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Cardiac Involvement in Patients with Mycosis Fungoides: A Narrative Review

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ABSTRACT

Background: Primary cutaneous lymphoma (PCL), specifically mycosis fungoides (MF), is a rare type of non-Hodgkin lymphoma primarily affecting the skin. While MF mostly manifests as skin lesions, it can progress to involve any organ, including the heart. Cardiac involvement in MF is a rare complication associated with poor prognosis, emphasizing the importance of early recognition and intervention. This review aims to explore cardiac involvement in MF and its implications for patient prognosis, providing valuable insights for clinical practice.

Methods: A comprehensive literature search was conducted using PubMed and relevant keywords and Mesh terms. Case reports and editorials evaluating cardiac involvement in patients with MF were included in the study. Furthermore, a thorough examination of the references cited in each study was carried out to identify relevant reports. The cases included in the review were analyzed, and common cardiac manifestations and diagnostic approaches were identified.

Results: This review study found multiple instances of cardiac involvement in patients with MF, characterized by symptoms such as heart failure and arrhythmias. Detecting cardiac involvement in MF necessitates a comprehensive approach that combines different imaging methods like echocardiography, cardiac MRI, and CT scans, along with histopathological analysis.

Conclusion: Cardiac involvement in MF is a rare but serious complication that can manifest with various symptoms and cardiac abnormalities. Routine non-invasive imaging techniques play a crucial role in early detection, even in asymptomatic patients. Timely intervention through personalized management approaches, including surgery, when necessary, can contribute to positive cardiovascular outcomes. This review provides valuable insights for clinical practice in managing cardiac complications in MF.

Keywords: Primary Cutaneous Lymphoma; Mycosis Fungoides; Cardiac Involvement; Prognosis; Diagnosis; Management

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Introduction

Primary cutaneous lymphoma (PCL) is a group of rare non-Hodgkin lymphomas that primarily affect the skin. In this article the main focus is on mycosis fungoides (MF) and Sézary syndrome [1]. Prognosis of MF varies depending on the stage, ranging from a 10-year survival rate of 98% for stage IA (limited patch or plaque) to 30-40% for stage IVA. As the disease progresses slowly, it can extend to involve other organs systemically [2]. The organs most frequently affected, listed in declining prevalence, include lymph nodes (60%), spleen (50%), lungs (43%), liver (41%), bones (27%), kidneys (27%), tongue and mucous membranes (19%), heart (17%), pancreas (17%), and thyroid (14%) [3].

Cardiac involvement is observed in around 33-35% of lymphoma autopsies and given that MF is the most prevalent type of cutaneous T-cell lymphoma, we may encounter it in certain patients [4, 5]. The majority of individuals with myocardial infiltration do not show symptoms; however, in certain instances, extensive infiltration may precede heart failure accompanied by severe symptoms, typically associated with a bleak prognosis [6, 7]. Dermatologists need to be vigilant about early recognition of myocardial infiltration through routine non-invasive imaging techniques, even in asymptomatic MF patients [6].

This review article has a primary focus on exploring the phenomenon of cardiac involvement in MF and its significance in patients' prognoses. This review aims to provide a comprehensive understanding of managing cardiac complications in MF through a comprehensive review of various cases and diverse treatment approaches. It aspires to offer insights that can be applied in real-world clinical practice, thereby enhancing the care and outcomes of individuals affected by this complex condition.

Methods

We conducted a comprehensive exploration on PubMed, utilizing pertinent keywords and corresponding Mesh terms. Inclusion criteria: Case reports including patients with MF and cardiac Involvement were included. Review articles, conference, abstracts, book chapters, studies on animal subjects, and non-English articles were excluded from this review. Furthermore, a meticulous analysis of the references cited in each study was undertaken to identify relevant research and reports. Our study incorporated case reports and editorials assessing cardiac involvement in individuals with MF.

