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Dermatologic Manifestations of Cardiac Sarcoidosis: Diagnostic Significance and Clinical Implications

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ABSTRACT

Cardiac sarcoidosis, a complex and often insidious systemic granulomatous disease, presents a myriad of dermatologic manifestations that may precede or coincide with cardiac involvement, serving as pivotal diagnostic indicators. However, the comprehensive spectrum of these cutaneous findings and their diagnostic significance in the context of cardiac sarcoidosis warrant a more in-depth exploration. This qualitative review embarks on a meticulous synthesis of qualitative evidence drawn from a multitude of sources, including extensive case reports, case series, and histopathological studies. Through a meticulous examination of the diverse dermatologic manifestations observed in patients with cardiac sarcoidosis, ranging from erythema nodosum and lupus pernio to less recognized presentations such as scar sarcoidosis and hypopigmented macules, this review aims to unravel the intricacies of these dermatologic clues. Moreover, it addresses the nuanced histopathological features underlying these cutaneous manifestations, shedding light on their diagnostic specificity and clinical relevance. By analyzing the myriad dermatologic phenotypes of cardiac sarcoidosis, this review not only aims to enrich clinicians' understanding but also strives to empower them with the knowledge to recognize and interpret these dermatologic clues effectively. Such insights are pivotal in facilitating timely referral for cardiac evaluation and instituting appropriate therapeutic interventions, ultimately enhancing patient outcomes in the challenging landscape of cardiac sarcoidosis management.

Keywords

Cardiac Sarcoidosis, Dermatologic Manifestations, Granulomatous Skin Lesions, Cutaneous Sarcoidosis, Diagnostic Challenges.

Introduction

Cardiac sarcoidosis (CS) is a multifaceted and elusive systemic granulomatous disease characterized by the formation of non-caseating granulomas in various tissues, including cardiac muscle. This disease can manifest in several ways, most commonly affecting multiple organs such as the lungs, lymphatic system, eyes, and skin. The development of granulomas in the myocardium, which are mainly composed of multinucleated giant cells encircled by lymphocytes, clusters of macrophages, and epithelioid cells, is thought to be the pathophysiology behind the development of CS. The disruption of normal myocardial structure and function by these granulomas can result in abnormalities in the heart's

conduction system and lead to serious complications including arrhythmias, heart block, heart failure, and sudden cardiac death [1,2]. Although the precise mechanisms causing granuloma formation are still unknown, an exaggerated immune response to an unidentified antigen is thought to be involved. The prevalence of CS is difficult to determine due to being frequently asymptomatic and the variability in its clinical presentation. However, it is estimated that approximately 5% of patients with sarcoidosis have some clinical manifestations of cardiac involvement, and that 25-30% of patients may have asymptomatic cardiac involvement [3]. Some studies suggest the prevalence of silent myocardial involvement may be significantly higher, as myocardial damage from sarcoidosis has been found in 20-60% of patients at autopsy. These studies highlight the challenges in early detection and the need to improve detection methods.

Dermatological manifestations of sarcoidosis often serve as early diagnostic indicators of systemic and cardiac involvement. Given the visibility of dermatological manifestations to the naked eye and easy biopsy potential, the skin provides a non-invasive means of obtaining diagnostic tissue. Approximately 25% of sarcoidosis patients present with skin manifestations, including erythema nodosum, lupus pernio, and maculopapular eruptions [4]. These clinical signs are among the most obvious and accessible indicators of sarcoidosis, often prompting further investigation into the potential of systemic involvement. By identifying these dermatologic symptoms early, cardiac sarcoidosis can be diagnosed and treated promptly, potentially preventing serious cardiac complications.

The full range and diagnostic significance of cutaneous findings in cardiac sarcoidosis require thorough exploration. Several barriers exist in utilizing dermatologic manifestations for early detection of CS. The variability and subtlety of skin lesions can lead to misdiagnosis or under-recognition, delaying appropriate investigation. Additionally, there is a lack of widespread awareness among healthcare providers regarding the link between specific dermatologic signs and cardiac sarcoidosis. Dermatologists have the potential to play a pivotal role in the multidisciplinary management of sarcoidosis, as they are often the first to identify these cutaneous manifestations. However, limited access to dermatologic expertise in some healthcare settings can hinder timely and accurate diagnosis. Through an in-depth analysis of the various dermatologic phenotypes associated with cardiac sarcoidosis, this review seeks to enhance clinicians' understanding and equip them with the knowledge to accurately recognize and interpret these skin signs. By examining diverse dermatologic manifestations in patients with cardiac sarcoidosis ranging from erythema nodosum and lupus pernio to less common presentations like scar sarcoidosis and hypopigmented macules this review aims to elucidate the complexities of these dermatologic clues. It also delves into the detailed histopathological features of these dermatologic manifestations, describing their diagnostic specificity and clinical importance. By addressing these barriers and enhancing awareness, this review aims not only to enrich clinicians' understanding, but also strives to empower them with the knowledge to recognize and interpret these dermatologic clues effectively. This approach is pivotal in facilitating timely referral for cardiac evaluation and instituting appropriate therapeutic interventions, ultimately enhancing patient outcomes in the challenging landscape of cardiac sarcoidosis detection and management.

