominent loss of CD5 and near-complete loss of CD7 within the epidermotropic atypical lymphocytes. Because of the marked epidermotropism, several differential diagnoses

were considered, especially primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (discussed by Quintanilla-Martinez et al²⁹ in this issue of the journal), which has a much more aggressive clinical behavior and presents as eruptive papulonodules with ulceration or necrosis.³⁰

Early MF, as the name implies, is evaluated and diagnosed without the benefit of having a classic clinical course of evolution from patches to plaques and, in some cases, to tumor lesions. It may lack the characteristic features of epidermotropism, including formation of Pautrier microabscess, which occurs in about 20% of the cases. Therefore, it may be indistinguishable from reactive dermatoses and is often misdiagnosed initially as eczema or psoriasis, as seen in cases 165 and 65. In this situation, clinical information may be invaluable in avoiding misdiagnosis. The characteristics of reactive dermatoses mimicking MF are discussed by Sarantopoulos et al³¹ in this issue of the journal. To diagnose early MF with confidence, a comprehensive assessment of clinical history is absolutely essential, and pathologic criteria alone may be insufficient. In several cases of MF submitted to this session, the panel was unable to make a definitive diagnosis because of a lack of clinical information, such as a description of the skin lesions and drug history. Clinical photographs are invaluable to the overall assessment as the skin patches or thin plaques in early MF display heterogeneity in size and shape,²⁵ whereas unilesional MF is rare.³² Because morphologic findings of early MF or treated lesions often show only minimal to mild epidermotropism without Pautrier microabscess, obtaining repeat or multiple biopsy specimens from various lesions may be helpful. T-cell aberrancies such as loss of CD7 in a significant component (eg, >50% at the very least) of the epidermotropic lymphocytes and/or loss of CD2, CD3, or CD5 may also be contributory.²⁵ T-cell gene rearrangement studies when performed may not be helpful in the diagnosis of early MF because negative results do not necessarily exclude the diagnosis of MF, as in case 165, whereas clonal T-cell gene rearrangements can be detected in benign dermatoses, as in case 271.

Assessment of Nodal Involvement

Assessment of lymph node involvement is an important component for staging MF and has significant prognostic implications. Patients with nodal or other extracutaneous involvement have a reported 10-year disease-specific survival of less than 20%. In 2007, the ISCL and European Organization for Research and Treatment of Cancer (EORTC) proposed updates of the staging and classification of MF and Sézary syndrome (SS).³³ These updates were incorporated in the histopathologic staging of lymph nodes in MF and SS by the current World Health Organization (WHO) classification,^{2,3} in which clinically abnormal lymph nodes (>1.5

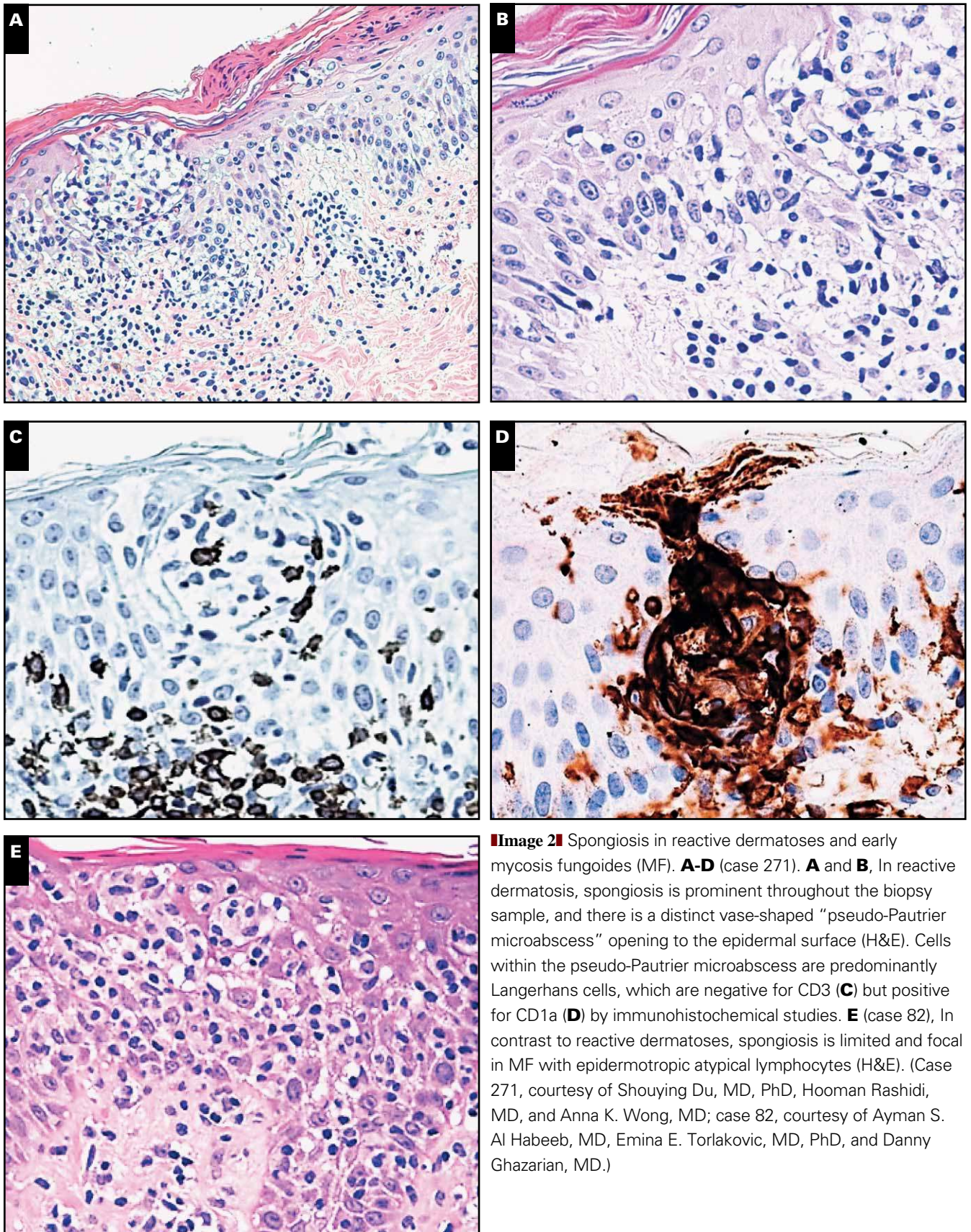


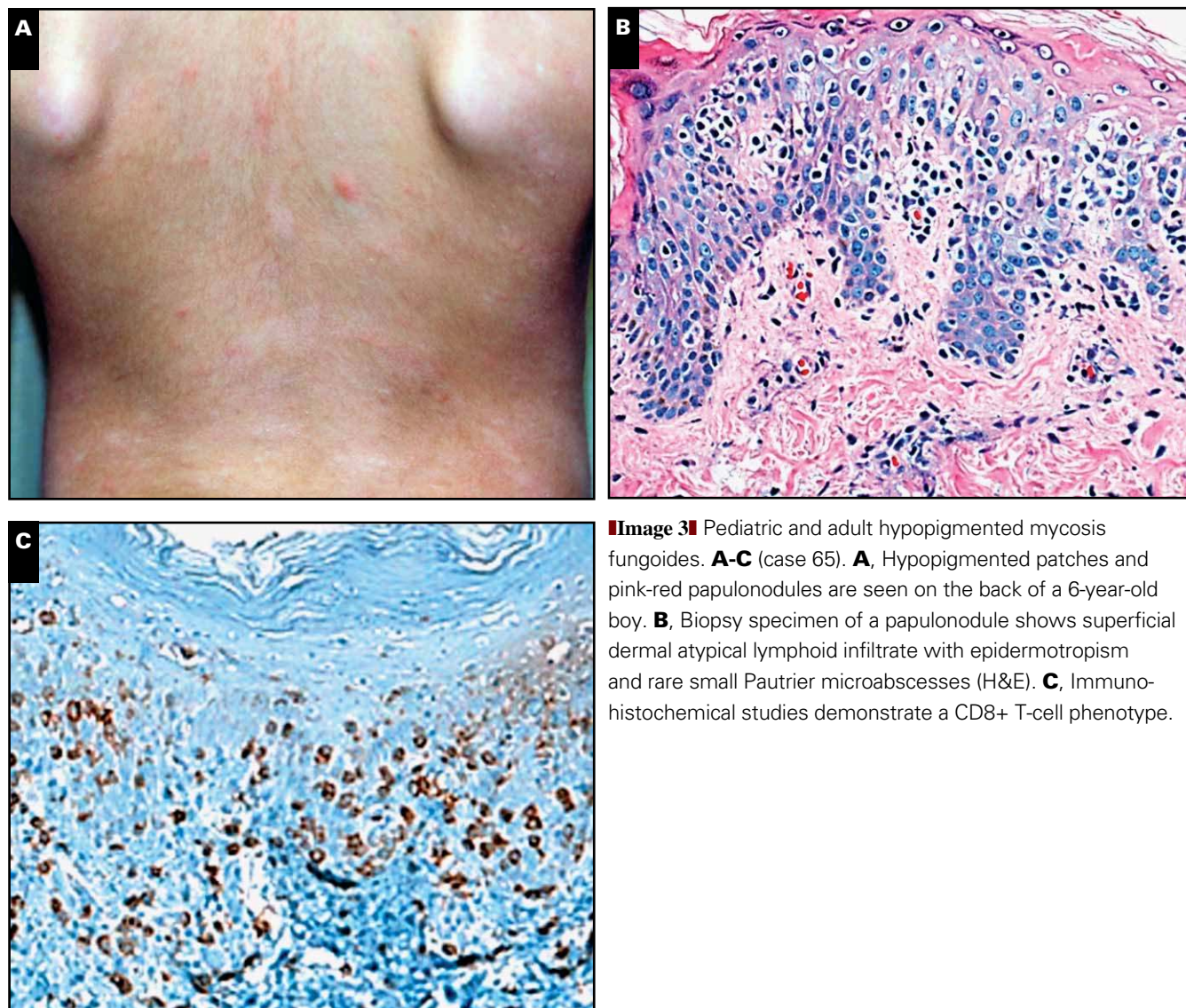
Image 2 Spongiosis in reactive dermatoses and early mycosis fungoides (MF). **A-D** (case 271). **A and B**, In reactive dermatosis, spongiosis is prominent throughout the biopsy sample, and there is a distinct vase-shaped “pseudo-Pautrier microabscess” opening to the epidermal surface (H&E). Cells within the pseudo-Pautrier microabscess are predominantly Langerhans cells, which are negative for CD3 (**C**) but positive for CD1a (**D**) by immunohistochemical studies. **E** (case 82), In contrast to reactive dermatoses, spongiosis is limited and focal in MF with epidermotropic atypical lymphocytes (H&E). (Case 271, courtesy of Shouying Du, MD, PhD, Hooman Rashidi, MD, and Anna K. Wong, MD; case 82, courtesy of Ayman S. Al Habeeb, MD, Emrina E. Torlakovic, MD, PhD, and Danny Ghazarian, MD.)

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cm) in MF/SS are divided into 3 categories (N1, N2, and N3), depending on the degree of involvement. Recognition of early nodal involvement, such as in categories N1 and N2, can be extremely difficult by morphologic examination alone, because the lymph nodes display only dermatopathic changes without architectural effacement and cerebriform lymphocytes are sparse in single forms or very small clusters of fewer than 6 cells. The ISCL/EORTC recommended excisional biopsy as the preferred method in evaluating nodal involvement, in addition to having a portion of the node processed for ancillary studies, including immunophenotyping by immunohistochemistry and flow cytometry, and/or molecular genetic or cytogenetic analysis. Flow cytometric analysis may be of special value because it can detect T-cell aberrancies with relatively high sensitivity and specificity and, therefore, may confer a more precise histologic stage.