Metastatic cardiac masses

Cardiac Masses in Mycosis Fungoides

Cardiac masses are a specific manifestation of cardiac involvement in Mycosis Fungoides (MF). Among the cases included in this study, we identified 2 cases that explicitly mentioned cardiac masses in MF patients:

1. A 69-year-old woman with a 17-year history of MF presented with a large cardiac mass obstructing both the right atrium and the drainage orifice of the inferior vena cava [6]. The patient underwent cytoreductive surgery to address tumor invasion into the atrial wall, IVC, and pericardium. This intervention successfully relieved her heart failure symptoms. Follow-up care included adjuvant radiotherapy and various chemotherapy agents. Remarkably, six years post-surgery, there was no tumor recurrence, and heart failure symptoms had disappeared.

2. While not explicitly described as a mass, a 53-year-old man with MF showed left ventricle thickening, which could potentially represent a diffuse cardiac mass [9]. This patient with left ventricle thickening had a poor outcome. Despite no evidence of coronary artery disease, he experienced episodes of ventricular tachycardia. Tragically, resuscitation attempts failed, and a post-mortem examination confirmed widespread T-cell lymphoma infiltration in the heart.

Cardiac masses in MF are rare, and these cases represent a small subset of MF patients with cardiac involvement. These cases highlight the variable prognosis of cardiac masses in MF. While aggressive treatment can lead to positive outcomes in some cases, others may have a rapidly progressive course with fatal outcomes [11, 12]. Metastatic cardiac tumors usually arise from lung, breast, renal cancer, and lymphomas [13]. The term "secondary cardiac involvement" describes the spread of cancerous cells from an initial site outside the heart to the heart. It can happen in a variety of systemic lymphomas, including Hodgkin and non-Hodgkin lymphomas (as well as the uncommon MF) [6, 14]. The heart can become infiltrated by lymphoma cells, which can result in cardiac masses. Different areas of the heart may be affected, either locally or more widely [15].

In cardiac masses, both ventricles, right atrium, and interventricular septa can be affected [8] but, in many reports, it has been observed that the majority of intracavital tumors manifest on the right side of the heart, although the underlying cause for this phenomenon remains to be determined [16]. Ventricular tachycardia and acute heart failure are correlated with an unfavorable prognosis. Myocardial infiltration has the potential to impede blood flow between the atrium and

right ventricle, leading to the onset of right-sided heart failure [6]. If cardiac symptoms are seen in a patient with MF, neoplastic cell infiltration to the heart should be considered, even without a detectable mass lesion [8].

While the exact mechanism by which lymphoma cells spread to the heart in MF is not fully understood, it is clear that cardiac involvement is a serious complication that occurs in the advanced stages of the disease [6].

According to the location and extent of cardiac mass involvement in MF, cardiac symptoms can vary [17]. Patients can experience symptoms such as chest pain, shortness of breath, palpitations, arrhythmias, or cardiac complications [18]. Cardiac involvement can be asymptomatic and detected only by routine imaging studies or autopsies in some cases [7, 18]. Imaging studies such as echocardiography, cardiac magnetic resonance imaging (MRI), or computed tomography (CT) can assess the dimensions, placement, and potential influence of cardiac masses [19, 20].

Cardiac involvement presentation in MF

Cardiac involvement in MF can manifest with various symptoms. It is a rare occurrence in MF, but when present, it can cause specific cardiac manifestations. Patients may experience cardiac dysfunction, which can manifest as heart failure, decreased cardiac output, or impaired cardiac function [8]. Although patients with cardiac involvement are usually asymptomatic, the symptoms that some patients show can be influenced by the unique characteristics and comprehensive medical history of each.

Cardiac Involvement Presentation in MF Cardiac involvement in Mycosis Fungoides (MF) is rare but can manifest with various symptoms and complications. We can categorize these manifestations into three main groups:

A. Major Cardiovascular Adverse Events

1. **Heart Failure**: A 69-year-old woman with a 17-year history of MF experienced acute heart failure with right-sided symptoms. Examination revealed a large cardiac mass obstructing the right atrium and inferior vena cava drainage [6]. A 72-year-old female presented with symptoms of heart failure, including cough, tachycardia, and hypertension. Diagnostic findings showed left ventricular hypertrophy, massive pericardial effusion, reduced LVEF, and moderate mitral regurgitation [7].

2. **Arrhythmias**: A 53-year-old man with MF experienced episodes of ventricular tachycardia, despite no evidence of coronary artery disease [9]. A 66-year-old woman developed AV block with broad ventricular complexes [10].