Skin Manifestations in Systemic and Cardiac Sarcoidosis

Variations of Demographic and Dermatologic Manifestations

The spectrum of skin manifestations in systemic and cardiac sarcoidosis is diverse and can serve as critical diagnostic indicators of the underlying disease. Skin lesions are among the initial findings in 30% of patients with systemic sarcoidosis, with the skin often being cited as the second most commonly involved organ [3]. Skin manifestations in sarcoidosis tend to be more prevalent in specific patient populations, with studies showing a higher prevalence in females and higher rates of extracutaneous involvement, particularly cardiac, in African-American patients [5]. A study utilizing medical records from the Mass General Brigham Hospital analyzed 50 biopsy-proven cases of cutaneous sarcoidosis to examine demographic and extracutaneous involvement [6]. The findings revealed that African-American patients were 1.7 times more likely to be diagnosed with extracutaneous, cardiac involvement compared to caucasian patients. These findings highlight the diagnostic importance and demographic variations of skin manifestations in sarcoidosis.

Extracutaneous manifestations of cardiac sarcoidosis can present in various forms. The diverse spectrum of cutaneous lesions serves as critical indicators of systemic and cardiac involvement and underscores the need for heightened awareness and tailored diagnostic approaches, especially for demographic groups more likely to present with extracutaneous involvement of sarcoidosis. The most common dermatologic findings in systemic sarcoidosis are erythema nodosum and lupus pernio [5,7]. Less common cutaneous manifestations include scar sarcoidosis and hypopigmented macules, and even more rarely, nail involvement and Sweet Syndrome. Understanding the range of dermatologic manifestations is crucial for early diagnosis and intervention in cardiac sarcoidosis. Recognizing these skin lesions can lead to timely and appropriate management, improving patient outcomes.

Erythema Nodosum

Erythema Nodosum (EN) is one of the most common skin manifestations of sarcoidosis. EN, a form of panniculitis, presents as rounded, slightly raised nodules with erythema and are typically found on the anterior surfaces of the lower extremities [8]. Although these nodules are typically asymptomatic, some patients may experience mild tenderness. Histologically, EN lesions demonstrate inflammation of the septa between subcutaneous fat lobules, the absence of vasculitis, and the presence of noncaseating granulomas. While EN can be self-limited, further investigation for systemic diseases, such as sarcoidosis is essential for vigilant patient management. To illustrate the clinical significance and diverse presentations of erythema nodosum in sarcoidosis, case studies provide detailed insights into the diagnostic and management

challenges associated with this condition. Cotrim et al. described a severe case of cardiac sarcoidosis in a 57-year-old female presenting with sustained monomorphic ventricular tachycardia that rapidly progressed to hemodynamic instability [9]. After cardioversion and stabilization, a physical examination revealed skin lesions on her lower limbs consistent with EN. A skin biopsy confirmed EN, and cardiac imaging with endomyocardial biopsy confirmed cardiac sarcoidosis. Another case involved a 57-year-old female who presented with acute tender nodules on her calves, which were biopsied and identified histologically as sarcoid granulomas [10]. Further investigation revealed the involvement of her eyes and lungs, confirming Löfgren's syndrome–a triad of EN, sarcoidosis, and hilar lymphadenopathy on chest x-ray. A chronic sarcoidosis case reported by Krasowska et al. demonstrated polymorphous cutaneous presentation and multisystem involvement. A 56-year-old female had skin, eye, bone, heart, and lung disease over 10 years, initially presenting with EN and bilateral hilar adenopathy. Her cutaneous changes included annular plaques on the shins, nodules on both upper and lower extremities, and tender nodules on the shins, histologically confirmed as EN [8]. These cases highlight the common presentation of erythema nodosum (EN) on the lower extremities, but they also showcase atypical presentations on the upper extremities. These cases underscore the importance of investigating underlying systemic diseases whenever EN is detected, regardless of its location. Sarcoidosis is a known trigger for EN, and a thorough clinical evaluation, including laboratory tests and imaging studies, is essential for diagnosing the underlying cause. Early identification and management of the associated systemic disease can significantly impact patient outcomes and help prevent further complications.

Lupus Pernio

Lupus pernio (LP) is a chronic, disfiguring form of cutaneous sarcoidosis characterized by violaceous nodules and plaques, primarily affecting the nose, cheeks, ears, and digits, and can progressively infiltrate underlying structures such as cartilage and bone [11,12]. The prevalence of LP in CS ranges from 2.7% to 11.8% and is more common in females of African and Asian descent [6,7,13]. Although LP is a rarer manifestation, it is the most characteristic skin lesion of sarcoidosis and is frequently linked with more severe and chronic forms of the disease. Histopathological diagnosis of LP involves the presence of noncaseating epithelioid cell granulomas with a variety of Langerhans giant cells. Several case reports have been published denoting the relationship between LP and systemic sarcoidosis. A case report of a 34-year-old male with no significant past medical history presented with facial swelling, nodules on the nose, cheeks, and ears, as well as purpuric purple lesions on the right leg that had slowly evolved over eight years [14]. A biopsy revealed epithelioid granulomas surrounded by a noncaseating inflammatory crown, confirming the diagnosis of lupus pernio and prompting further investigation for systemic sarcoidosis. This patient was found to have destructive arthropathy and bone erosions within the joints of his hands and feet on x-ray; an ultrasound of these same regions shows inflammatory synovitis, tenosynovitis, and dactylitis. A CT scan of the chest showed several bilateral micronodules on both lungs, confirming the diagnosis of systemic chronic sarcoidosis. Although this patient did not have sarcoidosis with cardiac involvement at the time of diagnosis, close follow-up with an echocardiogram should be considered since cardiac sarcoidosis can be clinically silent and life-threatening. Early recognition and treatment of LP are crucial to prevent cosmetic disfigurement and psychological impact, as well as to manage and monitor systemic involvement. Clinicians should maintain a high index of suspicion for cardiac involvement in patients presenting with LP, ensuring comprehensive evaluation and management to mitigate the risk of severe cardiac complications.

