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Histopathological Features Analysis of Sarcoidosis in Different Organs

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Abstract. Sarcoidosis is a complex inflammatory disease involving many systems and its exact cause is still unknown. The characteristic in histopathology of it is the occurrence of epithelioid cell granulomas. The most common type of lymph node involvement is the lungs and chest has risks of other organs. Common diagnostic methods rely on clinical symptoms, imaging, and histopathology. Histopathology is the microscopic study of tissues affected by a disease and is essential for diagnosing sarcoidosis and differentiating it from other granulomatous disorders. According to different affected organs, the histologic pattern of sarcoidosis is also different. Lungs is the most affected organ. Granulomas are usually found within the interstitium, often with varying degrees of fibrosis. Cutaneous manifestations include a range of lesions such as erythema nodosum and lupus chilblain, and histological test may present dermal granulomas and lymphocytic infiltrates. Although liver involvement usually asymptomatic, its characteristics is a portal with a triple granuloma, occasionally accompanied by mild portal inflammation. This paper aims to investigate the histopathological findings of sarcoidosis in different organs.

Keywords: Histopathology; Sarcoidosis.

1. Introduction

Histopathological refers to studies at the micro level caused by disease or abnormal biological tissues and cells changes. It has a crucial function in the identification and comprehension of different clinical situations, particularly in the diagnosis of cancer [1]. By conducting thorough analysis of specimens, histopathologists can discern the structural modifications that diseases cause in organs and tissues, offering crucial understanding of the characteristics, advancement, and possible therapeutic approaches for these conditions. Tissue analysis typically entails tissue fixation, sectioning, staining, and microscopic examination to detect cellular abnormalities, disruptions in tissue architecture, and pathological entities such as granulomas, tumors, and inflammatory infiltrates. Histopathology offers precise histological characteristics for therapeutic management and has significantly enhanced our capacity to diagnose intricate disorders, track disease advancement, and assess therapy outcomes.

Sarcoidosis is a systemic inflammatory disease that causes human immune system to overreact and make lumps or nodules called granulomas. Different organs have different symptoms of sarcoidosis, common expression is lymph node enlargement, pulmonary infiltrates, joint pain, eye and skin lesions. The prevalence, symptoms and severity of sarcoidosis vary significantly among different ethnic groups, races and countries. African Americans have been reported to have a highest prevalence of 50 cases per 100,000 population. However, the incidence is lower in South America, other Asian countries, and Africa. In the United Kingdom and Finland, erythema was the sarcoidosis patient's main symptom, whereas this symptom was very rare in the Japanese hostages. In addition, the onset age of sarcoidosis is under 40 years old, and peaks at age 20 to 29 years old [2]. Women have a higher prevalence than men, and sarcoidosis rarely occurs in children and the elderly. Although the possible etiology of sarcoidosis has been studied intensively by many scientists, the exact etiology remains unclear. The current common view is genetic and environmental factors can result in sarcoidosis.

The correct diagnosis of sarcoidosis is mainly based on three criteria :(1) clinical manifestations and/or imaging findings; 2) whether non-caseating epithelial-cell granulomas are found on histological biopsy; 3) Other diseases with similar histological or clinical manifestations were

excluded. The biopsy site of noncaseating granulomas depends on the disease presentation. Bronchopulmonary biopsy by means of fiberoptic bronchoscopy yields a diagnostic yield of 70 to 80% when sufficient samples are obtained. Other potential sites for biopsy include visible skin lesions, lips, conjunctiva, or superficially enlarged lymph nodes [3].

Sarcoidosis is defined in histopathology as "All affected organs or tissues has occurred non-caseating epithelioid-cell granulomas, followed by gradual regression or transformation into clear connective tissue". non-caseating epithelioid-cell granulomas is composed of radial arrangement of epithelioid cells, lymphocyte infiltration around it [4]. Langerhans-type multinucleated giant cells were present, possibly containing Schauman bodies and stellate bodies. In the lungs, granulomas are located near or within the bronchioles, subpleural, and peri lobular Spaces, and in the connective tissue sheaths of small vessels (lymphatic distribution).

Ultimately, sarcoidosis exhibits distinct histological characteristics in various organs. Histopathological diagnosis in patients with sarcoidosis plays an indispensable role. Understanding these histopathological variants is essential for accurate diagnosis, appropriate treatments, and improved outcomes in sarcoidosis patients. The purpose of this paper is to clarify the histopathological features of sarcoidosis in various organs and emphasize the importance of comprehensive histological examination in understanding this complex disease.