Case 264 demonstrated a comprehensive approach to identify nodal infiltration by MF ■Image 4■ and illustrated

the utility of ancillary studies. The patient was a 57-year-old woman with pruritic rash for 5 years. She had several biopsies over a period of 9 months that demonstrated progression of MF. The most recent biopsy specimen of right brachial skin revealed a dense lichenoid dermal lymphoid infiltrate composed of admixed small- to intermediate-sized cerebriform lymphocytes and aggregates to sheets of large atypical lymphocytes with smooth nuclei, dispersed chromatin, and prominent nucleoli. A lymph node biopsy sample taken 3 months later showed partial effacement of the nodal architecture by large aggregates to sheets of small- to intermediate-sized cerebriform lymphocytes, in a background of dermatopathic changes. Flow cytometric studies indicated an abnormal CD4+ T-cell subset (about 30% of the T cells) with aberrant dim CD3 and complete loss of CD7. Molecular analysis detected identical clonal T-cell gene rearrangements in the skin and lymph node biopsy specimens. The panel diagnosis of the right brachial skin was large-cell transformation (LCT) of mycosis



■Image 3■ Pediatric and adult hypopigmented mycosis fungoides. **A-C** (case 65). **A**, Hypopigmented patches and pink-red papulonodules are seen on the back of a 6-year-old boy. **B**, Biopsy specimen of a papulonodule shows superficial dermal atypical lymphoid infiltrate with epidermotropism and rare small Pautrier microabscesses (H&E). **C**, Immunohistochemical studies demonstrate a CD8+ T-cell phenotype.

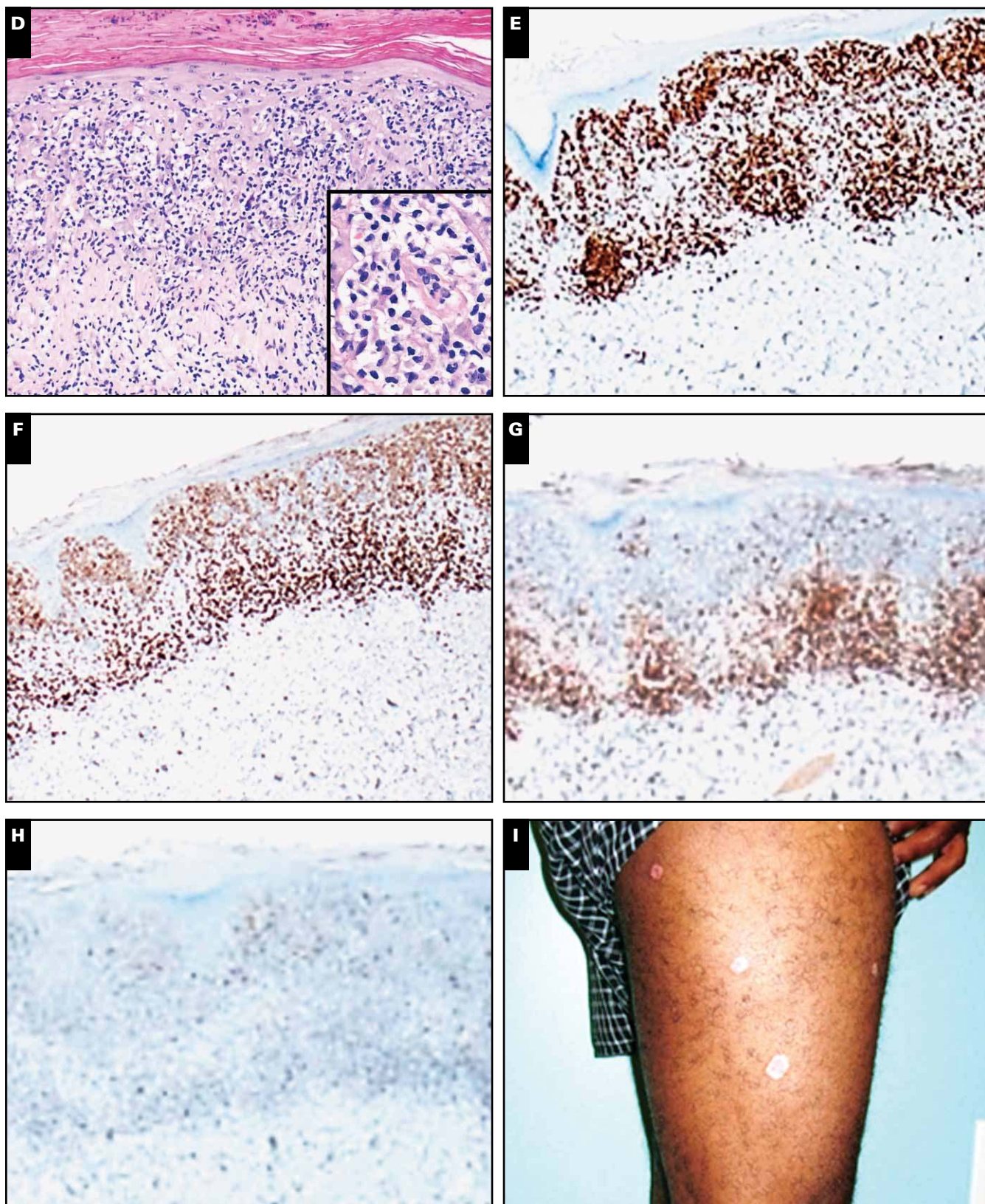


Image 3 (cont) **D-I** (case 313). **D**, Biopsy specimen of a hypopigmented lesion displays striking epidermotropism with cerebriform lymphocytes (inset) (H&E). Immunohistochemical studies reveal abundant CD3+ (**E**) and CD8+ (**F**) T cells within the epidermis, with prominent loss of CD5 (**G**) and near-complete loss of CD7 (**H**). **I**, Hypopigmented patches and erythematous plaques are seen on the leg of a 38-year-old man. (Case 65, courtesy of Jeffrey Zwerner, MD, PhD, Annette S. Kim, MD, PhD, Cindy Vnencak-Jones, PhD, and Alan S. Boyd, MD; case 313, courtesy of Russell A. Higgins, MD, and Jacqueline Losi-Sasaki, MD.)

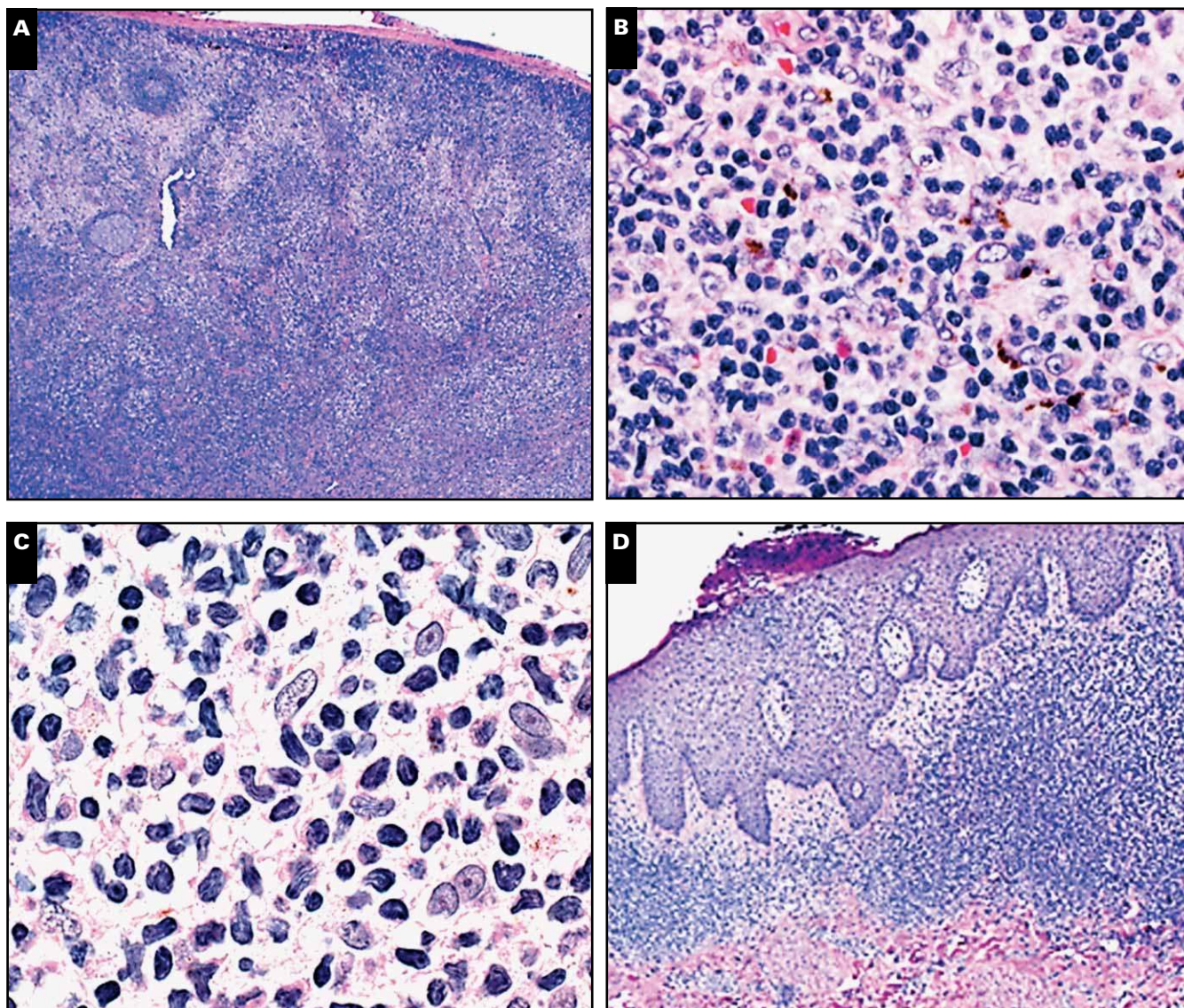


Image 4 Nodal involvement of mycosis fungoides. **A**, Lymph node biopsy specimen demonstrates partial effacement of the nodal architecture with dermatopathic changes (**B**) and infiltration by large aggregates to sheets of small- to intermediate-sized cerebriform lymphocytes (**C**) (H&E). **D**, Right brachial skin reveals dense lichenoid dermal lymphoid infiltrate composed of aggregates to sheets of large atypical lymphocytes with smooth nuclei, dispersed chromatin, and prominent nucleoli (**E**), as well as mixed small- to intermediate-sized cerebriform lymphocytes (**F**) (H&E).

fungoides, and the diagnosis of the lymph node was involvement by mycosis fungoides. This patient had stage IV disease by the current WHO classification and stage IVA₂ according to the revised staging system by the ISCL/EORTC.^{3,33}

Definition, Prognosis, and Differential Diagnosis of Transformed MF

Transformation of MF is generally associated with aggressive clinical behavior and poor survival,³⁴⁻⁴⁰ so-called progression of disease. Diagnosis of LCT is defined as the presence of large T cells in more than 25% of the total

lymphoid infiltrate or forming microscopic nodules,³⁹ but it may be difficult to diagnose in an individual case. The recognition of LCT relies on combined clinical history and pathologic criteria. In a recent large cohort study of 100 transformed MF cases,⁴⁰ the lymphoid infiltrate was mainly composed of mixed large T cells with cerebriform nuclei, blast (large transformed) cells with prominent nucleoli, intermediate forms, and variable numbers of large anaplastic cells. In this study, the “percent of blast cells” was used for the histologic characterization of the transformed MF cases.