Scars and Previous Trauma

Sarcoidosis can manifest in old scars and areas of previous trauma, a condition known as scar sarcoidosis. This rare cutaneous form can develop in scars from various causes, including mechanical trauma, surgery, tattoos, and infections [15-17]. Histopathological examination of these lesions reveals noncaseating granulomas. Cases have been reported where scar sarcoidosis led to the diagnosis of systemic sarcoidosis, including pulmonary and cardiac involvement, emphasizing the importance of considering sarcoidosis in patients with spontaneous changes in scar appearance [18,19]. Kocak et al. describe a patient with scar sarcoidosis on the forehead [15]. The scar was acquired from a fall 30 years prior and had no concerns until the appearance suddenly changed. The patient was found to have bilateral mediastinal lymphadenopathy on high-resolution CT, indicative of systemic involvement of sarcoidosis. Similarly, another case involved a woman whose scar sarcoidosis led to the diagnosis of stage II pulmonary sarcoidosis [19]. Recognizing scar sarcoidosis is crucial for early diagnosis and management of potential systemic sarcoidosis to improve patient outcomes. Furthermore, timely intervention can prevent the progression of systemic involvement and reduce the risk of long-term complications. Given the potential for scar sarcoidosis to signal underlying systemic disease, clinicians should maintain a high index of suspicion and promptly investigate any suspicious changes in scar appearance.

Hypopigmented Macules

Hypopigmented macules can be an unusual but notable dermatological manifestation in patients with CS. Hypopigmented macules localized above deep dermal and subcutaneous sarcoid granulomas have been documented, with sparse melanin distribution in the upper stratum malpighi, suggesting a visual vignette of sarcoidal montage requiring diagnostic biopsy [20]. Biopsies of hypopigmented skin in suspected sarcoidosis cases have been instrumental in addressing diagnostic challenges, as sarcoidal granulomas have been identified in the hypopigmented skin of several patients. The hypopigmented macules can present in various forms, such as asymptomatic patches on the buttocks and legs, which may not respond to topical treatments like steroids or antifungals. In some cases, these macules are associated with other conditions, such as mycosis fungoides, which can present similarly but require different management [21]. The presence of hypopigmented macules in sarcoidosis can sometimes be confused with other dermatological conditions like Bier spots,

which are asymptomatic and histologically normal [22], or with conditions like tinea versicolor and morphea [23]. These varying etiologies highlight the need for differential diagnosis through biopsy. The histological examination of these macules often reveals psoriasiform hyperplasia and epidermotropism of atypical lymphocytes, which can also be mistaken for other dermatological conditions [24]. Therefore, recognizing hypopigmented macules as a potential cutaneous manifestation of sarcoidosis, especially in the context of systemic involvement, is crucial for timely and accurate diagnosis and management. This comprehensive understanding underscores the importance of dermatological evaluation and biopsy in patients presenting with such skin lesions to rule out or confirm sarcoidosis and guide appropriate treatment strategies.

Nail Involvement and Other Manifestations

Nail involvement in sarcoidosis is a significant indicator of systemic and cardiac sarcoidosis. Nail changes in sarcoidosis can include dystrophy, onycholysis, subungual hyperkeratosis, nail hyperkeratosis, and longitudinal ridging, and are frequently accompanied by bony cysts on radiological examination [25,26]. These nail abnormalities, which can be identified radiographically, should prompt a thorough evaluation for systemic involvement, including cardiac assessment, as sarcoidosis can affect multiple organ systems. Patients may not recognize changes in their nails as a sign of systemic involvement, but these signs can be critical for providers in diagnosing underlying conditions. A 53-year-old woman with ocular and cutaneous sarcoidosis exhibited nail dystrophy and bony cysts, indicating the need for systemic evaluation [27]. Similarly, a 37-year-old woman with pulmonary sarcoidosis presented with nail changes, and histopathological examination confirmed granulomas, pointing to the chronic nature of the disease and the necessity for systemic screening [28]. Imaging of hands, feet, and chest is crucial in suspected cases to evaluate for bone cysts and potential pulmonary involvement, which can be indicative of broader systemic issues, including cardiac sarcoidosis. These imaging techniques can reveal the extent of the disease and help tailor a more effective treatment plan. Nail involvement can sometimes be the presenting feature of sarcoidosis, necessitating a comprehensive systemic evaluation even in the absence of other cutaneous signs. This initial sign can often be a crucial hint, leading to the discovery of more extensive disease. Treatment with corticosteroids has shown improvement in nail changes, but the presence of nail dystrophy should always prompt a detailed investigation for systemic involvement, including cardiac assessment, to manage the disease effectively [29,30]. Recognizing nail involvement in sarcoidosis is crucial for early detection and management of potential systemic involvements, including cardiac sarcoidosis, to improve patient outcomes. Early identification and treatment can significantly reduce morbidity and prevent the progression of the disease. Providers should maintain a high index of suspicion for systemic involvement when encountering nail abnormalities in sarcoidosis patients. A multidisciplinary approach, involving dermatologists, cardiologists, and other specialists, is essential to ensure comprehensive care. Through vigilant monitoring and appropriate intervention, we can improve the prognosis and quality of life for patients with sarcoidosis.

