

Mycosis Fungoides with Large-Cell Transformation Metastatic to the Central Nervous System

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Case Report

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Abstract

Background

Central nervous system (CNS) involvement by mycosis fungoides (MF) is an uncommon but serious manifestation of advanced disease. Large-cell transformation (LCT) is associated with aggressive clinical behavior and increased risk of extracutaneous dissemination; however, CNS involvement remains rare and is infrequently confirmed by molecular studies.

Case Presentation:

We report a 77-year-old man with a 13-year history of MF who presented with progressive generalized weakness, gait instability, and weight loss. Brain magnetic resonance imaging demonstrated multiple bilateral enhancing intraparenchymal lesions concerning for primary CNS lymphoma. Cerebrospinal fluid cytology and flow cytometry were nondiagnostic. Stereotactic biopsy of a right frontal lesion revealed diffuse infiltration of brain parenchyma by large atypical lymphoid cells with a predominantly perivascular distribution. By immunohistochemistry, the lymphocytes express CD3, TCR β F1, CD30, and demonstrate diffuse p53 overexpression, complete loss of p16, and a high proliferative index (70–80%). Comparison with a prior skin biopsy which showed typical MF morphology with limited CD30 expression (< 10% of atypical lymphocytes). Polymerase chain reaction–based T-cell receptor gene rearrangement studies performed on both CNS and skin specimens demonstrated similar clonal rearrangements, confirming CNS dissemination of the original MF clone with large-cell transformation.

Discussion

CNS involvement in MF is rare and may occur years after the initial diagnosis, particularly in the setting of transformation. This case highlights several important features, including multifocal intraparenchymal CNS disease, nondiagnostic cerebrospinal fluid studies, and molecular confirmation of clonal relatedness between skin and CNS lesions. These findings underscore the limitations of cerebrospinal fluid-based diagnostic studies and emphasize the importance of tissue biopsy and molecular analysis in establishing the diagnosis.

Conclusion

We describe a rare case of MF with large-cell transformation presenting as multifocal intraparenchymal CNS disease. Molecular demonstration of identical T-cell receptor **rearrangements** in skin and brain lesions provided definitive evidence of metastatic dissemination. Recognition of this rare complication is essential, as new neurologic symptoms in patients with MF should prompt evaluation for CNS involvement regardless of the extent of active cutaneous disease.

Introduction

Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL), accounting for approximately 50% of all primary cutaneous lymphomas. The disease is characterized by the proliferation of mature skin-homing CD4-positive T-lymphocytes and typically follows an indolent clinical course, progressing through patch, plaque, and tumor stages over many years. Although MF is initially confined to the skin, advanced disease may disseminate to extracutaneous sites, including lymph nodes, spleen, liver, lungs, and gastrointestinal tract (1, 2).

Large-cell transformation (LCT) is a well-recognized adverse event in MF, occurring in approximately 8%–55% of cases. Histologically, LCT is defined by the presence of large atypical lymphocytes comprising at least 25% of the infiltrate or forming microscopic nodules (3, 4). Transformation is associated with aggressive clinical behavior, increased risk of extracutaneous dissemination, treatment resistance, and significantly reduced survival. Recent studies have reported median overall survival ranging from approximately 2 to 4 years following transformation (5, 6).

Central nervous system (CNS) involvement in MF is rare. While autopsy studies have identified CNS disease in up to 10%–14% of patients with advanced MF, clinically recognized CNS involvement occurs in fewer than 2% of cases (7, 8). CNS manifestations may include leptomeningeal disease, cranial neuropathies, parenchymal brain lesions, or spinal cord involvement. Among these presentations, intraparenchymal CNS disease is particularly uncommon and is usually encountered in patients with advanced-stage disease and widespread extracutaneous involvement (9, 10).