2. Histopathology of Sarcoidosis

2.1. Common Findings

Sarcoidosis has various manifestations and can affect most or even all organs and tissues of the human body. Clinical manifestations of four kinds of forms: no symptoms, acute, subacute or chronic. In addition to clinical features and radiological techniques, the diagnosis is usually determined by whether the biopsy shows a noncaseating granuloma. Classic sarcoidosis consists of well-structured, tightly packed no necrotizing granulomas surrounded by layered clear collagen. (Figure 1) Granulomas is mainly composed of epithelioid cells, lymphocytes, white blood cells to form the boundary clear, well-structured inflammation area. Epithelioid cells sometimes fuse to form giant cells, which can be located around or in the center of the granuloma [5]. Sometimes, the granulomas had more edematous, myofibroblast-rich tissue at the margins. In addition, the presence of some inclusion bodies within granulomas may raise suspicion of sarcoidosis (Figure 2). These inclusions include Schaumann bodies, also known as shell-like bodies, which are lamellar nodules of calcium and protein and are often found in the cytoplasm of giant cells; Stellate bodies are a common spicle-like structure in multinucleated giant cells, and also exist in the cytoplasm of giant cells. Hamazaki-Wesenberg bodies are usually brown, vary in shape, and may be derived from lysosomes [6].

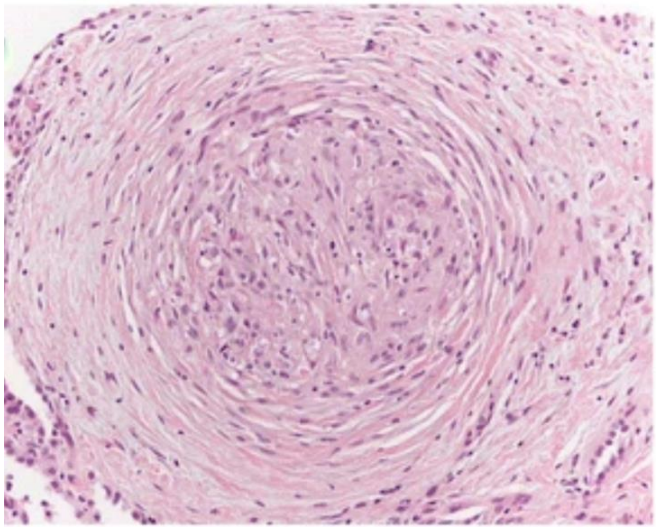

Figure 1. Fibrosis sarcoid granulomas stained by H&E X200.

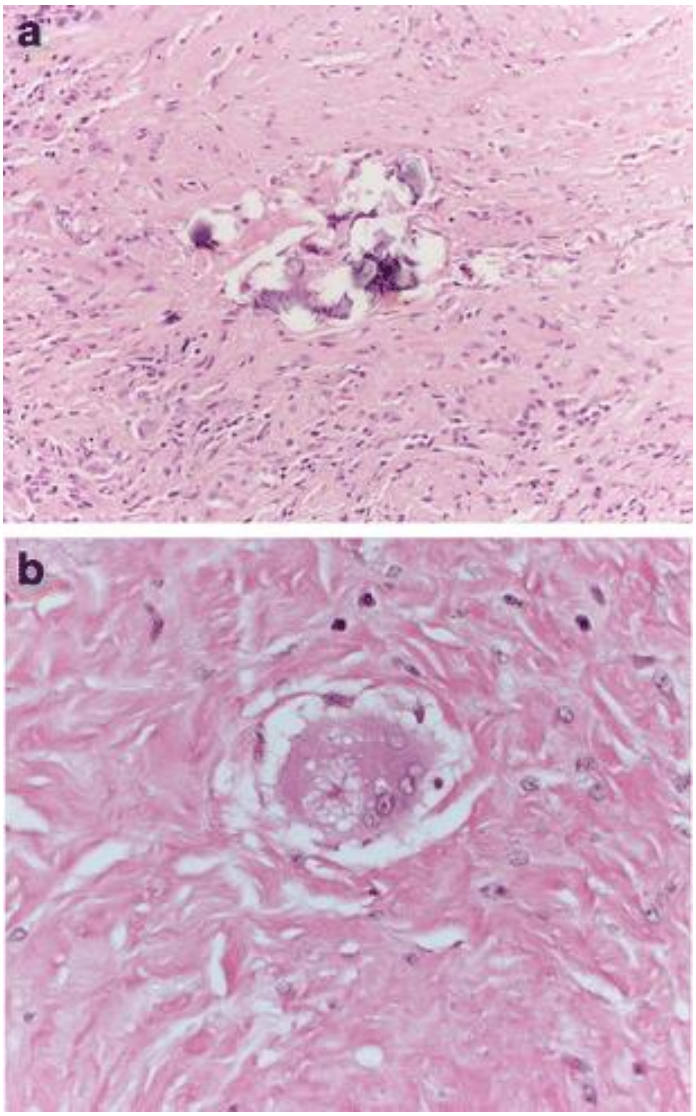

Figure 2. a. Schaumann bodies (stained by H&E, X400). b. asteroid bodies (stained by H&E, X400)