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is a rare inflammatory disorder characterized by the sudden onset of fever, neutrophilia, and tender, erythematous skin lesions, often presenting as painful, raised plaques or nodules primarily on the upper limbs, face, or neck [31]. The pathogenesis involves an exaggerated immune response, with cytokines like granulocyte colony-stimulating factor (G-CSF) playing a significant role. Histopathologically, it is marked by dense neutrophilic infiltrates in the dermis without vasculitis. Sweet syndrome can be associated with various conditions, including malignancies like acute myeloid leukemia and myelodysplastic syndrome, infections, drug reactions, and autoimmune diseases such as systemic lupus erythematosus. Sweet syndrome also happens to be another rare dermatologic manifestation of sarcoidosis. It has been reported in 11 patients in a review conducted by Saliba et al. [32]. The cutaneous manifestations were accompanied by fever, leukocytosis, and a positive response to steroids. The lesions of SS were found primarily on the upper limbs, and some atypical papules were found as well. The combination of SS and sarcoidosis was found to be diagnosed simultaneously. Lastly, some case reports describe non-specific cutaneous findings in patients with cardiac sarcoidosis. Vu et al. describe the case of a 63-year-old female who presented to the emergency room with episodes of syncope for four weeks [33]. The patient was given an outpatient heart monitor that detected a high-grade atrioventricular block. This patient had a known history of cutaneous sarcoidosis, first described as a discoid, erythematous, and non-itchy patch on her arm. Over time, her condition progressed, and she eventually developed noncaseating granulomas in her skull, bone, and heart. This case exemplifies the importance of early detection and diagnosis of cardiac involvement in patients with cutaneous sarcoidosis. The initial presentation of skin lesions in sarcoidosis can sometimes be misleading, as they might appear benign and non-specific. In the case described by Vu et al., the cutaneous manifestation was a simple, non-itchy patch that might not have raised immediate concern for systemic disease [33]. However, the progression to cardiac involvement underscores the critical need for vigilance and comprehensive evaluation in patients with known sarcoidosis, even when initial symptoms seem mild or isolated. Early identification and continuous monitoring are essential, especially in patients presenting with skin lesions typical of sarcoidosis. Physicians should maintain a high index of suspicion for systemic involvement, including cardiac sarcoidosis, which can present insidiously and lead to severe complications if not diagnosed and treated promptly. This case also highlights the interconnected nature of sarcoidosis, where cutaneous findings can serve as harbingers of more severe systemic disease, necessitating a multidisciplinary approach to management. Moreover, this case illustrates the diverse clinical manifestations of sarcoidosis and the importance of integrating dermatologic and cardiologic evaluations in patient care. The patient's journey from cutaneous to cardiac involvement illustrates the potential for sarcoidosis to affect multiple organ systems progressively. Ensuring that patients with cutaneous sarcoidosis undergo regular and thorough

systemic assessments can facilitate early intervention and improve outcomes, particularly in preventing severe cardiac complications.

Histopathological Features of Dermatologic Manifestations

The differential diagnosis of sarcoidosis involves distinguishing it from other granulomatous diseases, such as tuberculosis and fungal infections, which require different management strategies. This differentiation is essential for ensuring accurate diagnosis and appropriate treatment. The histopathological features of sarcoidosis, characterized by non-caseating granulomas composed of epithelioid cells and multinucleated giant cells, are critical for its diagnosis. These granulomas are well-circumscribed, compact, and organized collections often surrounded by a sparse but distinct layer of lymphocytes. Within these granulomas, multinucleated giant cells frequently harbor asteroid bodies, which are star-shaped inclusions, or Schaumann bodies, composed of calcium and protein complexes [34]. Although these features are not unique to sarcoidosis, their presence is indicative of an ongoing chronic granulomatous process. The absence of necrosis is a critical histopathological criterion that helps differentiate sarcoidosis from other granulomatous diseases, such as tuberculosis, which shows central necrosis within granulomas [35].

The differential diagnosis of sarcoidosis involves distinguishing it from other granulomatous diseases, which require different management strategies. Tuberculosis granulomas exhibit caseation necrosis, typically seen as a cheese-like appearance within the granuloma center, which is absent in sarcoidosis. Fungal infections, such as histoplasmosis or coccidioidomycosis, are identified by fungal organisms within granulomas using special fungal stains like Gomori methenamine silver or Periodic Acid-Schiff (PAS), which do not show pathogens in sarcoidosis [36-38]. Moreover, diseases like granuloma annulare or foreign body reactions might mimic sarcoidosis but can be differentiated by their distribution, depth, and the presence of mucin or foreign materials.

Biopsy procedures for diagnosing sarcoidosis are critical, requiring samples from deep tissue layers to ensure granulomas are captured for examination. The histopathological analysis uses standard H&E staining to evaluate the granuloma structure, supplemented by special stains to exclude infections or foreign materials. In CS, these granulomas are often accompanied by CD68+ CD163− pro-inflammatory (M1) macrophages and a high CD4/CD8 T-cell ratio, which are indicative of an active immune response [39]. Additionally, the presence of Cutibacterium acnes components, lymphangiogenesis, confluent fibrosis, and fatty infiltration can further aid in the diagnosis. While endomyocardial biopsy remains the gold standard for diagnosing CS, its low sensitivity and high complication rate make non-invasive methods like skin biopsies valuable, especially when cutaneous lesions are present [40,41]. Further, advanced techniques like immunofluorescence or electron microscopy can be utilized to identify microscopic features such as small inclusions within cells or specific types of collagen deposition, enhancing diagnostic accuracy.