Nineteen cases were submitted as transformed MF, plus several as tumor stage MF, together accounting for greater

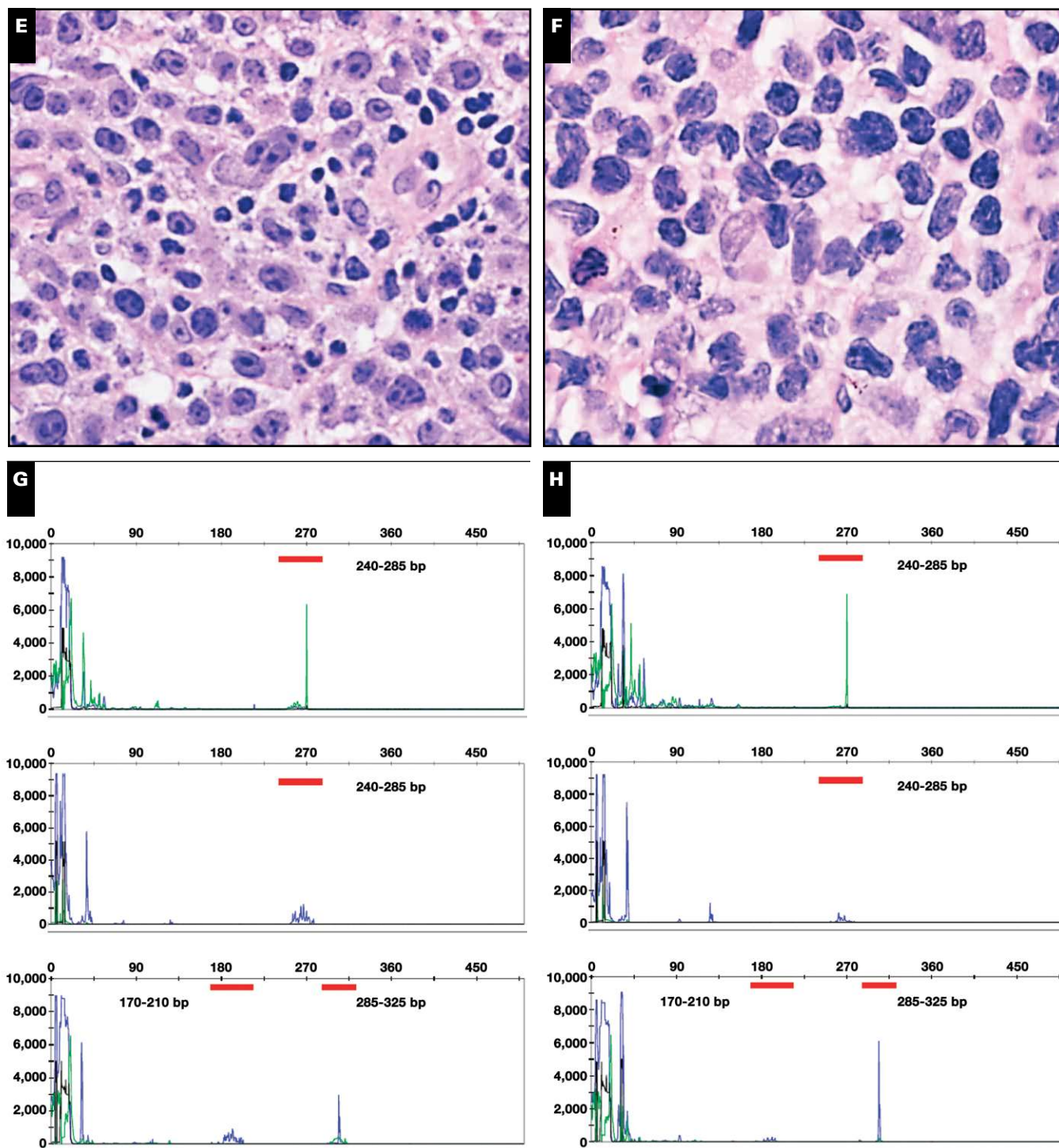


Image 4 (cont) Polymerase chain reaction analysis shows identical clonal T-cell gene rearrangements in the lymph node (**G**) and right brachial skin (**H**) biopsy specimens. (Case 264, courtesy of Rong He, MD, and William R. Macon, MD.) bp, base pair.

than 30% of all cases in this session and revealing a broad spectrum of clinical as well as pathologic features. Case 12 revealed LCT at presentation of skin lesions with both plaques and nodules, case 276 was an LCT that developed in the setting of unilesional MF, and cases 186, 196, and several others had LCT at more advanced stages. Besides

variations in clinical stage, the submitted cases of LCT demonstrated different morphologic and immunophenotypic features. For example, case 119 presented an early LCT in a background of folliculotropic MF. Expression of CD30 was seen in several cases (cases 71, 119, 123, 137, 205, and 276), but coexpression of CD15 and CD30 was observed in

only 2 (cases 123 and 186). In addition, immunophenotypic switch of the neoplastic T cells was detected in cases 137 (CD4+ and CD8+ MF to CD4+ LCT) and 279 (CD4+ MF to CD8+ LCT). Furthermore, cross-lineage aberrancy was observed in case 63 with expression of CD20 in a subset of the neoplastic T cells.

Patients who present with LCT at more advanced stages have worse prognosis, and extracutaneous transformation is frequently associated with poor survival.^{35,36,40} However, a recent study reported that some cases of LCT may follow a more indolent course.⁴⁰ Using multivariate analysis, this study showed that CD30 negativity, folliculotropic MF, extent of skin lesions, and extracutaneous transformation were associated with reduced disease-specific survival, with the latter two being associated with reduced overall survival.

Case 63 presented a 78-year-old man with a long-standing history of skin patches and plaques that were first diagnosed as psoriasis. The patient developed skin tumors **Image 5A**, and after 6 months a biopsy was performed **Image 5B**, **Image 5C**, **Image 5D**, and **Image 5E**, revealing extensive and dense lymphoid infiltration of the dermis with epidermotropism. The lymphoid infiltrate was composed mainly of admixed small to large cerebriform lymphocytes, as well as large transformed cells (or blasts) with slightly irregular nuclei, dispersed chromatin, and prominent nucleoli. Immunophenotypic analysis revealed double-negative (CD4– and CD8–) T cells expressing CD3 with loss of both CD5 and CD7, as well as aberrant expression of CD20. The conclusion of the panel was that the number of large transformed T cells was less than 25%, and hence a diagnosis of tumor stage without transformation was rendered. Case 196 presented tumor stage of MF, as well as LCT with sheets of large transformed cells. In cases similar to 63 and 196, the morphologic distinction between non-transformed vs transformed tumor stage MF can be made. However, distinguishing tumor stage MF with or without LCT may not be clinically relevant because studies suggest no difference in survival in patients with tumor stage MF regardless of transformation status.^{34,40,41}

Case 186 was a classic case of MF that progressed to advanced stage with transformation and extracutaneous involvement. It described a patient with stage Ib MF at age 41 years. Over the next 15 years, the disease recurred several times and continued to progress with ulcerated tumors in 2008, despite multiple local and systemic treatments. Clinical photograph and skin biopsy specimen several years prior to 2008 showed findings consistent with patch/plaque stage MF **Image 6A**. In 2008, the skin biopsy specimen of an arm tumor **Image 6B**, **Image 6C**, **Image 6D**, and **Image 6E** revealed dense dermal infiltration by predominantly large transformed cells and scattered large cerebriform lymphocytes, with frequent mitoses. Immunohistochemical studies

detected abnormal CD4+ T cells with significant loss of CD7 expression. Occasional large pleomorphic lymphocytes were also positive for CD30 and CD15. Several months prior to the occurrence of the skin tumor, the patient developed B symptoms and generalized lymphadenopathy, and a bone marrow biopsy specimen **Image 6F**, **Image 6G**, **Image 6H**, **Image 6I**, and **Image 6J** revealed an atypical lymphoid infiltrate composed of scattered large pleomorphic lymphocytes resembling Hodgkin and Reed-Sternberg cells in a background of admixed cerebriform lymphocytes, as well as eosinophils, plasma cells, and histiocytes. By immunohistochemical studies, the large pleomorphic lymphocytes were positive for CD4 (Image 6H) as well as CD30 (Image 6I), CD15 (Image 6J) (subset), CD2, and CD5 (subset). In 2009, the patient presented neurologic deficits, and magnetic resonance imaging detected a left temporal lobe lesion. A biopsy specimen of the brain **Image 6K**, **Image 6L**, and **Image 6M** revealed a lymphoid infiltrate with morphologic and immunophenotypic findings similar to those described in the bone marrow. Immunohistochemical studies again highlighted scattered large pleomorphic cells positive for CD30 and occasional ones positive for CD15 **Image 6N**. Molecular analysis demonstrated identical clonal TCR γ gene rearrangements in both the skin and brain biopsy specimens **Image 6O**.

Although the diagnosis of transformed MF is made based on comprehensive analysis of both the clinical and pathologic criteria, considerations of the key differentials are important for staging, prognosis, and therapy. Because of the shared morphologic features with an abundance of large blast cells and common expression of CD30, it is critical to distinguish LCT of MF from primary cutaneous anaplastic large-cell lymphoma (cALCL), which is discussed in the next section, as well as from cutaneous manifestation of systemic ALCL. Expression of CD15 is uncommon in transformed MF,⁴² but when it occurs, it is frequently accompanied by expression of CD30. ALCL may show similar immunophenotypic features to LCT because a subset of either systemic or cutaneous ALCL may express CD15.⁴² Peripheral T-cell lymphoma not otherwise specified coexpressing CD30 and CD15 should also be considered because it may also involve cutaneous sites.^{43,44} Last, because MF can coexist with classical Hodgkin lymphoma (CHL), the distinction of concurrent MF and CHL from transformed MF with CHL-like features is necessary.

Relationship With Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

According to the 2008 WHO classification,^{2,3} patients with cutaneous ALCL should not have clinical evidence or a history of MF. When they do, the diagnosis should be