The association between LCT and CNS dissemination has been described only rarely. Several studies have suggested that transformed MF may exhibit a greater propensity for CNS involvement than conventional MF, and that neurological manifestations may occur despite relatively controlled cutaneous disease (11, 12). Because clinical and radiologic findings are often nonspecific, diagnosis remains challenging and frequently requires tissue biopsy for definitive confirmation. To our knowledge, molecular confirmation of clonal identity between cutaneous and CNS lesions has not been reported in cases of mycosis fungoides with large cell transformation and CNS involvement. Herein, we report a rare case of mycosis fungoides with large-cell transformation presenting as multifocal intraparenchymal CNS disease in a 77-year-old man. The diagnosis was established by stereotactic brain biopsy and supported by similar T-cell receptor gene rearrangements in both skin and brain specimens, confirming CNS dissemination of the original neoplastic clone. This case highlights the diagnostic challenges of CNS involvement in transformed MF and expands the limited literature regarding the clinicopathologic and molecular features of this uncommon manifestation.

Case Presentation

A 77-year-old man with a history of mycosis fungoides (MF) diagnosed in 2012 from a right ankle skin biopsy, presented in 2025 with progressive neurologic symptoms, including progressive generalized weakness, gait instability, and unintentional weight loss. His prior treatment history included

pembrolizumab therapy through 2021, after which his disease was managed with topical clobetasol and imiquimod. There was no known history of systemic lymphoma or prior central nervous system (CNS) involvement.

Magnetic resonance imaging (MRI) of the brain demonstrated multiple bilateral enhancing intracerebral lesions with restricted diffusion, raising concern for primary CNS lymphoma (Fig. 1). Cerebrospinal fluid (CSF) cytologic examination and flow cytometric analysis were nondiagnostic. Given the progressive neurological symptoms and radiologic findings, a stereotactic biopsy of a right frontal lobe lesion was performed.

Histologic examination revealed gliotic brain parenchyma extensively infiltrated by large atypical lymphoid cells with irregular nuclear contours, vesicular chromatin, prominent nucleoli, in a predominantly perivascular distribution. Immunohistochemical studies demonstrated that the large lymphocytes express CD3, TCR β F1, and CD30 (Fig. 2A-C). Additional studies showed diffuse p53 overexpression, complete loss of p16 expression, and a markedly elevated proliferative index of 70–80% by Ki-67. The lymphoma cells are negative for TIA-1, granzyme B, CD20, PAX5, GFAP, OLIG2, IDH1 R132H, and SV40, excluding alternative lymphoid and primary glial neoplasms.

For comparison, review of a previous skin biopsy obtained in 2021 demonstrated morphologic features typical of MF, including marked epidermotropism and a nodular dermal infiltrate of small lymphoma cells. The lymphoma cells are positive for CD3, while less than 10% showed CD30 expression (Fig. 2D-F). Additionally, the skin lesion lacked large cell morphology, which was observed in the CNS lesion.

Polymerase chain reaction (PCR)-based T-cell receptor (TCR) gene rearrangement studies performed on both the brain biopsy and skin biopsy demonstrated similar clonal rearrangements, confirming clonal relatedness and establishing CNS dissemination of a transformed MF.

Discussion

The present case is remarkable because CNS dissemination developed after a prolonged 13-year history of MF and manifested as multifocal intraparenchymal brain lesions. Similar delayed CNS involvement has been reported only rarely. Li et al. described a patient who developed parenchymal CNS disease approximately 10 years after the diagnosis of transformed MF, while maintaining relatively limited extracutaneous disease (10).

Importantly, cerebrospinal fluid (CSF) cytology and flow cytometry were nondiagnostic in our patient. Previous reports have demonstrated variable sensitivity of CSF studies, with some patients showing malignant lymphocytes while others require tissue biopsy for definitive diagnosis (10). The present case highlights the limitations of CSF-based investigations and emphasizes that negative CSF findings do not exclude CNS involvement by MF. In patients with suspicious radiographic findings and progressive neurological symptoms, tissue biopsy remains the diagnostic gold standard.