Granulomatous inflammation is chronic. In the early stage, CD4 and T helper cells release specific cytokines to promote the formation of granulomatous lesions. Most granulomatous lesions heal spontaneously. In other cases, a typical ring of collagen fibers will form around the granuloma, which will then be replaced by a clear and tight scar. Fibrosis may be accompanied by the deposition of substances such as oxalate or calcium carbonate. Then the number of T-helper lymphocytes within the granuloma decreases, which leading to an increase in CD8+ [7].

2.2. Sarcoidosis in Lung

The most common organ of sarcoidosis is lung. Caseous granulomatous lesions are mainly distributed in the bilateral lungs, bronchial blood vessel bundles, subpleural parenchyma, and interlobular septa. Histopathological examination usually reveals non-caseating granulomas. Lymphocytic alveolitis is common in the early stages of sarcoidosis, and there is no obvious abnormality in lung morphology. White micronodules were seen in the pleura and lung parenchyma as the disease progressed [8].

Granulomas is visible in 57% of lung biopsy specimens of sarcoidosis bronchi or bronchioles. About half of tuberculosis patients undergoing bronchoscopy show a normal mucosal appearance. The most common abnormalities in bronchoscopy are mucosal thickening, edema, and hyperemia [9]. When abnormal mucosal appearance is present, the occurrence of granulomas is about twice that of normal mucosa. As many as 8% of patients with sarcoidosis may develop airway stenosis. Stenotic lesions are often multiple and common present on the lobar or subsegmental bronchi.

Long term pulmonary sarcoidosis can result in pulmonary fibrosis. Fibrosis accompanied by sarcoidosis presents when the severity and duration of damage to the alveolar wall prevent its return to normal architecture. It is characterized by an increased number of surrounding fibroblasts and collagen that extends into the center of the granuloma. The increased amount of type I collagen leads to the loss of the epithelial basement membrane and the inability of the epithelial alveolar cells to regenerate. In long-term pulmonary sarcoidosis, fibrosis associated with bronchiectasis and destruction of lung parenchyma gradually results in cystic changes and the formation of a honeycomb structure. These changes are most rare in the upper lobes of the lung and below the pleura [10]. Additionally, granulomatous vasculitis can seriously damage blood vessel walls, leading to partial or complete obstruction of the lumen and resulting in pulmonary arterial hypertension.

2.3. Sarcoidosis in Skin

In sarcoidosis, in approximately 10% to 35% of patients occurs with skin lesions. The characteristic histology of skin lesions includes the occurence of nodular non-caseating granulomas in the dermis that may be accompanied by lymphocytic infiltration. (Figure 3) Occasionally, granulomas exhibit fibrinoid changes or noticeable necrosis. Dermal scars are primarily associated with chilblain lupus or necrotic and ulcerative lesions. Associated epidermal hyperplasia is present in verrucous lesions, while hyperkeratosis occurs in rare ichthyosis-like variants [11]. However, under normal circumstances, the overlying skin in sarcoidosis appears normal or atrophic. Cutaneous sarcoidosis has various manifestations, including plaques, maculopapular eruptions, and subcutaneous nodules. Some of lesions can be accompanied by enlarged lymph nodes or pulmonary involvement.