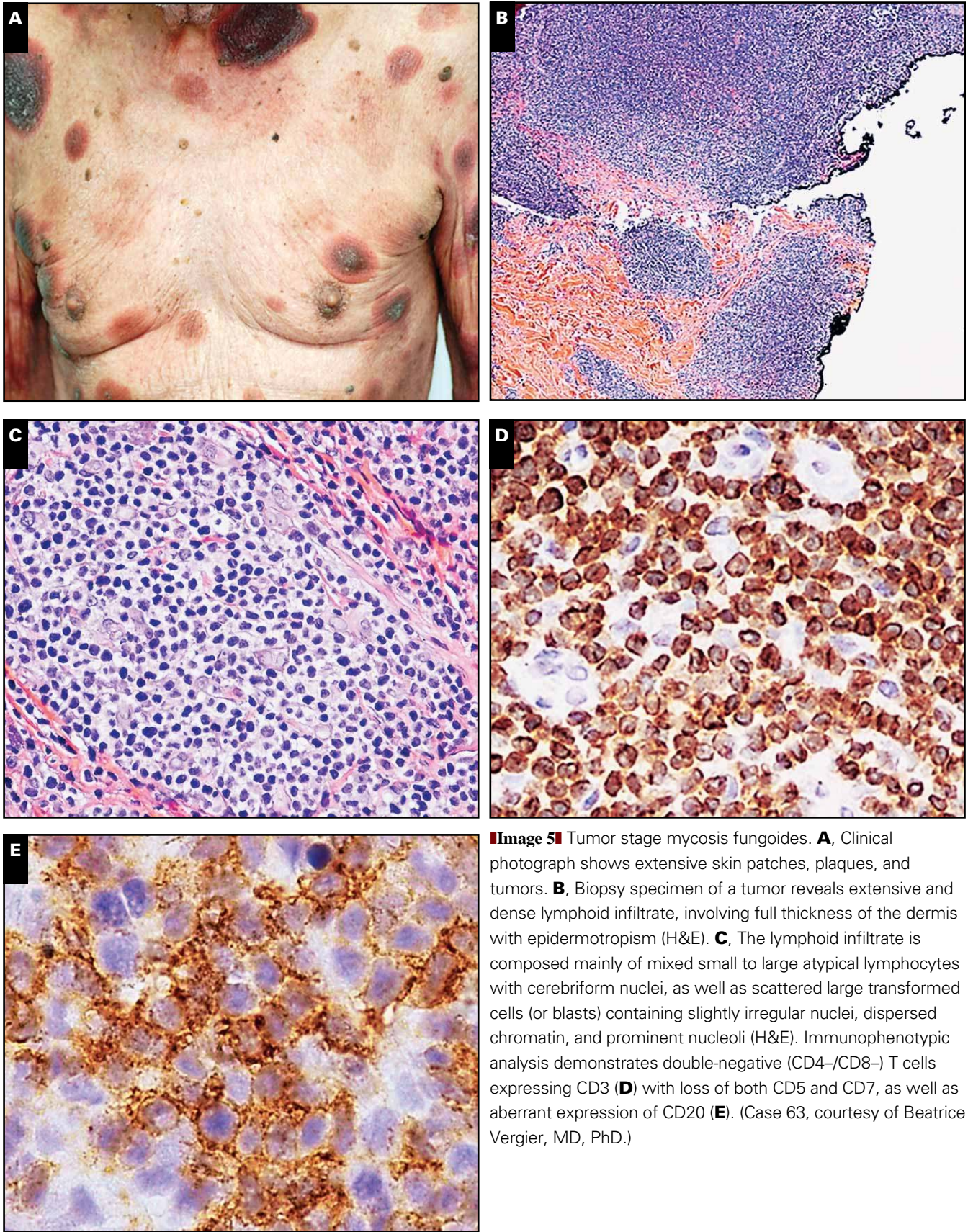


Image 5 Tumor stage mycosis fungoides. **A**, Clinical photograph shows extensive skin patches, plaques, and tumors. **B**, Biopsy specimen of a tumor reveals extensive and dense lymphoid infiltrate, involving full thickness of the dermis with epidermotropism (H&E). **C**, The lymphoid infiltrate is composed mainly of mixed small to large atypical lymphocytes with cerebriform nuclei, as well as scattered large transformed cells (or blasts) containing slightly irregular nuclei, dispersed chromatin, and prominent nucleoli (H&E). Immunophenotypic analysis demonstrates double-negative (CD4-/CD8-) T cells expressing CD3 (**D**) with loss of both CD5 and CD7, as well as aberrant expression of CD20 (**E**). (Case 63, courtesy of Beatrice Vergier, MD, PhD.)

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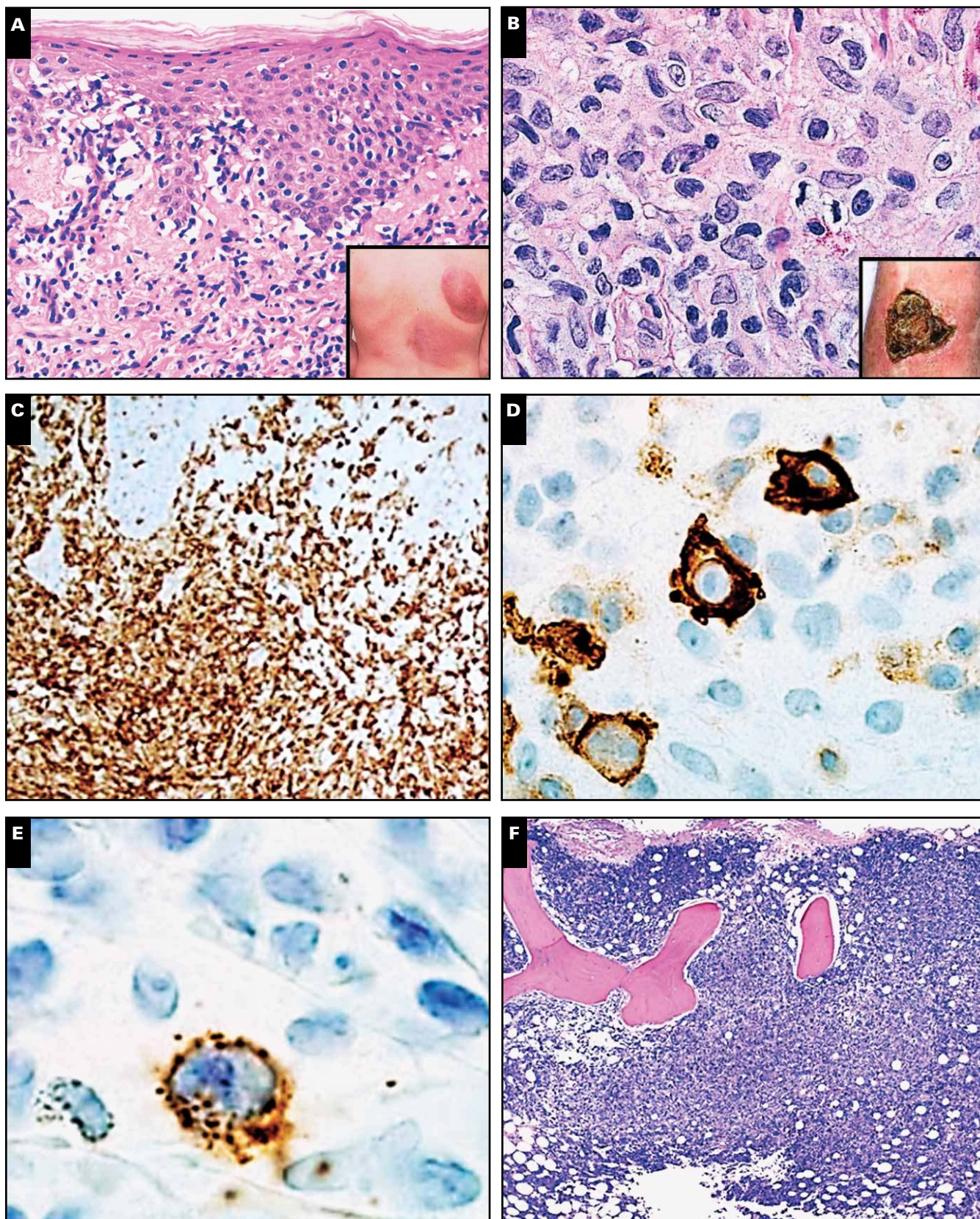


Image 6 Advanced-stage mycosis fungoides (MF) with transformation and extracutaneous involvement. **A**, Clinical photograph (inset) and skin biopsy specimen show findings consistent with patch/plaque stage MF (H&E). **B**, Several years later, skin tumor (inset) develops, and the biopsy specimen reveals dense dermal infiltration by predominantly large transformed cells and scattered large cerebriform lymphocytes, with frequent mitoses (H&E). Immunohistochemical studies detected abnormal CD4+ T cells (**C**) with significant loss of CD7 expression. Occasional large pleomorphic lymphocytes were also positive for CD30 (**D**) and CD15 (**E**).

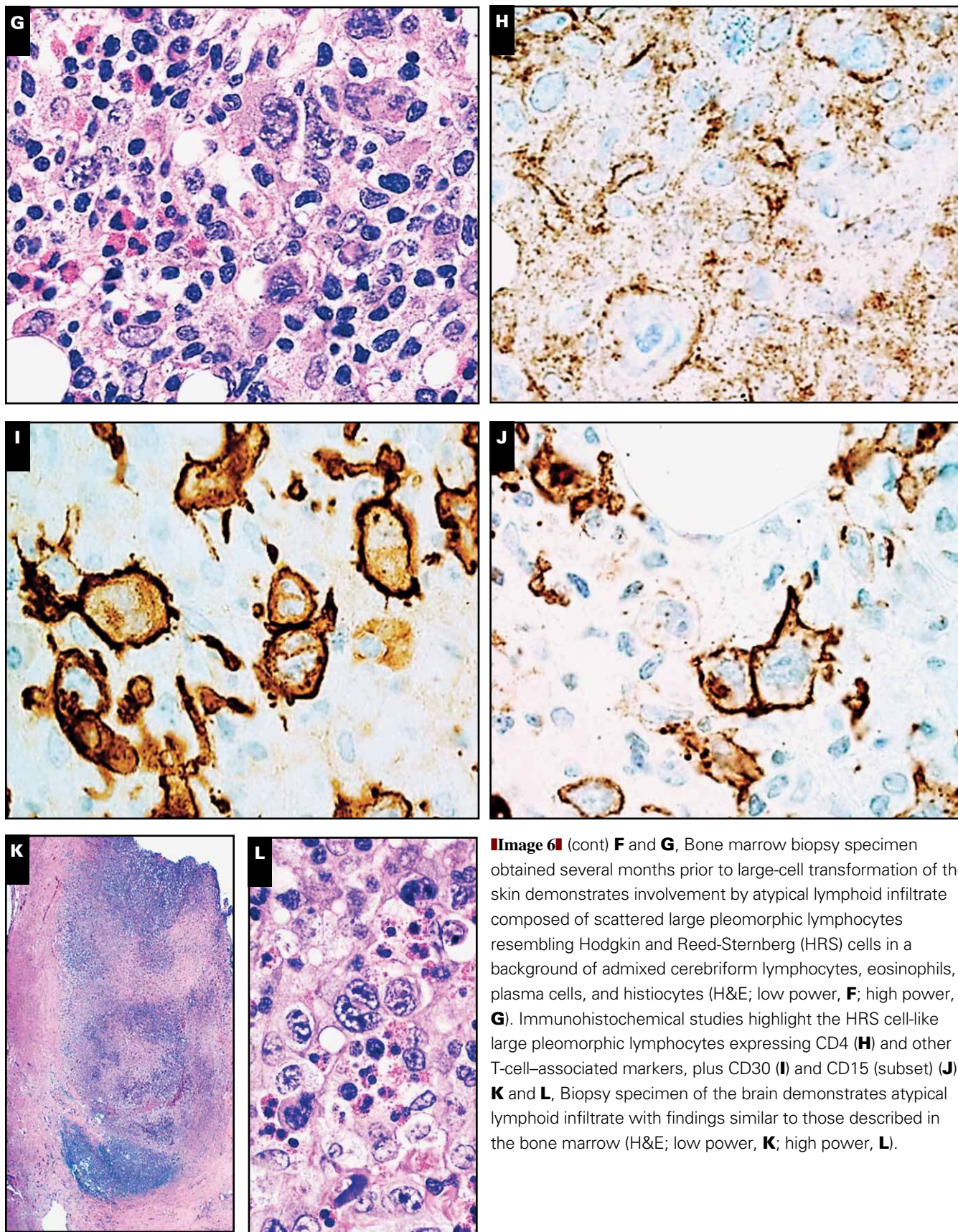


Image 6 (cont) **F** and **G**, Bone marrow biopsy specimen obtained several months prior to large-cell transformation of the skin demonstrates involvement by atypical lymphoid infiltrate composed of scattered large pleomorphic lymphocytes resembling Hodgkin and Reed-Sternberg (HRS) cells in a background of admixed cerebriform lymphocytes, eosinophils, plasma cells, and histiocytes (H&E; low power, **F**; high power, **G**). Immunohistochemical studies highlight the HRS cell-like large pleomorphic lymphocytes expressing CD4 (**H**) and other T-cell-associated markers, plus CD30 (**I**) and CD15 (subset) (**J**). **K** and **L**, Biopsy specimen of the brain demonstrates atypical lymphoid infiltrate with findings similar to those described in the bone marrow (H&E; low power, **K**; high power, **L**).