Diagnostic Significance of Dermatologic Manifestations

Correlation with Cardiac Involvement

Dermatological manifestations of sarcoidosis, particularly cutaneous sarcoidosis, have been found to correlate significantly with cardiac involvement, which is a critical prognostic factor in sarcoidosis. Cardiac sarcoidosis is often asymptomatic and insidious, making early detection challenging but crucial due to its association with severe outcomes. These skin manifestations can precede or coincide with systemic involvement, making them valuable for early diagnosis [42,43]. A skin biopsy, which is significantly less invasive than visceral biopsies, can confirm sarcoidosis through the identification of non-caseating granulomas, thus facilitating early detection and proactive management of the disease [44,45]. Research has shown that patients with cutaneous sarcoidosis, even those without apparent cardiac symptoms, should be screened for cardiac involvement. A study by Norimatsu et al. found that sarcoid lesions on the face significantly increased the risk for cardiac sarcoidosis [46]. In several other cases, skin manifestations such as erythema nodosum or lupus pernio have been documented as early indicators of cardiac sarcoidosis, preceding cardiac symptoms by months or even years [44]. Given the potential severity of cardiac involvement, it is recommended to screen for cardiac sarcoidosis in patients with extracardiac sarcoidosis, especially those with cutaneous manifestations. Dermatologists, therefore, can play a pivotal role in the multidisciplinary approach to sarcoidosis by recognizing skin lesions that may indicate underlying cardiac pathology, prompting further cardiovascular evaluation and potentially life-saving interventions. This interdisciplinary collaboration enhances the overall understanding and management of cardiac sarcoidosis, ensuring comprehensive care for affected patients.

Diagnostic Pathways

The diagnostic significance of dermatologic manifestations in cardiac sarcoidosis lies in their potential to provide early, non-invasive clues to CS. Imaging modalities are commonly used to detect abnormalities, scarring, and inflammation of the heart in suspected cardiac involvement. Echocardiography remains the first-line imaging modality due to its availability and cost-effectiveness, although it lacks the ability to characterize tissue or assess disease activity [47]. Recent advancements in non-invasive imaging modalities have significantly improved the diagnostic pathways for CS. Cardiac magnetic resonance imaging (CMR), useful for detecting myocardial scarring, and 18-fluorodeoxyglucose positron emission tomography (FDG-PET), the gold standard for identifying active inflammation, offer insights into myocardial inflammation and fibrosis [48,49]. The gold standard for diagnosis is endomyocardial biopsy demonstrating non-caseating granulomas, but this technique, while also being an invasive procedure, has limited sensitivity due to the patchy distribution of granulomas [50]. Despite these advancements, the diagnosis of isolated CS remains particularly challenging. While these diagnostic tools are useful in confirming a diagnosis of CS, due to the commonly asymptomatic nature of the disease, these tools are often not employed as there is no clinical presentation prompting

the investigation. The diagnostic significance of dermatologic manifestations in cardiac sarcoidosis lies in their potential to provide early, non-invasive clues to systemic involvement, prompting further cardiac evaluation. Recognizing and monitoring dermatological manifestations in sarcoidosis patients is crucial for early identification and management of cardiac involvement, which can ultimately improve patient outcomes.

Predictive Value and Clinical Relevance

The predictive value of dermatologic signs in cardiac sarcoidosis lies in their sensitivity and specificity for indicating underlying cardiac involvement. Certain dermatologic manifestations, particularly lupus pernio and scar sarcoidosis, have shown higher predictive value in identifying patients at risk for cardiac sarcoidosis [51]. Clinical algorithms incorporating these dermatologic clues can enhance the predictive accuracy for cardiac involvement, aiding clinicians in making informed decisions about further cardiac assessment. Understanding the nuances of these skin findings and their histopathological features can enhance diagnostic specificity, allowing for more precise and targeted management. Ultimately, recognizing the clinical relevance of dermatologic manifestations in cardiac sarcoidosis not only facilitates early diagnosis but also improves patient outcomes by enabling timely and appropriate therapeutic interventions. Establishing a standardized approach that links dermatologic findings to subsequent cardiac evaluation can streamline the diagnostic process, ensuring that cardiac sarcoidosis is identified and managed promptly.

Clinical Implications for Management

Timely Referral and Cardiac Evaluation

Identifying the dermatologic manifestations of sarcoidosis is crucial as they can serve as an early warning system for cardiac involvement, which is often more insidious and potentially life-threatening. For example, erythema nodosum is frequently associated with acute sarcoidosis and may indicate a more favorable prognosis. In contrast, lupus pernio is typically linked with chronic disease and a higher likelihood of systemic involvement, including the heart [2]. Scar sarcoidosis, which manifests as granulomatous lesions at previous injury sites, and hypopigmented macules, though less common, should also prompt consideration of systemic disease. These dermatologic findings can precede or coincide with cardiac involvement, serving as early warning signs [52]. Given the potential for severe cardiac complications, patients presenting with dermatologic findings should be referred for a comprehensive cardiac evaluation. The American College of Cardiology and the Heart Rhythm Society recommend that such evaluations include an electrocardiogram (ECG), echocardiography, and cardiac magnetic resonance imaging (MRI) to detect possible cardiac sarcoidosis [53]. These diagnostic tools help identify asymptomatic cardiac involvement, which is crucial for preventing severe complications such as arrhythmias, heart failure, and sudden cardiac death.