3. **Sudden Cardiac Events**: The 53-year-old man mentioned above suffered cardiac arrest, and resuscitation attempts failed [9].

B. Infiltration of Myocardium with Tumoral Cells

1. **Direct Cardiac Infiltration:** A 43-year-old male with MF showed cardiac involvement characterized by atypical lymphocytic infiltration in the cardiac muscle, leading to sustained ventricular tachycardia [8]. Post-mortem examination of the 53-year-old man confirmed widespread T-cell lymphoma infiltration in the heart [9].

2. **Cardiac Masses:** The 69-year-old woman had a sizable cardiac mass obstructing both the right atrium and the drainage orifice of the inferior vena cava [6].

3. **Structural Changes:** The imaging of the 53-year-old man revealed left ventricle thickening and weakened contractions [9]. The 66-year-old woman showed irregularities and reduced contractility in the ventricular walls, particularly in the inferior and apical regions [10].

Common Findings: Across these categories, common manifestations included: Symptoms: Shortness of breath, fatigue, chest pain, dizziness, and near-fainting - Clinical signs: Tachycardia, hypertension, and hypotension - Laboratory findings: Elevated BNP, AST, ALT, and troponin levels - Imaging results: Abnormal ECGs, reduced ejection fraction, and various structural abnormalities It's important to note that while some patients present with clear symptoms, others may be asymptomatic, with cardiac involvement only detected through routine imaging or post-mortem examination. Clinicians should be alert to unexplained tachyarrhythmias, conduction disturbances, low voltage ECG readings, and unexplained cardiac enlargement as potential indicators of cardiac involvement in MF patients [13].

The details of the included case reports are presented in Table 1.

Diagnosis of cardiac involvement in MF

Physicians face a considerable challenge in diagnosing cardiac involvement in MF. The rarity of this condition, along with its diverse clinical presentations and the fact that it is often asymptomatic according to autopsies, adds to the complexity of the diagnosis [7]. Despite advancements in the combination of chemotherapy treatments, the overall prognosis for secondary cardiac involvements remains bleak. A significant contributing factor to this outcome is the delay in diagnosing the condition. Therefore, it is vital to maintain a high level of attentiveness and promptly identify any early indications of cardiac involvement, particularly with the aid of imaging techniques [21].

Table 1. Overview of the case reports incorporated in our article.

Author, Year	Case Description	Management	Cardiovascular Findings	Diagnostic Methods	Outcome
Borderías Villarroel T, 2022 [6]	69-year-old woman with 17-year history of MF; presented with dyspnea on moderate exertion.	Corticosteroids, psoralen + UVA, skin radiotherapy, chemotherapy (gemcitabine + oxaliplatin, 6 cycles).	Narrow QRS, T-wave inversion in III/aVF, cardiac mass extending into right atrium and obstructing IVC drainage.	Transthoracic echo, TEE, cardiac MRI, intraoperative histology.	Cytoreductive surgery + radiotherapy led to favorable cardiovascular recovery.
Tabata T, 2018 [7]	72-year-old woman with 17-year history of MF; presented with cough, tachycardia, hypertension, and hypoxemia.	UVB, psoralen + UVA.	Sinus tachycardia, LV enlargement, pericardial effusion, reduced LVEF, moderate MR, nodular enhancement of LV wall.	Cardiac MRI.	Pericardial drainage performed; patient died after 3 weeks. Autopsy revealed MF metastases in epicardium, myocardium, and pleura.
Kaku Y, 2015 [8]	43-year-old man with 2-year history of widespread ichthyosis; malaise and night sweats for 3 months.	Gemcitabine, fluorometholone eye drops, chemotherapy.	Ventricular tachycardia; lymphocytic infiltration of myocardium.	Endomyocardial biopsy of septum, immunohistochemistry	Treated with amiodarone; cardiac function did not improve. Multiple umbilical cord blood transplantations attempted.
Carrilho-Ferreira P, 2014 [9]	53-year-old man with MF; presented with fever, dizziness, presyncope, and hypotension.	Not specified.	Ventricular tachycardia, diffuse ST depression, elevated troponin; LV wall thickening and reduced contractility.	Clinical + imaging assessment.	Resuscitation unsuccessful; autopsy showed diffuse T-cell lymphoma infiltration of heart.
Sleigh KA, 2007 [10]	66-year-old woman with 12-year history of MF; symptoms included fatigue, chest pain, dyspnea, left arm pain, weakness, and dizziness.	Steroids, UVA therapy, single dose localized radiotherapy.	Bradycardia, AV block, T-wave inversion in inferior leads, ST elevation in V3–V4.	Coronary angiogram (normal), ventricular wall abnormalities, endocardial biopsy confirmed MF (CD3+, CD4+; negative for CD8, CD20).	Temporary pacemaker placed; rapid deterioration; patient died before targeted therapy.