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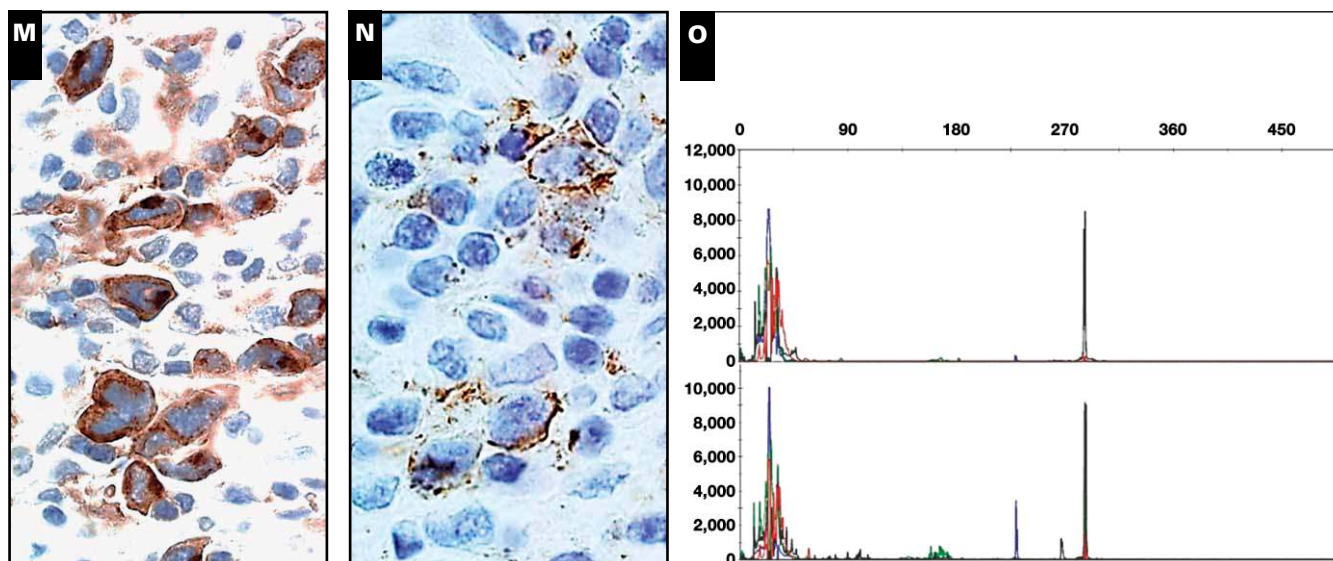


Image 6 (cont) Immunohistochemical studies again highlight scattered large pleomorphic cells positive for CD30 (**M**) and CD15 (**N**). **O**, Molecular analysis exhibits identical clonal T-cell receptor γ gene rearrangements in both the skin (top) and brain (bottom) biopsy specimens. (Case 186, courtesy of David A. Wada, MD, Mark R. Pittelkow, MD, Nneka I. Comfere, MD, Thomas E. Witzig, MD, and Andrew L. Feldman, MD.)

considered transformation of MF to tumor stage, which may be CD30+ or CD30-.^{42,45} Nevertheless, MF may coexist with primary cutaneous CD30+ LPDs (discussed in detail by Quintanilla-Martinez et al²⁹), including lymphomatoid papulosis (LyP) and cALCL.⁴⁵⁻⁴⁷ A clonal relationship between lesions of MF and primary cutaneous CD30+ LPD in the same patient may be demonstrable in some cases by molecular studies.⁴⁸ It has been suggested that MF with LyP may be associated with improved survival and decreased risk for disease progression.⁴⁹ It is critical to distinguish concurrent MF and primary cutaneous CD30+ LPD from transformed MF because their prognoses and therapeutic implications are significantly different. Such distinction relies primarily on clinical presentations as well as pathologic features. 6p25.3 *IRF4/DUSP22* rearrangements by fluorescent in situ hybridization analysis may be helpful because they were observed in about 26% of cALCL (see Quintanilla-Martinez et al²⁹) and only rarely in LyP or transformed MF.^{50,51}

Case 72 was a 36-year-old male patient who presented with patches and plaques on the trunk **Image 7A** and proximal limbs for several years. He was treated initially with intermittent UV-B, psoralen-UV-A, and oral retinoids with some response. A biopsy specimen of the left flank plaque **Image 7B**, **Image 7C**, and **Image 7D** revealed an epidermotropic atypical lymphoid infiltrate of the dermis with Pautrier microabscesses. Immunohistochemical studies demonstrated a T-cell phenotype, positive for CD2 and CD3, with partial loss of CD5 and significant loss of CD7. Staining for CD4 was focal and weak. The atypical

lymphocytes were negative for CD8, CD56, CD30, and ALK-1. The patient continued to develop patches, plaques, and ulcerating nodules and tumors that were associated with the plaques **Image 7E**. However, most of those nodules and tumors underwent spontaneous resolution. The biopsy specimen taken from 1 persistent nodule on the scalp **Image 7F**, **Image 7G**, **Image 7H**, **Image 7I**, **Image 7J**, and **Image 7K** revealed dermal atypical lymphoid infiltrates with aggregates of large atypical lymphocytes with blast-like morphology, admixed with small lymphocytes and eosinophils. The large atypical lymphocytes were positive for CD30 as well as T-cell-associated markers CD2, CD3 (patchy and weak), CD4, and CD5 (patchy and weak), plus perforin, but negative for CD7, CD8, and ALK-1. Based on the clinical information, the persistent nodule on the scalp and the nodules and tumors that underwent spontaneous resolution were more in keeping with primary cutaneous CD30+ LPD (cALCL and LyP) than transformed MF. The panel diagnosis was MF associated with primary cutaneous CD30+ LPD. Similarly, in case 140, the patient presented with concurrent folliculotropic MF and LyP.

In addition to coexistence with MF, primary cutaneous CD30+ LPD, especially LyP, is a key consideration in the differential diagnosis of MF due to their overlapping clinicopathologic features. Clinically, LyP has a characteristic presentation of recurrent self-healing papulonodules. Although reappearance and sometimes even spontaneous resolution may occasionally occur in MF, it typically does not present as a chronic, recurrent, and self-healing eruption. Histologically, type B LyP (MF-like) can display findings identical

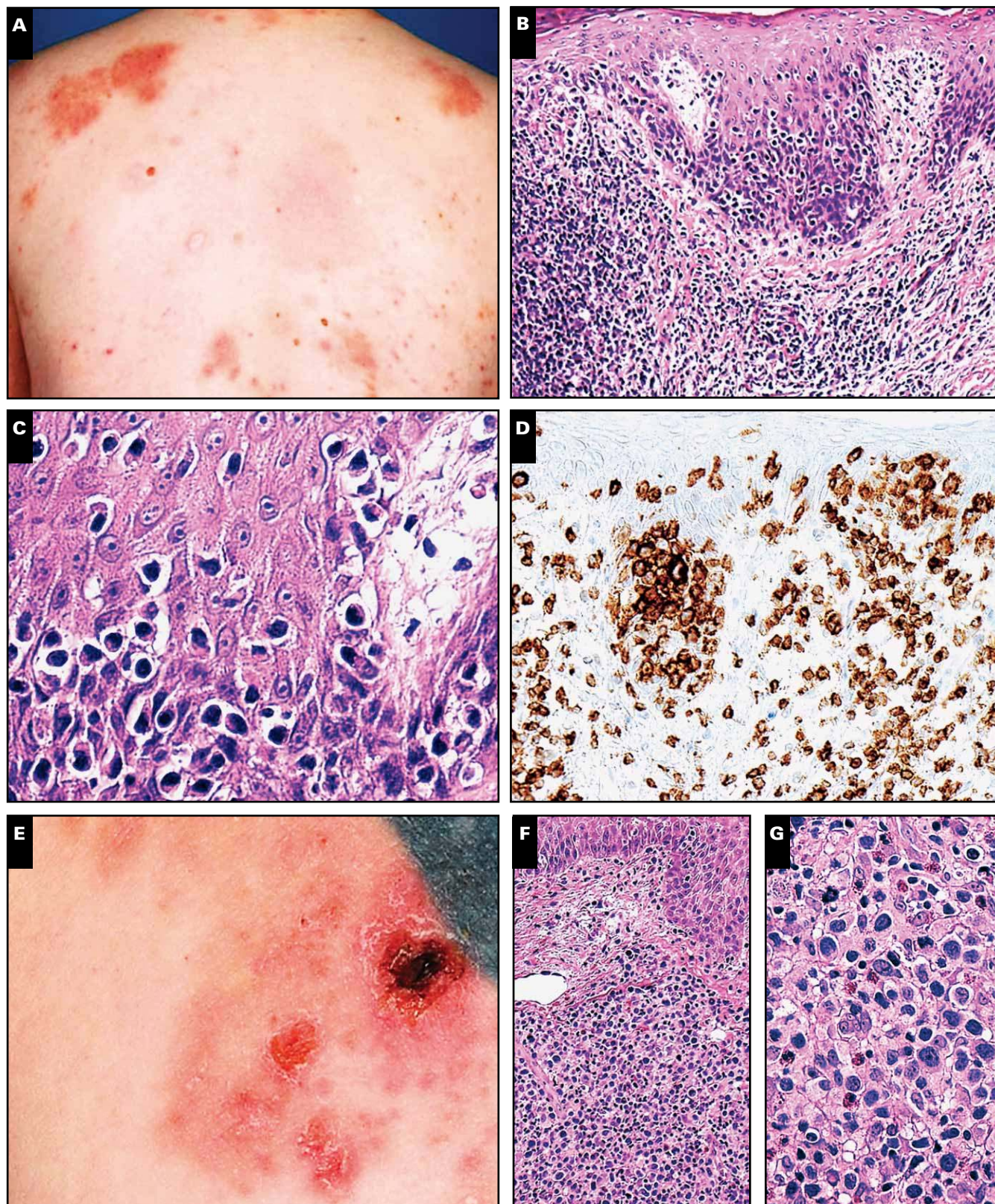
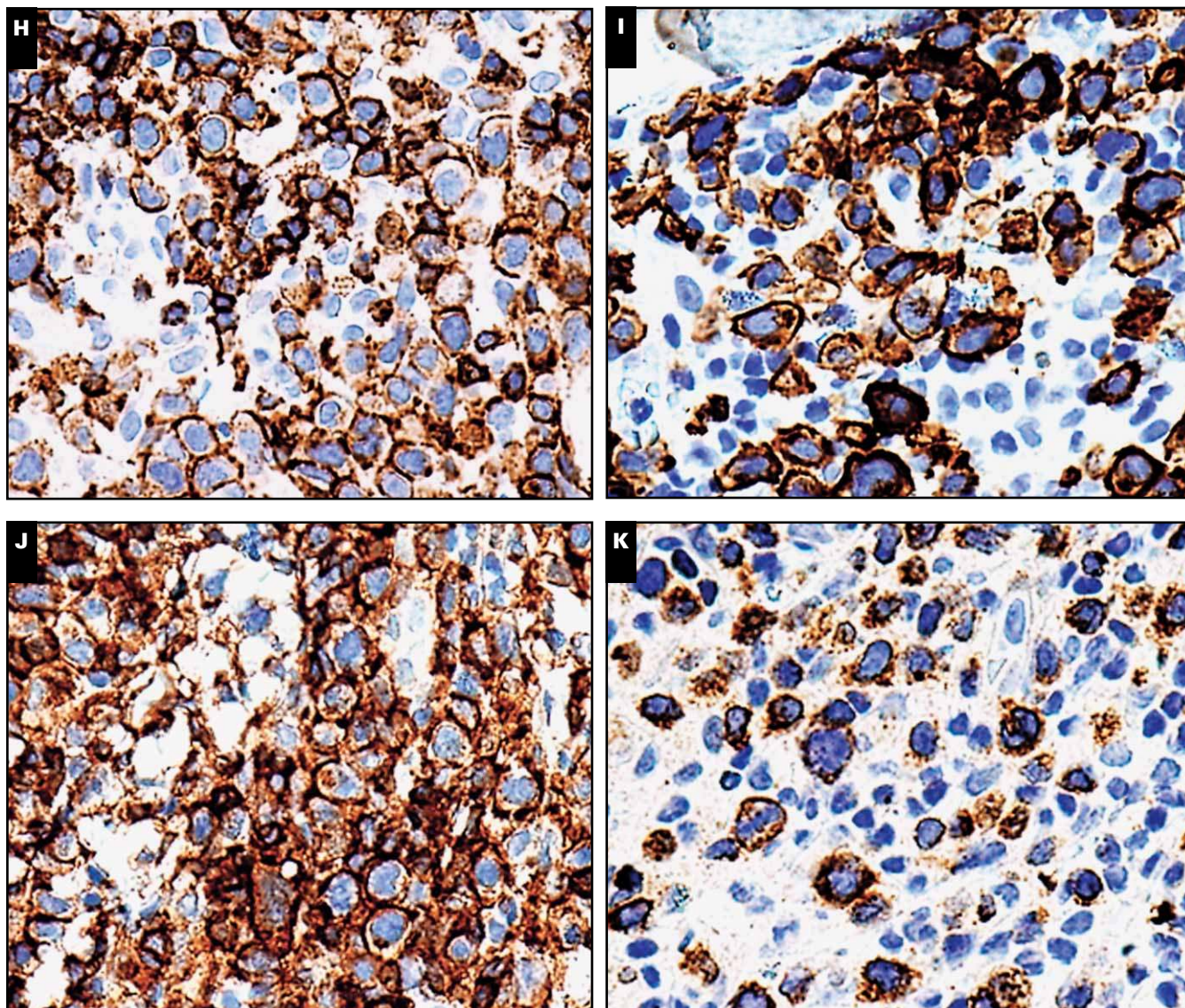