Managing cardiac sarcoidosis exemplifies the need for a collaborative, multidisciplinary approach. Dermatologists play a crucial role in early detection and referral based on cutaneous signs, while cardiologists provide critical evaluations and manage cardiac-specific treatments. With their expertise in systemic inflammatory diseases, rheumatologists contribute significantly to the overall treatment plan, particularly in managing immunosuppressive therapies often required for long-term control [4]. The multidisciplinary team works together to tailor treatment strategies, monitor disease progression, and adjust therapies as needed, ensuring a holistic approach to patient care. This collaboration not only enhances diagnostic accuracy and treatment efficacy but also helps mitigate the potential adverse effects of long-term treatment, thus improving patient outcomes and quality of life [54].

Therapeutic Interventions

The therapeutic management of cardiac sarcoidosis is complex and often requires a combination of treatments. Corticosteroids, such as prednisone, remain the cornerstone of therapy due to their effectiveness in reducing inflammation. However, long-term corticosteroid use is associated with significant adverse effects, including osteoporosis, hyperglycemia, and increased infection risk [55]. To mitigate these risks, immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil are used as steroid-sparing agents. These drugs help maintain disease control while minimizing corticosteroid exposure. Additionally, antimalarials like hydroxychloroquine are particularly useful for patients with predominant cutaneous involvement, providing additional anti-inflammatory effects and helping to manage skin lesions effectively [4]. The choice of therapeutic agents should be individualized based on the severity of cardiac and dermatologic involvement, patient comorbidities, and the risk-benefit profile of the medications.

Regular and systematic monitoring of both dermatologic and cardiac responses to therapy is crucial in managing cardiac sarcoidosis. Dermatologists should perform routine assessments of skin lesions, noting any changes in morphology, size, or resolution. Concurrently, cardiologists should employ a combination of ECG, echocardiography, and cardiac MRI to monitor cardiac function and detect early signs of disease progression [53]. Serial imaging and functional assessments are essential for evaluating the efficacy of the therapeutic regimen and making timely adjustments. This integrated monitoring approach ensures that skin and cardiac manifestations are managed effectively, reducing the risk of severe complications and improving long-term outcomes [55].

Monitoring and Follow-Up

Long-term management of cardiac sarcoidosis involves a structured follow-up plan to monitor disease stability and therapeutic response. Regular follow-up visits should include comprehensive clinical evaluations, laboratory tests, and imaging studies such as echocardiography and cardiac MRI. These imaging modalities are essential for assessing cardiac function and detecting new or worsening cardiac involvement. Repeated skin lesions or cardiac tissue biopsies may be necessary to evaluate ongoing granulomatous inflammation and guide treatment adjustments [56]. This proactive follow-up strategy helps in the early identification of disease progression and allows for timely intervention, thereby preventing

severe complications and improving patient prognosis. Managing cardiac sarcoidosis requires vigilant and continuous monitoring to detect disease progression and adjust treatment strategies accordingly. This involves regular clinical assessments, imaging studies, and laboratory tests. Patients with cardiac sarcoidosis should undergo periodic electrocardiograms (ECGs) to monitor for arrhythmias, which are a common and potentially severe complication of the disease [53]. Echocardiography is essential for evaluating cardiac function and detecting changes in left ventricular ejection fraction, wall motion abnormalities, and other signs of cardiac involvement. Cardiac magnetic resonance imaging (MRI) provides detailed information about myocardial inflammation and fibrosis, aiding in assessing disease activity and response to treatment. Additionally, laboratory tests, including complete blood counts, liver function tests, and renal function tests, are vital for monitoring the disease's systemic effects and the treatment's impact. Elevated levels of serum angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) can indicate active sarcoidosis and should be monitored periodically [56]. Routine blood tests are also beneficial in detecting potential adverse effects of medications, such as immunosuppressive agents, which can cause cytopenias, liver toxicity, and renal impairment. Patients on long-term corticosteroid therapy should undergo regular bone density scans to monitor for osteoporosis and periodic glucose and blood pressure measurements to manage hyperglycemia and hypertension. Immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil, used as steroid-sparing agents, also require regular monitoring to prevent and manage side effects. These medications can cause hepatotoxicity, myelosuppression, and increased infection risk. Regular liver function tests and complete blood counts are essential to promptly detect and address these adverse effects [4]. If patients are stable and showing signs of disease remission, it may be appropriate to taper corticosteroid doses to minimize side effects. Regular follow-up visits and a proactive approach to managing side effects are crucial for optimizing long-term outcomes for patients with cardiac sarcoidosis.