A major strength of the current report is the molecular confirmation of clonal identity between the skin and brain lesions. PCR-based T-cell receptor gene rearrangement studies demonstrated identical clonal populations in both specimens, providing definitive evidence that the CNS lesion represented dissemination of the original MF clone. Although previous reports have inferred a common origin based on morphology, immunophenotype, and clinical history, molecular confirmation has rarely been documented in the literature. This finding excludes the possibility of a second unrelated T-cell lymphoma and directly establishes metastatic spread of MF to the CNS.

The immunophenotypic evolution observed in this case is also noteworthy. The prior skin biopsy demonstrated classic MF with only limited CD30 expression (< 10% of atypical lymphocytes), whereas the CNS lesion showed diffuse CD30 positivity accompanied by large-cell morphology, diffuse p53 overexpression, complete loss of p16 expression, and a markedly elevated Ki-67 proliferation index of approximately 70–80%. These findings support progression to large-cell transformation and suggest acquisition of additional molecular abnormalities during tumor evolution. Previous studies have demonstrated that LCT is associated with aggressive clinical behavior, extracutaneous dissemination, and significantly reduced survival. The emergence of diffuse CD30 expression in the transformed CNS lesion further highlights the dynamic biological evolution of MF during disease progression.

Compared with the case reported by Li et al., several important differences exist. Their patient developed a solitary temporo-frontal lesion approximately 10 years after MF diagnosis and had evidence of lymphoma cells in the CSF (10), whereas our patient presented with multifocal bilateral intraparenchymal lesions and nondiagnostic CSF studies. Additionally, the current case provides molecular confirmation of identical T-cell receptor clonality between skin and CNS lesions, a feature not demonstrated in the earlier report. These findings provide particularly compelling evidence of true CNS dissemination of MF and strengthen the diagnostic certainty of the present case.

Our observations also support recommendations proposed by Nguyen Vu and colleagues, who noted that transformed MF patients may develop CNS disease even when cutaneous lesions are minimal or clinically controlled (11). Neurologic symptoms in such patients, including weakness, gait disturbance, cognitive decline, visual changes, speech abnormalities, or headaches, should therefore prompt immediate neuroimaging and consideration of CNS involvement. Delay in diagnosis may occur because radiologic and clinical findings are nonspecific and may mimic more common neurologic disorders.

In conclusion, we report a rare case of mycosis fungoides with large-cell transformation presenting as multifocal intraparenchymal CNS disease. The diagnosis was established by histopathologic examination and confirmed through identical T-cell receptor gene rearrangements in the skin and brain lesions. Compared with previously reported cases, our patient demonstrates several unusual features, including multifocal parenchymal involvement, nondiagnostic CSF studies, immunophenotypic evolution with diffuse CD30 expression, and molecular confirmation of clonal relatedness. This case expands the limited literature on CNS dissemination of transformed MF and underscores the importance of

maintaining a high index of suspicion for CNS involvement in patients with MF who develop new neurologic symptoms, regardless of the extent of active cutaneous disease.

Declarations

1. **Funding Declaration: This study was not supported by any funding.**
2. **Conflict of Interest: The authors declare that they have no conflict of interest.**
3. **Ethical approval: For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.**
4. **For this type of study informed consent is not required.**
5. **For this type of study consent for publication is not required.**