Image 7 Mycosis fungoides and concurrent primary cutaneous CD30+ lymphoproliferative disorder. **A**, Clinical photograph shows patches and plaques on the trunk. **B-D**, Biopsy specimen of a left flank plaque reveals epidermotropic atypical lymphoid infiltrate of the dermis (**B**) with Pautrier microabscesses (**C**) (H&E). Immunohistochemical studies show CD2+ T cells (**D**) also positive for CD3, with partial loss of CD5 and significant loss of CD7. The atypical lymphocytes were negative for CD30 and ALK-1. **E**, The patient develops ulcerating nodules and tumors that are associated with the plaques. Most of those nodules and tumors underwent spontaneous resolution. **F** and **G**, The biopsy specimen of 1 persistent nodule on the scalp reveals dermal atypical lymphoid infiltrates with aggregates of large atypical lymphocytes with blast-like features, admixed with small lymphocytes and eosinophils (H&E).



The large atypical lymphocytes are positive for CD2 (**H**), CD30 (**I**), and CD4 (**J**), plus perforin (**K**) by immunohistochemical stains. (Case 72, courtesy of John R. Goodlad, MD.)

to MF, with an epidermotropic infiltrate of small- to intermediate-sized cerebriform lymphocytes. Type D LyP, a recently described entity, shows prominent epidermotropism resembling a variant of MF, pagetoid reticulosis (PR), with a cytotoxic immunophenotype positive for CD8 and CD30.⁵²

Case 116 (by G. E. Nybakken, MD, PhD, Y. C. Chan, M. M. Shinohara, MD, et al, unpublished data, 2012) was a 53-year-old male patient who presented with recurrent and partially self-healing erythematous papulonodules of the right thigh and left forearm. A biopsy specimen of the right thigh lesion **Image 8** revealed a dermal lymphoid infiltrate with prominent epidermotropism. The epidermotropic lymphocytes were atypical and composed of intermediate-sized lymphocytes with hyperchromatic and

cerebriform nuclei, plus occasional clear haloes. Many of those epidermotropic lymphocytes accumulated along the basal layer. No Pautrier microabscesses were detected. Immunohistochemical studies demonstrated a CD8+ T-cell phenotype expressing CD2 and CD3 with partial loss of CD5 and marked loss of CD7. The epidermotropic lymphocytes were frequently positive for CD30. Staining for cytotoxic molecules was negative. Although the case displayed histopathologic features resembling PR-type MF, the panel rendered the diagnosis of type D LyP based on the overall clinicopathologic features, including clinical presentation of recurrent and partially self-healing papulonodules and striking epidermotropism, plus the CD8+ phenotype and frequent expression of CD30.

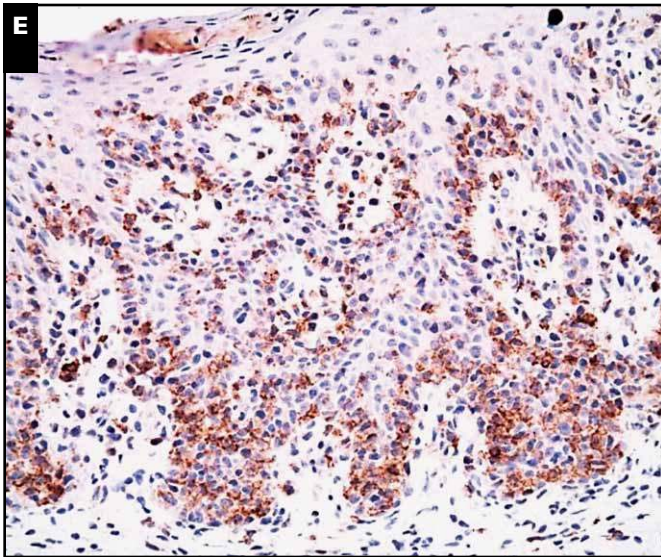
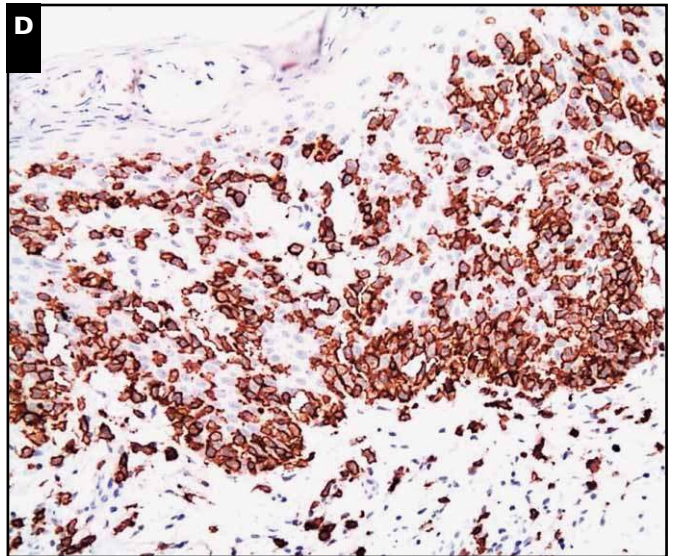
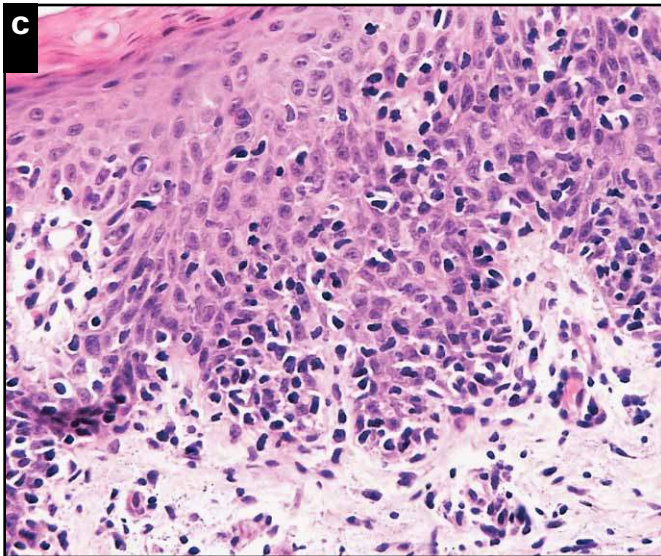
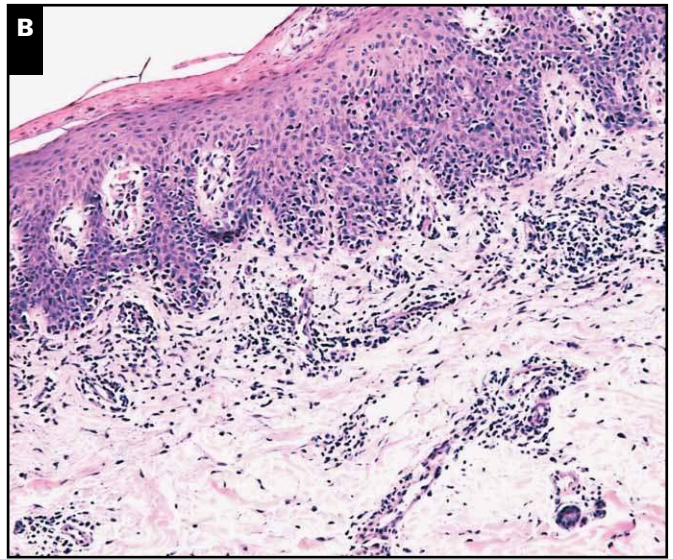


Image 8 Type D lymphomatoid papulosis (LyP) simulating mycosis fungoides. **A**, Papulonecrotic lesions at different stages of evolution are seen in a different patient with type D LyP. **B-E** (case 116). **B**, Biopsy specimen demonstrates dermal lymphoid infiltrate with prominent epidermotropism (H&E). **C**, The epidermotropic lymphocytes were atypical and composed of intermediate-sized cerebriform lymphocytes, plus occasional clear haloes. No Pautrier microabscesses are detected (H&E). Immunohistochemical studies highlight CD3+ T cells with CD8 phenotype (**D**), revealing partial loss of CD5 and marked loss of CD7. **E**, The epidermotropic lymphocytes are frequently positive for CD30. (**A**, courtesy of Rein Willemze, MD; case 116, courtesy of Grant E. Nybakken, MD, PhD, Ellen Kim, MD, PhD, Rosalie Elenitsas, MD, Howard Altman, MD, and Adam Bagg, MD.)

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MF Variants

Eighteen cases were submitted as various subtypes of MF (MF variants), accounting for approximately 29% of the cases in this session. Close to 15 early MF variants have been reported as of 2010.⁵² However, the panel is in agreement with the WHO/EORTC classification^{1,2} that the clinically significant variants are limited to folliculotropic MF, PR, and granulomatous slack skin (GSS). These 3 MF variants may be diagnostically challenging owing to their distinctive clinical and pathologic features.

Folliculotropic MF is important to recognize because it may imply a worse prognosis, with 5-year survival rates of approximately 60% to 70%, and may require more intensive treatment.^{49,53,54} Histologic diagnosis can be difficult because it often lacks the typical epidermotropism seen in MF. Instead, the atypical lymphocytes infiltrate the hair follicles, and abundant inflammatory cells are often present in the background, raising the differential of folliculitis. Some patients may have comedone-like distended hair follicles containing keratinaceous debris. Follicular mucinosis may or may not be present in folliculotropic MF,⁵³ and it can be seen in other entities, including benign conditions.⁵⁵ Case 154, which had typical features of folliculotropic MF, was a 38-year-old male patient who had a history of a pruritic rash for 9 months. Clinical photograph showed erythematous macules, plaques, and papules **Image 9A**. A biopsy specimen revealed hair follicles infiltrated by atypical lymphocytes, admixed with abundant plasma cells and eosinophils **Image 9B** and **Image 9C**. Epidermotropism was not prominent. The lymphoid cells were predominantly CD4+ T cells by immunohistochemical studies, and molecular analysis revealed clonal TCR β gene rearrangements. Similarly, case 119 exhibited folliculotropic MF, in which follicular mucinosis **Image 9D** was striking and LCT was also noted.