Discussion

The studies discussed underscore the crucial role of dermatologic manifestations in the early detection of CS. Dermatologic manifestations such as EN, LP, scar sarcoidosis, and hypopigmented macules serve as early indicators of systemic and cardiac sarcoidosis and provide a valuable window for early intervention. The consistent integration of qualitative data from case reports, series, and histopathological studies highlights the diversity and diagnostic significance of these dermatologic clues, but there are still gaps that remain within the existing research, especially with respect to the diagnostic value of cutaneous involvement. Patients with cutaneous sarcoidosis, particularly those with facial lesions, have a significantly increased risk of cardiac involvement [46]. Histopathological examination of skin lesions revealing non-caseating granulomas has been pivotal in enabling early and accurate diagnosis of sarcoidosis, as well as prompting further cardiac evaluation. These examples illustrate the need to advocate for further research in this domain. This intricate and clinically significant correlation between cutaneous and cardiac findings also underscores the necessity for an interdisciplinary approach in managing sarcoidosis, since skin lesions serve as both diagnostic and prognostic markers of systemic and cardiac disease.

Clinical Recommendations

Given the diagnostic importance of skin manifestations, clinicians and other healthcare providers should adopt best practices for recognizing and diagnosing CS via dermatologic findings. Dermatologists should maintain a high index of suspicion for systemic involvement in patients presenting with sarcoidosis-specific skin lesions.

Recommended clinical practices should include:

1. **Comprehensive Dermatologic Examination:** Conduct methodical skin inspections and biopsy any suspicious lesions to identify non-caseating granulomas.
2. **Interdisciplinary Collaboration:** Ensure close collaboration between dermatologists and cardiologists. Dermatologists should refer patients with confirmed cutaneous sarcoidosis for cardiac assessments, especially if a patient presents with higher-risk skin lesions such as lupus pernio.
3. **Advanced Imaging and Monitoring:** Use advanced imaging modalities such as CMR and 18-FDG-PET to obtain all-encompassing cardiac evaluations. Confirmed CS cases can be both managed and mitigated, reducing potential cardiac complications, through regular follow-up and monitoring.

Both the severity of the dermatologic manifestations, as well as the extent of cardiac involvement, should be examined to determine treatment regimens that are tailored and individualized from patient to patient. Corticosteroids remain the cornerstone of therapy but in refractory cases, additional immunosuppressive agents may be required for successful treatment. A recent prospective cohort study with a randomized controlled trial component by Morimoto et al. examined the effectiveness of the steroid prednisolone (PSL) and the immunosuppressive agent methotrexate (MTX) for CS [57]. The researchers aimed to determine if MTX would benefit patients who did not respond well to PSL or whose inflammation returned. They found that neither the MTX group nor the group continuing PSL showed a significant reduction in heart inflammation, suggesting that MTX was about as effective as just continuing with PSL. This research by Morimoto et al. is pivotal for our discussion on the need for further research in CS treatment as it underscores the lack of well-established alternative treatments and highlights the varied responses among patients. When CS is managed early and aggressively, the progression to more severe cardiac dysfunctions can be avoided which improves patient outcomes. There must be a proactive and integrative approach adopted by healthcare providers to effectively leverage these dermatologic manifestations for the early diagnosis of CS. Dermatologists and cardiologists need to collaborate closely, to guarantee that patients presenting with sarcoidosis-specific skin lesions undergo in-depth systemic evaluations. To consider these assessments to be truly in-depth and thorough, routine cardiac evaluations should be made even in the absence of overt cardiac

symptoms because subclinical cardiac involvement is common. Moreover, raising awareness among dermatologists, but especially among primary care providers who receive less training on these complications, about the significance of these dermatologic clues can result in more timely referrals and comprehensive care. Updating clinical guidelines to reflect the need to emphasize the dermatologic-cardiac link in sarcoidosis in addition to educational initiatives could significantly enhance both early identification of the disease and subsequent management strategies.

Research Gaps and Future Directions

Despite the significant advances in understanding the link between dermatologic and cardiac sarcoidosis, several research gaps remain. Three areas of focus stand out in particular that require further research. These include (1) genetic predispositions, (2) novel biomarkers, and (3) long-term outcomes.

Genetic predispositions towards developing CS and its various manifestations could provide insights into personalized medicine approaches. Spagnolo et al. discussed the latest findings on the genetic predispositions patients have to sarcoidosis [58]. Their review not only demonstrates that genetic studies have identified new and ancestry-specific gene associations with sarcoidosis but also emphasizes the gene-environment relationship as crucial in understanding how genetic information influences the disease. A study showed that genetics account for only 49% of sarcoidosis risk, indicating other significant factors such as the ones we are advocating for. However, this data still suggests the crucial role of genetic predisposition in the disease, which warrants further exploration to fully understand its genetic aspect and interactions with environmental factors. The research additionally underscores the importance of genetic studies and the need for continued focus on specific patient groups to uncover more genetic variants associated with sarcoidosis. The investigation of more of these genetic factors could help continue to identify specific genes or genetic markers associated with a higher risk of developing sarcoidosis. Understanding genetic predispositions could also explain why some individuals develop more severe or diverse manifestations of the disease, including cardiac involvement. These understandings and insights could lead to the expansion of therapies that are more targeted and address the underlying genetic causes of sarcoidosis, improving treatment outcomes.

Novel biomarkers should also be identified and validated in order to detect CS early and monitor the condition continuously. Exploration of these biomarkers could enhance diagnostic accuracy and treatment efficacy. Biomarkers could offer non-invasive methods for monitoring disease progression and response to treatment, reducing the need for invasive procedures. By focusing on biomarkers, researchers could also uncover new pathways involved in the pathogenesis of sarcoidosis, leading to innovative therapeutic targets. Additionally, biomarkers could help differentiate between sarcoidosis from other granulomatous diseases, ensuring accurate diagnosis. In 2024, Seman et al. were able to develop a validated laboratory in vitro human granuloma model using patient-derived peripheral blood mononuclear cells (PBMCs) [59]. Because this model required fresh PBMCs, and it was uncertain how freezing and thawing these cells affect their behavior, the researchers examined whether frozen sarcoidosis cells could still form granulomas like fresh cells. Their results showed that the frozen cells performed just as well, denoting that cryopreserved cells can be successfully used in research for CS (Seman 2024). This finding is significant because it supports the use of cryopreservation to maintain specific cell markers and functional responses, aligning with the need for continued research on novel biomarkers for CS diagnosis and treatment.