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Figures

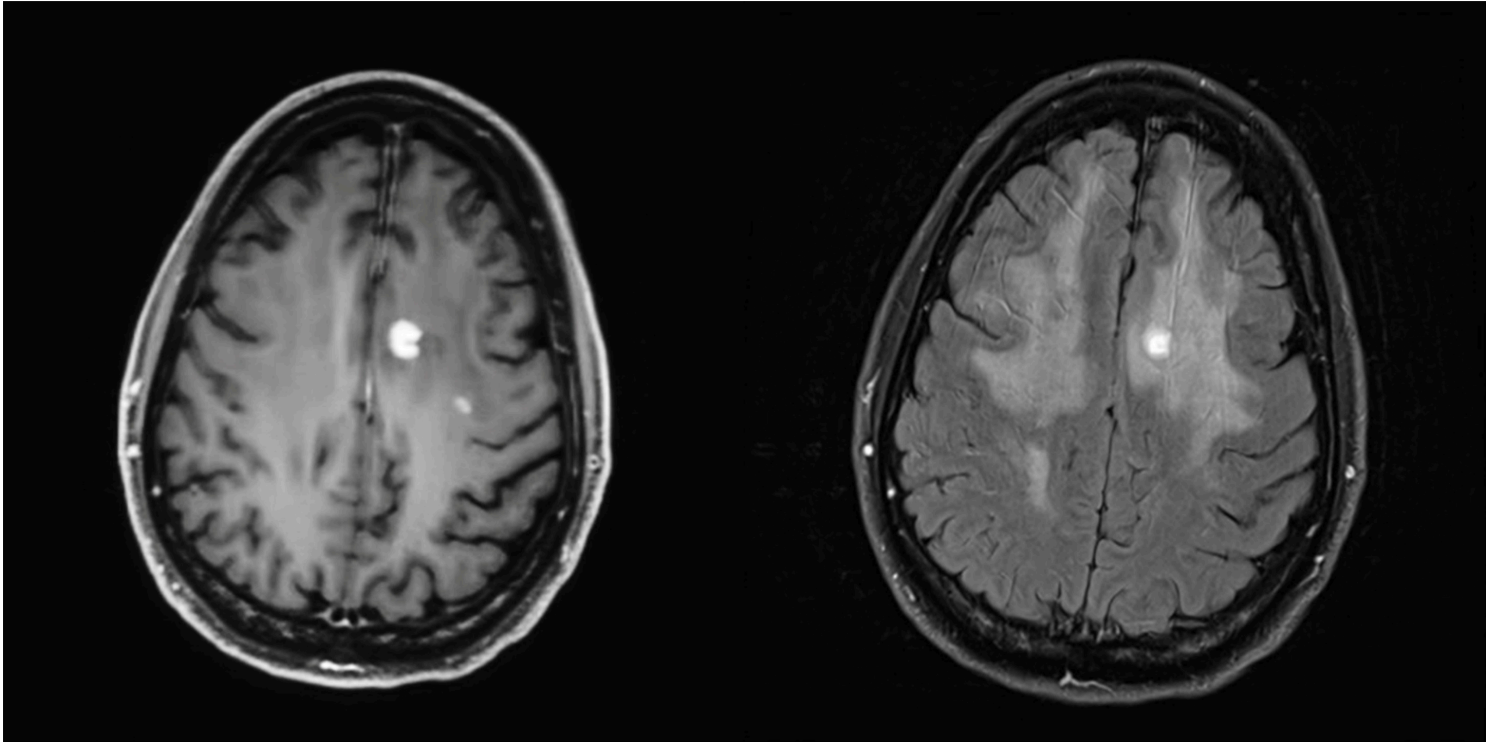


Figure 1

Brain magnetic resonance imaging (MRI) demonstrating multifocal intracerebral lesions. (A) Axial post-contrast T1-weighted image demonstrates multiple bilateral enhancing intracerebral lesions. (B) Axial T2-weighted FLAIR image demonstrates extensive confluent abnormal hyperintensity predominantly involving the bilateral frontal white matter surrounding the enhancing lesions. The left-sided lesion shows comparatively mild surrounding FLAIR hyperintensity. Overall, the multifocal enhancing lesions with associated white-matter signal abnormalities raised concern for central nervous system lymphoma