In contrast to folliculotropic MF, PR and GSS, both of which are rare variants of MF, have an indolent clinical course with excellent prognosis.⁵⁶⁻⁵⁸ Cases 257 and 106 presented clinicopathologic features consistent with PR, and case 257 was reported previously.⁵³ The typical presentation of PR (Woringer-Kolopp type) is a solitary plaque on the distal extremities. Multiple, disseminated lesions are seen in the Ketron-Goodman type. There is characteristic epidermal hyperplasia with striking epidermotropism of atypical lymphocytes **Image 9E**. A CD8+ immunophenotype is common in PR, and expression of CD30 **Image 9F** is seen in a proportion of cases. The key differentials are MF palmaris et plantaris and primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. GSS^{1,58} presents as slowly evolving hanging folds of lax skin in the major skin folds, with dermal granulomatous infiltration by clusters of histiocytes and giant cells surrounded by small lymphocytes that are typically clonal. Epidermotropism may be minimal. Giant

cells may be abundant, displaying emperipolesis of small lymphocytes (lymphophagocytosis), and/or contain phagocytized elastic fibers (elastophagocytosis). It can be associated with Hodgkin lymphoma or MF, and it can be confused with other granulomatous processes. Case 306 was a 59-year-old female patient who presented with GSS and a history of pre-existing MF. At age 22 years, the patient developed patches and plaques consistent with MF, was treated with total skin electron beam therapy with complete remission, but relapsed 8 years later at age 30 years. At age 40 years, the patient presented with slowly progressive hanging lax skin folds in preexistent MF lesions on the breasts, abdomen, and axillary skin folds, shown in the inset of **Image 9G**. A biopsy specimen of the hanging skin folds (**Image 9G**), **Image 9H**, and **Image 9I** revealed dermal granulomatous infiltration with small atypical lymphocytes and abundant giant cells containing numerous nuclei, many of which formed a wreath-like arrangement. There was epidermotropism with small cerebriform lymphocytes, consistent with MF. Lymphophagocytosis was easily seen, which was also a prominent feature of case 239 **Image 9J**. Like GSS, formation of granulomatous aggregates is the main histologic feature of granulomatous MF as well, which only differs clinically from GSS by the development of hanging skin folds in GSS.

Sézary Syndrome

SS, categorized as a separate entity from MF by the WHO/EORTC classification system, is an aggressive disease with a poor prognosis.^{1,4,59} SS is defined by a classic triad of erythroderma, generalized lymphadenopathy, and clonally related neoplastic T cells with cerebriform nuclei (Sézary cells) in skin, lymph nodes, and peripheral blood.⁵⁸ The absolute Sézary cell count is at least 1,000 cells/ μ L in peripheral blood with a CD4 to CD8 ratio of greater than 10 and/or T-cell aberrancies by immunophenotyping.^{59,60}

Case 74 was illustrative of SS. This 84-year-old male patient presented with a 1-year history of progressive non-pruritic erythema. Prior skin biopsy specimen was nondiagnostic, and treatment included topical plus oral steroids. Laboratory studies showed a WBC count of 17,000/ μ L with 60% lymphocytes. The patient had revealed generalized erythroderma **Image 10A**. A skin biopsy specimen **Image 10B**, **Image 10C**, **Image 10D**, **Image 10E**, **Image 10F**, and **Image 10G**, however, showed only a mild lichenoid atypical lymphoid infiltrate of the dermis with minimal epidermotropism. Immunohistochemical studies highlighted CD4+ T cells displaying loss of CD5 and significant loss of CD7. The panel performed immunohistochemical studies for programmed death 1 (PD-1), which stained many of the atypical lymphocytes. PD-1 is a marker of follicular

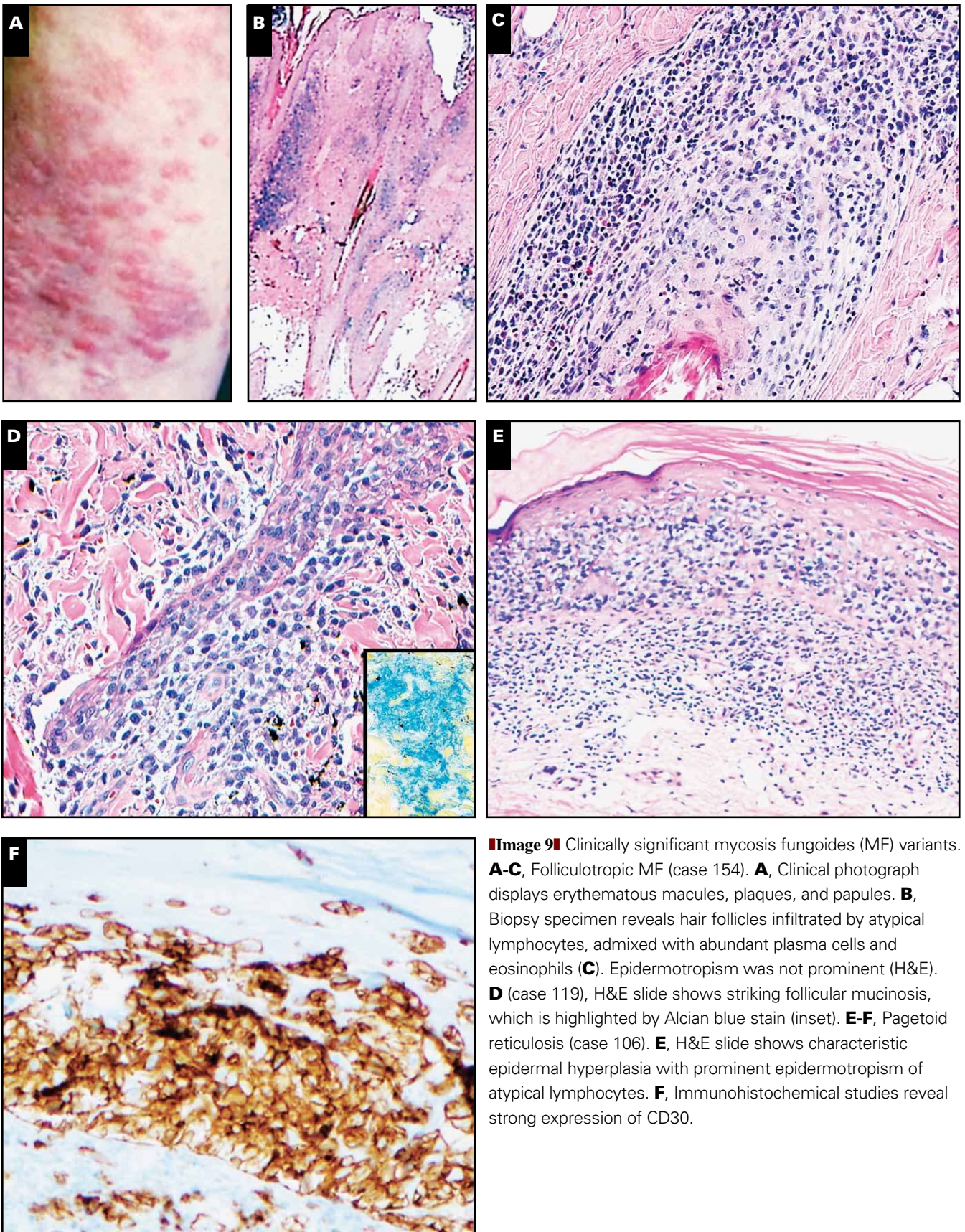
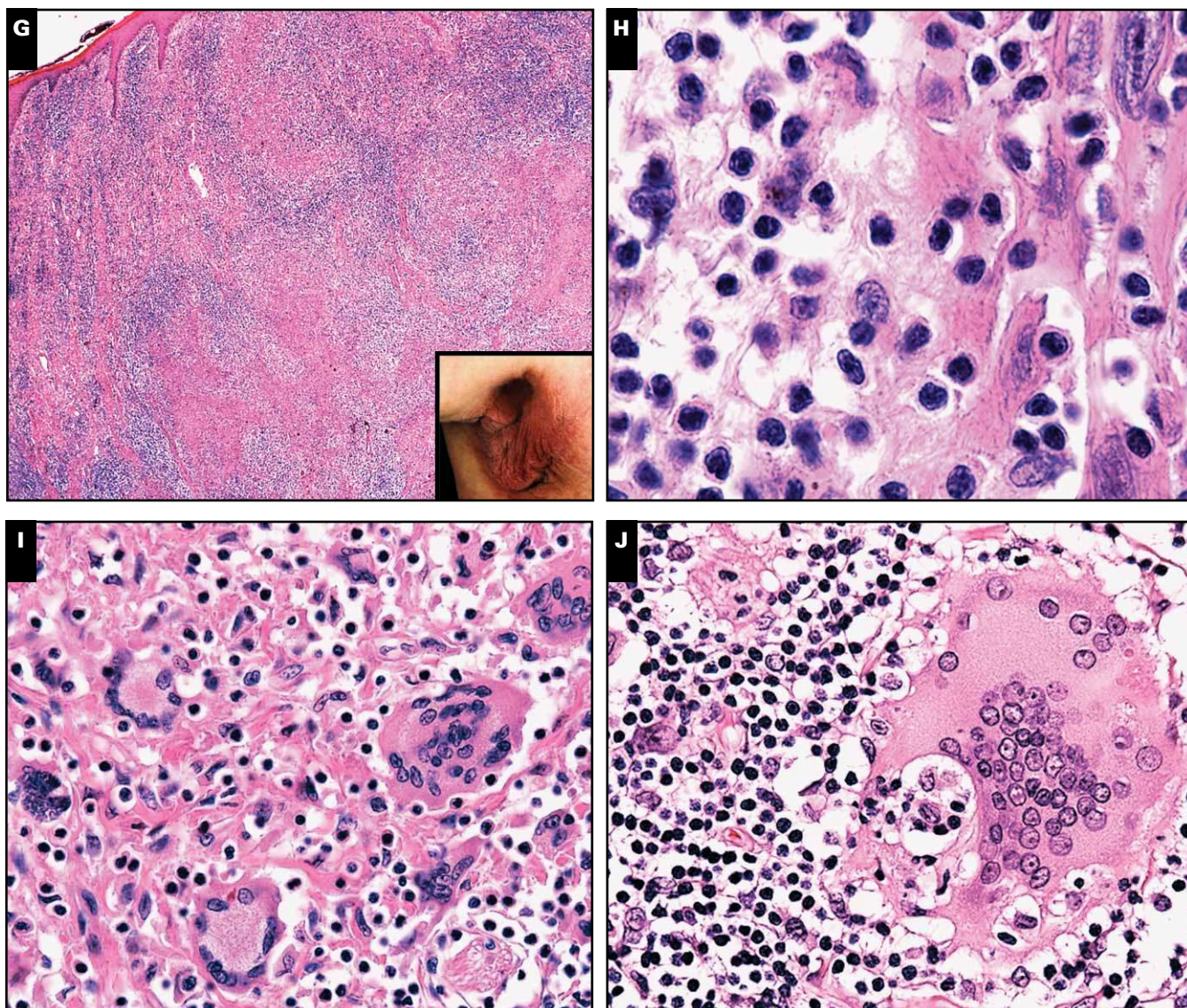


Image 9 Clinically significant mycosis fungoides (MF) variants. **A-C**, Folliculotropic MF (case 154). **A**, Clinical photograph displays erythematous macules, plaques, and papules. **B**, Biopsy specimen reveals hair follicles infiltrated by atypical lymphocytes, admixed with abundant plasma cells and eosinophils (**C**). Epidermotropism was not prominent (H&E). **D** (case 119), H&E slide shows striking follicular mucinosis, which is highlighted by Alcian blue stain (inset). **E-F**, Pagetoid reticulosis (case 106). **E**, H&E slide shows characteristic epidermal hyperplasia with prominent epidermotropism of atypical lymphocytes. **F**, Immunohistochemical studies reveal strong expression of CD30.