Lastly, studying long-term outcomes associated with cardiac sarcoidosis is essential, particularly for patients identified through their dermatologic manifestations, to inform clinical practice and improve prognosis. Further research in this area is necessary to understand the full spectrum of systemic involvement and to develop targeted treatment strategies that can enhance patient outcomes. This research can be achieved through prospective studies that examine the progression of CS over time in patients with known cutaneous involvement. Insights from long-term outcomes can inform more effective follow-up protocols and indicate the benefits of early dermatologic diagnosis on the disease trajectory. Furthermore, long-term studies can reveal the impact of early diagnosis and intervention on the overall quality of life and survival rates of sarcoidosis patients. By analyzing these outcomes, healthcare providers can refine their approaches to managing sarcoidosis, ultimately leading to better patient care and improved prognoses. A recent study by Sink et al. demonstrated the need for further investigation into long-term outcomes with CS [60]. The study examined the dissimilarities between patients with isolated cardiac sarcoidosis (iCS) versus patients with cardiac sarcoidosis with extra cardiac involvement (nonisolated CS). Over 20 years, 50 patients with CS were analyzed and those patients with iCS had more frequent sustained ventricular tachycardia did experience a significant delay in diagnosis compared to nonisolated CS patients. However, despite these differences, long-term outcomes, including mortality, heart transplants, and ventricular assist device implantations, were similar between the two groups over a median follow-up of nearly 10 years. This study suggested an alternative possibility, that diagnostic delays may affect initial clinical presentations but not the overall long-term outcomes, but further research is required in order to accurately determine this outcome. Understanding the long-term impact of early dermatologic diagnosis on the clinical outcomes of cardiac sarcoidosis patients will be crucial in shaping future clinical practice.

These potential avenues for future research can include conducting larger cohort studies and randomized controlled trials to evaluate the efficacy of different diagnostic and treatment strategies. If future research explores the role of emerging imaging technologies and molecular diagnostics in the early detection and management of cardiac sarcoidosis, more effective and less invasive diagnostic pathways could be discovered. Addressing these existing research gaps requires a multifaceted approach. To definitively validate the predictive value of dermatologic manifestations in CS, large-scale, multicenter studies are essential. There should be further

investigations of the pathophysiological mechanisms that link cutaneous and cardiac involvement. Additionally, research should focus on developing and validating non-invasive biomarkers that can reliably predict cardiac involvement in sarcoidosis patients presenting with skin lesions. Exploring the potential of advanced imaging techniques, such as hybrid PET/MRI, could provide deeper insights into the early detection of myocardial inflammation and fibrosis, thereby refining diagnostic approaches and uncovering novel therapeutic ones.

Conclusion

This review highlights the critical role dermatologic manifestations play in the early detection and management of cardiac sarcoidosis. Cutaneous signs such as erythema nodosum, lupus pernio, scar sarcoidosis, and hypopigmented macules serve as pivotal diagnostic indicators of systemic disease and potential cardiac involvement. Early identification and subsequent cardiac evaluation can significantly alter the disease trajectory, emphasizing the need for vigilance among dermatologists and other healthcare providers. Recognizing and understanding these dermatologic clues enable timely referral for cardiac evaluation and appropriate therapeutic interventions, ultimately enhancing patient outcomes in cardiac sarcoidosis management. The diagnostic pathway for cardiac sarcoidosis should integrate comprehensive dermatologic assessments, especially in patients presenting with sarcoidosis-related skin lesions. Upon identifying granulomatous inflammation in the skin, further cardiac evaluation using advanced imaging modalities such as cardiac MRI or PET scans should be considered to detect myocardial involvement early. This integrated approach can guide therapeutic decisions, ensuring timely initiation of appropriate treatments to manage both dermatologic and cardiac manifestations effectively.

Enhancing early diagnosis and treatment of cardiac sarcoidosis through the recognition of dermatologic manifestations can profoundly impact patient outcomes. Early detection allows for prompt therapeutic interventions, which can prevent the progression of cardiac complications, improve prognosis, and enhance the overall quality of life for patients. By adopting a multidisciplinary approach that includes dermatologic and cardiac evaluations, healthcare providers can offer more comprehensive care to sarcoidosis patients, ultimately improving survival rates and reducing morbidity associated with the disease. Future research should focus on further elucidating the pathophysiological mechanisms linking cutaneous and cardiac sarcoidosis, as well as developing standardized guidelines for the early detection and management of the disease. Large-scale, multicenter studies are needed to validate the diagnostic significance of various dermatologic manifestations and to refine imaging techniques for early myocardial involvement. Additionally, exploring novel therapeutic strategies targeting both skin and cardiac manifestations will be crucial in advancing the comprehensive management of sarcoidosis. By addressing these research gaps, we can improve diagnostic accuracy, treatment efficacy, and overall patient outcomes in cardiac sarcoidosis.

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