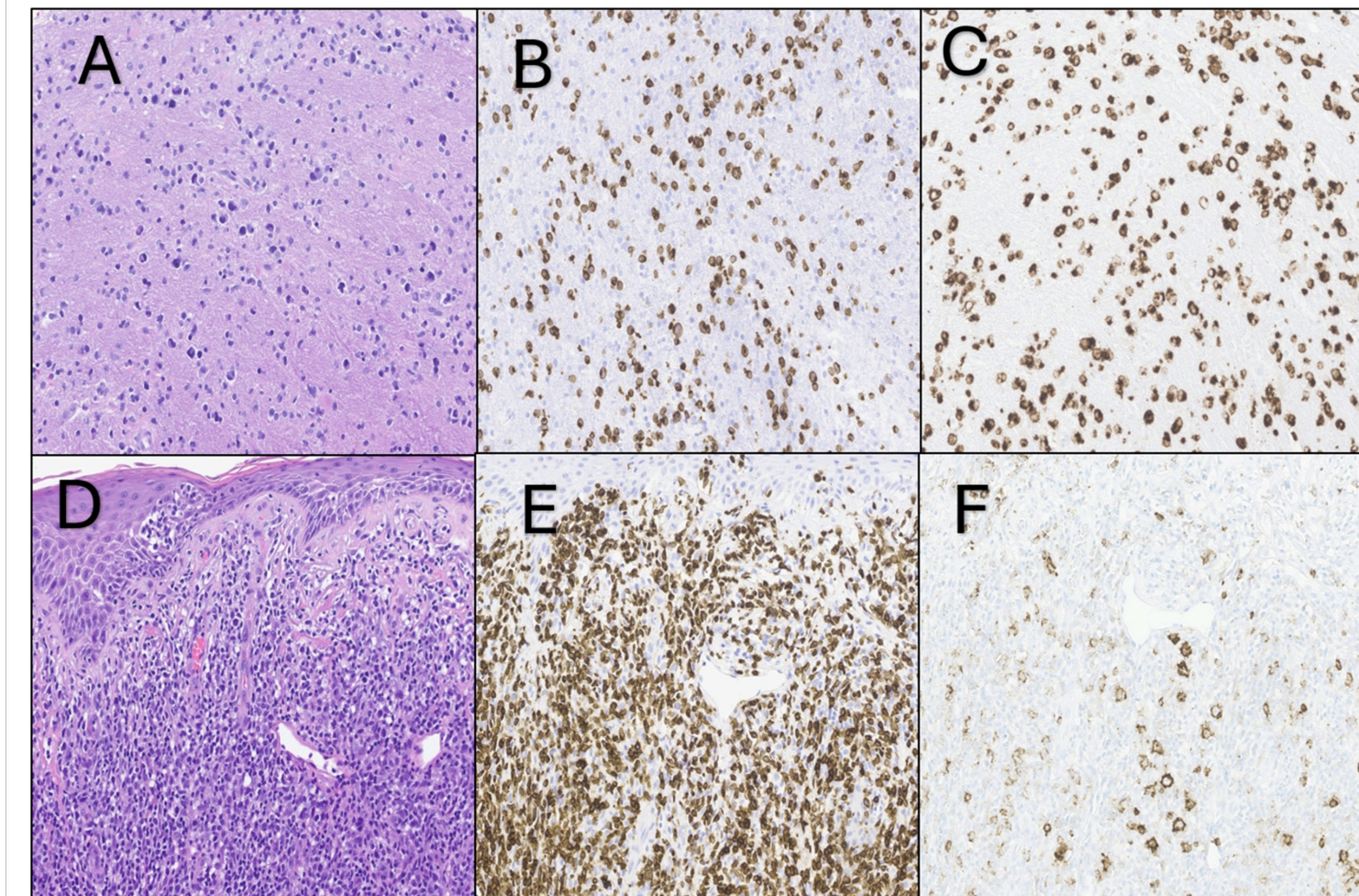


Figure 2

Histopathologic and immunophenotypic features of Mycosis Fungoides with central nervous system involvement. **(A–C)** Brain biopsy: **(A)** Gliotic parenchyma infiltrated by large, atypical lymphoid cells with prominent nucleoli (H&E stain). **(B)** Immunohistochemistry showing diffuse CD3 positivity, consistent with T-cell lineage. **(C)** CD30 staining demonstrates expression in large atypical lymphoid cells. **(D–F)** Skin biopsy: **(D)** Numerous epidermotropic, hyperchromatic lymphocytes and a band-like lymphoid infiltrate in the superficial dermis (H&E stain). **(E)** CD3 positivity in neoplastic T-cells. **(F)** CD30 highlights atypical lymphocytes in the skin.