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G-I, Granulomatous slack skin (case 306). **G**, Biopsy specimen of hanging skin folds of the right axilla (inset) reveals epidermotropic atypical lymphocytes containing hyperchromatic and cerebriform nuclei (**H**), consistent with MF, as well as dermal granulomatous infiltration with small atypical lymphocytes and abundant giant cells (**I**) containing numerous nuclei, many of which form a wreath-like arrangement (H&E). **J**, Lymphophagocytosis is a prominent feature of case 239 (H&E). (Case 154, courtesy of Stefan Dojcinov, MD, Eve Gallop-Evans, MD, PhD, Alex Anstey, MD, and Vincent Piguët, MD, PhD; case 119, courtesy of Jonathan W. Said, MD; case 106, courtesy of Weifen Zeng, MD, PhD, and Eric D. Hsi, MD; case 306, courtesy of Rein Willemze, MD, and Patty Jansen, MD, PhD; case 239, courtesy of Rebecca McClure, MD, and Ahmet Dogan, MD, PhD.)

helper T cells, and recent studies identified PD-1 expression in subgroups of CTCLs.^{61,62} The expression of PD-1 was much more frequent in SS than in MF (with >50% neoplastic T cells positive in 89% of SS vs 13% of MF).⁶³ A bone marrow biopsy specimen revealed an interstitial lymphocytosis, and flow cytometric studies **Image 10H** detected a discrete population of abnormal T cells (>90% of the total T cells) with several aberrancies, including dim CD2, dim CD3, bright CD4, and complete loss of CD7. Molecular studies demonstrated identical clonal TCR γ

gene rearrangements in both the skin and bone marrow biopsy specimens.

Although erythroderma is one of the characteristic presentations of SS, it can also be seen in MF. When that occurs, the term *erythrodermic MF* is used, and it may be categorized as secondary SS if the other criteria of SS are fulfilled.^{33,60} Case 118 presented a case of erythrodermic MF at tumor stage. Because no information was available regarding the peripheral blood lymphocyte count, assessment of secondary SS could not be made. The patient was a 43-year-old man

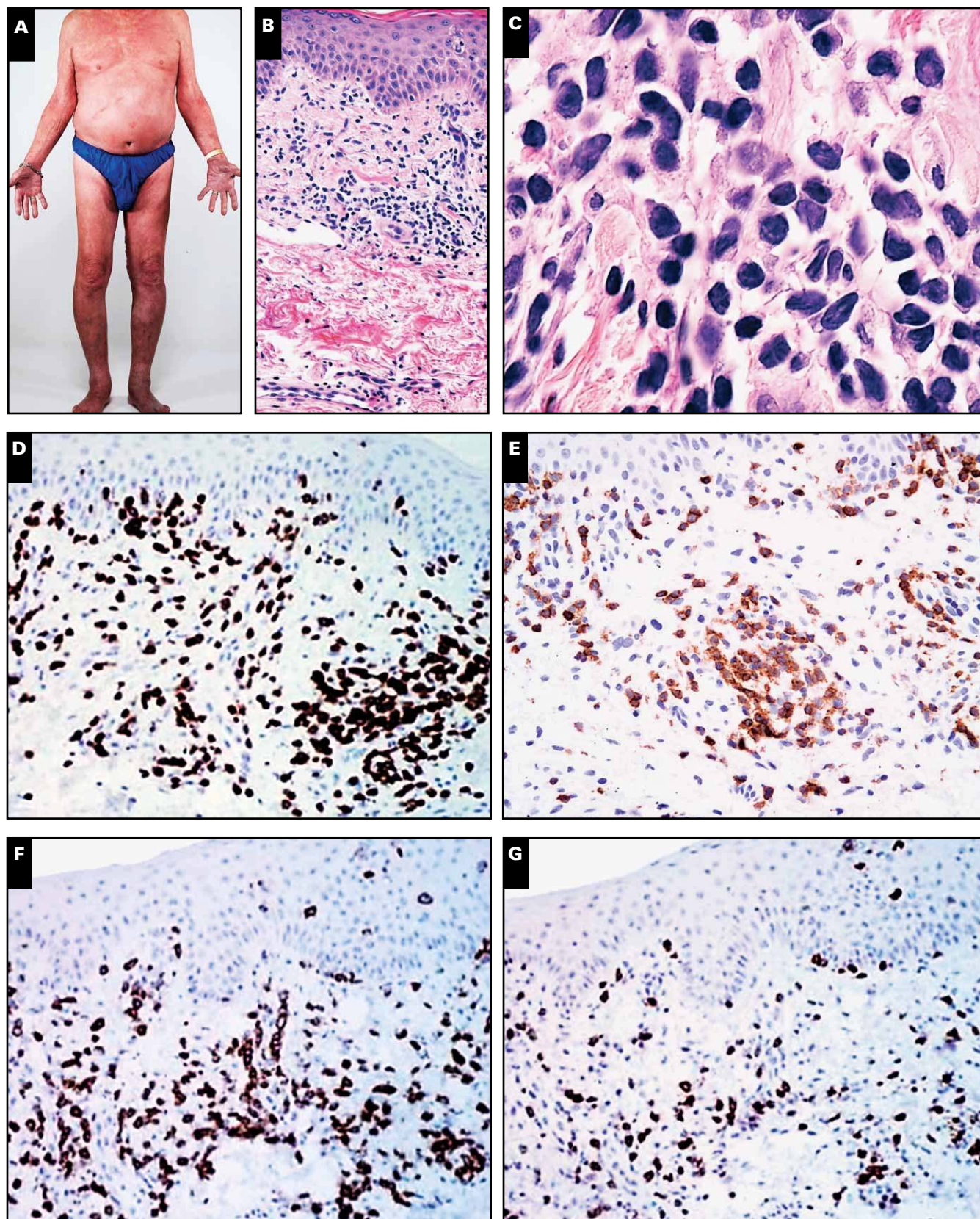
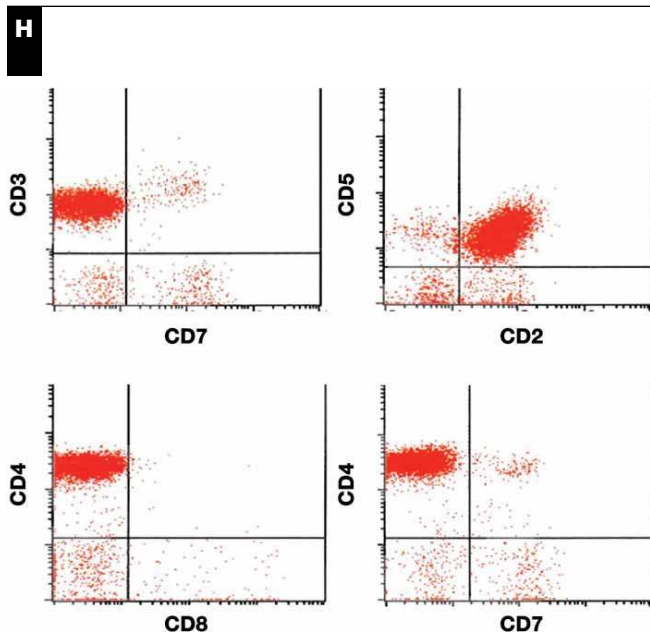


Image 10 Sézary syndrome. **A**, Generalized erythroderma involves greater than 85% of the skin. **B**, Skin biopsy specimen shows only mild lichenoid atypical lymphoid infiltrate of the dermis with minimal epidermotropism (H&E). **C**, Scattered atypical lymphocytes are noted with hyperchromatic and cerebriform nuclei (H&E). **D**, The atypical lymphocytes are positive for CD3 and PD-1 (**E**), displaying loss of CD5 (**F**) and significant loss of CD7 (**G**) by immunohistochemical studies.



H, Flow cytometric analysis of the bone marrow detects a discrete population of abnormal T cells (>90% of the total T cells) with multiple aberrancies, including dim CD2, dim CD3, bright CD4, and complete loss of CD7. (Case 74, courtesy of Dragan Jevremovic, MD, PhD, Nneka Comfere, MD, and David Viswanatha, MD.)

with a history of chronic skin lesions and generalized erythroderma for 3 to 4 years who presented with progressive rash and fevers. The patient had diffuse erythema and numerous plaques, nodules, and tumors, of which many had erosion, covering more than 90% of the body surface. There were multiple large tumor nodules on his scalp and forehead. Computed tomography examination revealed lymphadenopathy without visceral involvement. The WBC count was 29,000/ μL , but no differentials were available. A biopsy specimen of 1 large tumor nodule demonstrated an atypical lymphoid infiltrate involving the full thickness of skin with epidermotropism, including 1 Pautrier microabscess. The atypical lymphocytes were predominantly small to intermediate sized with cerebriform nuclei. A blood smear showed scattered atypical lymphocytes with irregular nuclei, and abnormal CD4+ T cells were detected by flow cytometry. Testing for human T-lymphotrophic virus types 1 and 2 was negative. The panel performed a PD-1 immunohistochemical stain on the skin biopsy specimen, and the result was negative. The panel diagnosis was tumor stage MF based on the clinical presentation of chronic skin lesions with plaques and progressive tumor nodules, skin biopsy specimen findings with characteristic histologic features of tumor stage MF, lymphadenopathy, PD-1 negativity, and the lab results.

Recognition of SS can be challenging, and skin biopsy specimens alone may not be informative. Skin biopsy specimens of SS may not show changes that are typical of MF, and patients may go through several “nondiagnostic” biopsies, as in case 74. Ancillary studies may be helpful in aiding the diagnosis of SS. Multiparametric flow cytometry is useful in detecting and enumerating the neoplastic lymphocytes of SS in the blood. It can reveal pan-T-cell aberrancies, even in a subset of the T cells, using the gold standard approach of “pattern recognition.” In addition to the pan-T-cell aberrancies, studies suggest that a cutoff value of 30% CD4+, CD26– and a phenotype of CD4+, CD26–, CD27+ may be useful markers in identifying the neoplastic lymphocytes in SS.⁶⁴⁻⁶⁹

Detection of T-cell clonality by PCR analysis of Southern blot may be of value if the presence of Sézary cells can be supported by morphology and flow cytometric immunophenotyping.

Conclusions

MF is usually a chronic indolent disease, and most patients have a long history of patch or plaque lesions on non-sun-exposed skin, such as the buttocks. The diagnosis should not be made without knowledge of the clinical findings. The cytologic appearance of the cerebriform lymphocytes and their location in the epidermis are critical diagnostic features. Folliculotropic cases are often associated with mucinosis and may have minimal epidermal involvement. Most cases are derived from CD4+ memory T cells, but phenotypic aberrancies and CD8+ cases occur. CD30+ large cells may be present and increase with LCT. Patients with a history of MF and CD30+ LCT should not be misclassified as having cutaneous ALCL. Although rare, MF and primary cutaneous CD30+ LPDs, such as LyP, may be seen in the same patient. Loss of CD7 is common but lacks specificity because it occurs in benign skin infiltrates, and loss of CD5 or CD2 may be more significant. Similarly, the finding of clonal T-cell gene rearrangements should be interpreted with caution because they are known to occur in benign skin infiltrates. Repeated biopsies showing the same clonal population may be helpful. In doubtful cases with early lesions, it is preferable to defer a definite diagnosis of malignancy to follow-up biopsies. Differential diagnosis includes both benign and neoplastic conditions, such as adult T-cell leukemia/lymphoma, which can mimic MF when they involve the skin. Although patients with MF may have erythroderma and circulating neoplastic cells, they should not be confused with cases of SS, which requires erythroderma, lymphadenopathy, and a significant population of neoplastic circulating Sézary cells for the diagnosis.

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