PMH: Past medical history, SOB: Shortness of breath, MRI: Magnetic resonance imaging, TEE: Transesophageal echocardiography

A comprehensive approach that integrates multiple diagnostic modalities is necessary to detect cardiac involvement in MF [14]. Although Cardiac involvement in mycosis fungoides (MF) is uncommon and tends to appear more in advanced stages, it can occur at any stage. Its presentation varies depending on factors such as tumor location and extent of invasion. Symptomatic cardiac manifestations are rare and are often discovered incidentally in about 20-25% of lymphoma cases during autopsy [6]. Based on the case studies, routine cardiac evaluations for all MF patients may not be necessary but could benefit certain high-risk groups. Cardiac involvement in MF generally appears in advanced disease stages, particularly in patients with a long history of MF or comorbidities. Age and extended disease duration, such as over a decade, were common factors among those with cardiac manifestations. Patients with prior chemotherapy may also be more vulnerable to cardiac complications. Therefore, cardiac screening may be more beneficial for older MF patients, those in advanced disease stages, or those with significant comorbidities.

Echocardiography is an effective and convenient imaging method for accurately detecting cardiac tumors which can be easily conducted at the patient's bedside. It should be considered as a recommended protocol for screening MF patients for heart disease by defining baseline cardiac evaluation for all newly diagnosed MF patients, regular cardiac follow-ups for asymptomatic patients, and immediate cardiac evaluation for patients developing any cardiac symptoms. Transthoracic echocardiography (TTE) reveals important details about tumor characteristics, whereas transesophageal

echocardiography (TEE) is particularly advantageous in visualizing small and posterior tumors [13].

ECG-gated computed tomography (CT) and magnetic resonance imaging (MRI) are also two key imaging modalities used in the diagnosis and management of cardiac infiltration [14, 22]. They can distinguish between benign and malignant cardiac masses by evaluating calcification, fat content, and small lesions. They are effective in staging malignant tumors and can identify lymphomas based on the homogeneity of a mass due to compact cellularity. MRI's post-contrast sequences enhance the visualization of tumor vascularity and help define tumor borders. Furthermore, multi-detector CT and MRI are vital in distinguishing between thrombi and cardiac tumors [23].

Although imaging plays a significant role in diagnosing cardiac involvements, histopathology remains the preferred and most reliable diagnostic method [14]. Immunohistochemical and histopathological analyses can confirm the infiltration of myocardial muscle by peripheral T-cell lymphoma with the immunophenotype of MF. Neoplastic T cells in MF typically express CD4+ but may show variable loss of other T-cell markers, including CD2, CD3, CD5, CD7, and CD26. A CD8+ T-cell phenotype is detected in around 20% of cases. A monoclonal T-cell receptor (TCR) gene rearrangement may also suggest an early-stage MF diagnosis [6, 7, 24].

Management of MF patients with cardiac involvement

Management is based on primary tumors and is personalized. For patients with intracavitary metastases resulting in significant hemodynamic complications and cardiac decompensation, resection is the best option [6].

The treatment of cardiac masses caused by MF is customized and focused on the fundamental condition. MF is a rare cause of gigantic cardiac mass that has been identified as a possible cause of cardiac mass due to its visceral development [6, 25]. MF is a low-grade lymphoma that, when advanced, can cause cardiac tamponade due to epicardial infiltration [26]. Radiation therapy, immunotherapy, and topical or systemic chemotherapy are available treatments for MF. When the cardiac mass results in substantial blockage or hemodynamic impairment, surgery may be recommended in some cases [6].

In Borderias et al. study [6], the 69-year-old woman, with a history of 17-year MF, previously received corticosteroids and skin radiotherapy for two years, along with a six-cycle chemotherapy a year earlier. While hospitalized, underwent cytoreductive surgery to address tumor invasion into the atrial wall, IVC, and pericardium, relieving heart failure symptoms. Adjuvant radiotherapy was administered, and various chemotherapy agents and decompressive radiotherapy were attempted over the following year. Additionally, radiotherapy and topical chlormethine were explored. Subsequent follow-ups revealed no tumor recurrence, and heart failure symptoms vanished six years post-surgery.

In Tabata et al. study [7], the 72-year-old woman, who had a 12-year history of MF, underwent NB-UVB, psoralen, and PUVA light therapy for plaque-stage MF. Hospitalization included pericardial drainage for heart failure and substantial pericardial effusion. DE-MRI revealed numerous nodular enhancements on the left ventricle wall. Heart failure developed rapidly due to severe MR, LV asynergy, and LV dysfunction. She died after 3 weeks of hospitalization. The autopsy reported metastatic lesions on the epicardium, myocardium, and pleura. The histopathology result demonstrated myocardial infiltration by MF.

In Kaku et al. study [8], the patient in this case had stage IVB mycosis fungoides, characterized by dual CD4/CD8-positive ichthyosiform MF, along with lymph node, peripheral blood, and cardiac involvement and was successfully treated with gemcitabine, leading to the resolution of ichthyosis. Subsequent administration of fluorometholone eye drops and chemotherapy resulted in the disappearance of uveitis. Because of ventricular tachycardia, amiodarone was applied. However, his cardiac dysfunction remained after chemotherapy. He also took umbilical cord blood transplantation several times.

In Sleigh et al. study [10], the 66-year-old woman, who had been successfully treated with a combination of steroids and PUVA therapy for MF, was admitted due to fatigue and radiating left chest pain. A coronary angiogram during hospitalization revealed anomalies in the dye pattern on the inferior and apical walls, along with infero-apical hypokinesis. In response to bradycardia and atrioventricular block, a pacemaker was inserted. However, her disease rapidly developed. Before any special intervention, she passed away.

Monoclonal antibody therapy such as alemtuzumab, recently is used in the management of MF. Alemtuzumab is a humanized monoclonal antibody that Targets CD52 which is expressed on the surface of T-cells. The mechanism of this antibody is binding to cell surfaces and causing lysis of tumor cells [27, 28].

In Ferreira et al. study [9], the 53-year-old man with a history of 15 years of MF was referred with fever, dizziness, and pre-syncope. Transthoracic and transesophageal echocardiography demonstrated LV concentric hypertrophy and diffused hypokinesia.

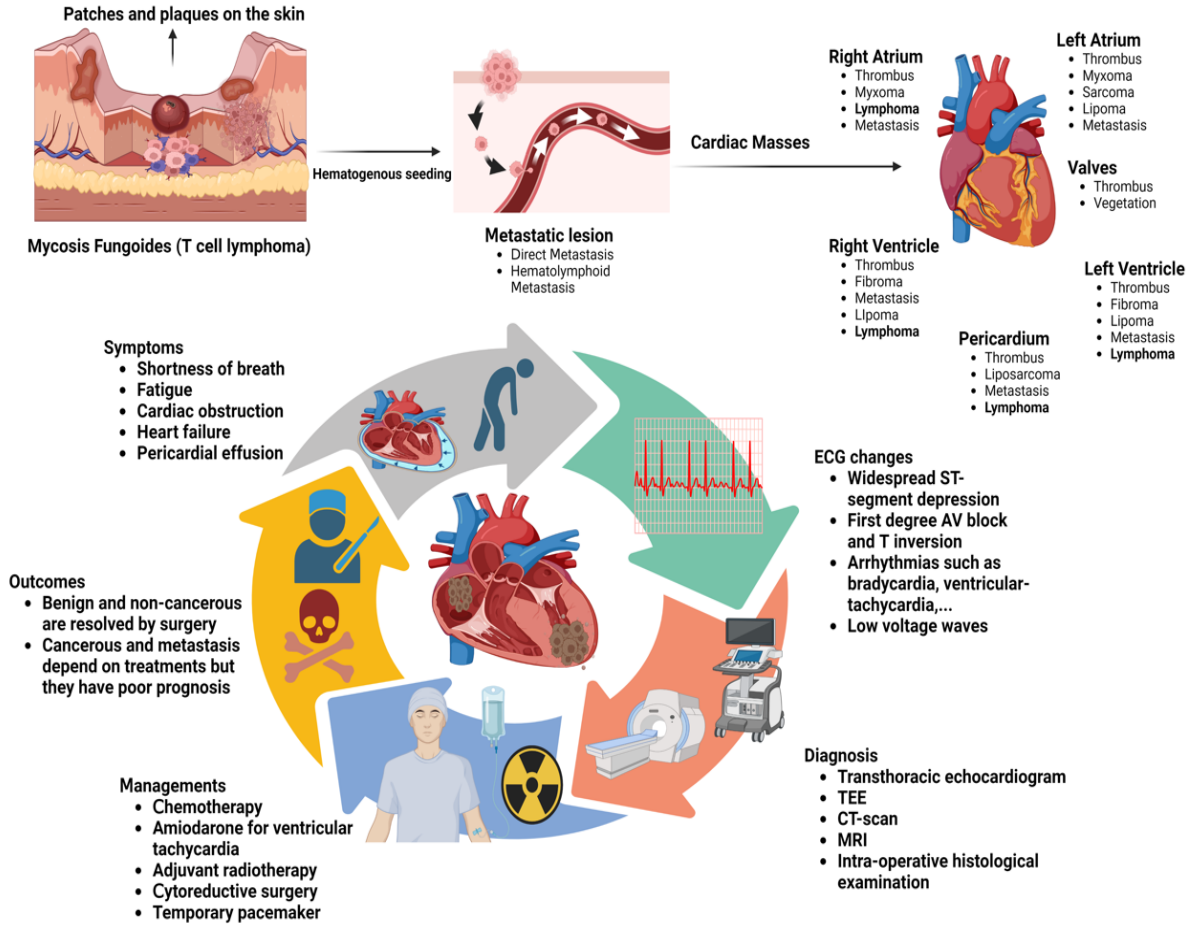

Figure 1. Cardiac involvement in MF.

Cardiac MRI identified mass infiltration on the pericardium and LV myocardium. After 15 days of hospitalization, several MVT occurred. Although he needed electrophysiology interventions, he died due to cardiac arrest. Histological reports showed T-cell lymphoma infiltration.

In conclusion, Management of MF with cardiac involvement is individualized, primarily addressing the underlying condition. Surgical resection may be necessary for intracavitary metastases causing hemodynamic complications. Radiation therapy, immunotherapy, and chemotherapy are available treatments, with surgery considered in cases of significant blockage or hemodynamic impairment. Monoclonal antibody therapy, like alemtuzumab, has also shown promise in MF management. Cardiac involvement in MF, symptoms, diagnosis, and management is demonstrated in Figure 1.

Conclusion

We, as healthcare practitioners and researchers, assert that this review underscores the potential importance of incorporating regular cardiac examinations and advanced imaging techniques into the multifaceted management of mycosis fungoides to potentially prevent sudden cardiac deaths, even in asymptomatic patients. Several case studies illustrate the diverse clinical courses and treatment strategies for MF patients with cardiac involvement, emphasizing the need for a personalized approach. Ultimately, early detection and tailored management strategies are essential for improving outcomes in these challenging cases.

Based on these potential considerations, we suggest that integrating regular cardiac evaluations into the care of MF patients might be crucial for identifying and addressing potential cardiac complications. This approach may, hypothetically, reduce the risk of sudden cardiac deaths and, theoretically, optimize overall patient care.

Conflict of interest

The authors declare no conflict of interest.

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Author's Contributions

Maryam Abdolmaleki and Saba Maleki searched and prepared the primary draft of the manuscript.

Sahar Dadkhahfar and Ifa Etesami contributed to the review and revision of the manuscript. Sahar Dadkhahfar served as the corresponding author and was responsible for coordinating the revision process and the final approval of the manuscript. All Authors read and approved the final version of the manuscript.

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