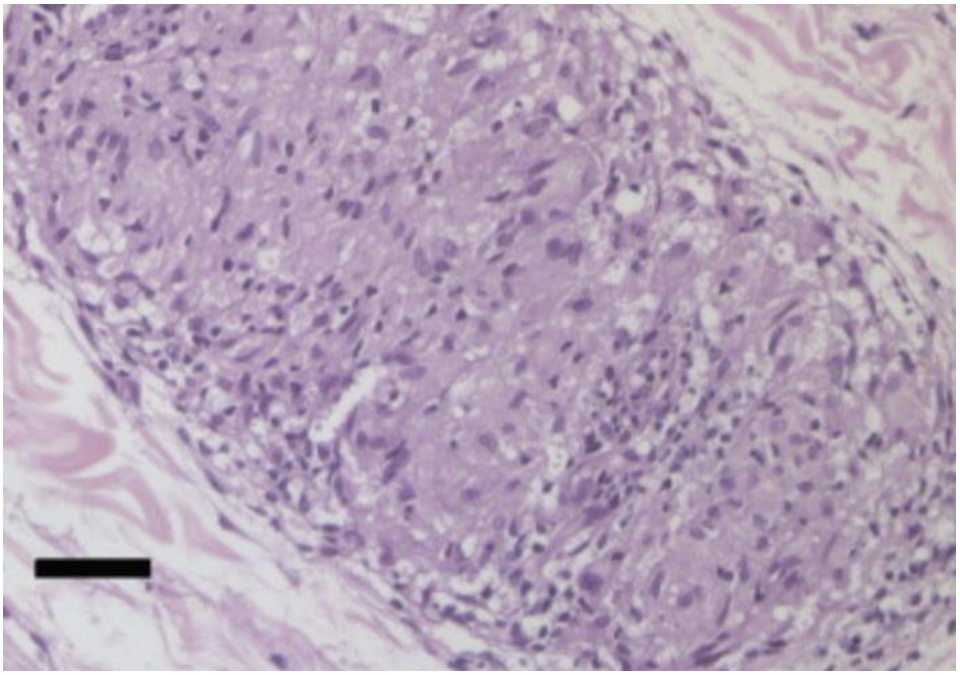

Figure 3. Plaque type lesions in the reticular dermis of epithelioid granulomas.

The most common presentation of sarcoidosis is popular skin lesions. Popular sarcoidosis involves only mild infiltration, with skin changes being very small and usually reddish-brown to purple. These lesions typically occur on the face, especially around the eyelids and neck. A typical light green color was observed under the microscope, which is characteristic of skin granulomatous lesions. The papules may expand or fuse to form ring-shaped lesions or plaques. Plaques are larger and differently shaped than papules and involve deeper infiltration and granulomatous inflammation [12]. These lesions usually resolve spontaneously or with treatment, leaving no substantial scarring. However, plaques are more likely to fade and leave permanent scars. In addition, subcutaneous nodules account for 16% of sarcoidosis skin lesions. It presents as hard and movable nodules, usually painless or slightly painful, and is mainly distributed in the limbs. Biopsy typically shows granulomas in the deep dermis and subcutaneous tissue.

2.4. Sarcoidosis in Breast

Sarcoidosis also be associated with granulomas of the breast, but this is rare, accounting for about 1% of sarcoidosis cases. Breast sarcoidosis appears as an irregular spiculated mass or a small round mass with well-defined boundaries on mammography. In biopsy specimens, typical well-structured granulomas of epithelioid cells can be found within the interlobular stroma (Figure 4). A mild infiltration of lymphocytes surrounds the granulomas and is associated with fibrosis [13]. The characteristics of duct dilatation caused by sarcoidosis have not been found in current studies.

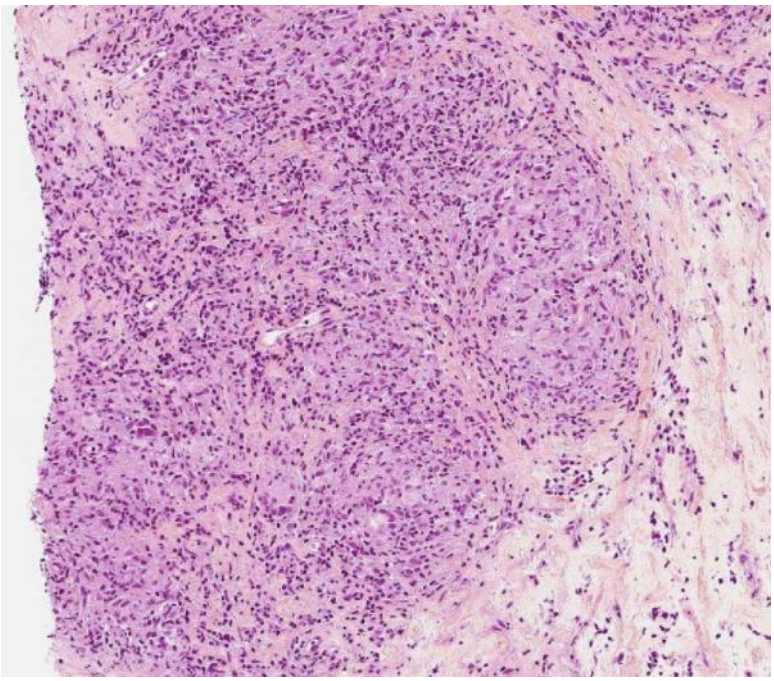

Figure 4. Micrographs of biopsy specimen (Stained by H&E) presents non-necrotizing granulomatous inflammation involving the lobules.

2.5. Sarcoidosis in Liver

In addition to the lungs and lymph nodes, sarcoidosis often involves the liver. Liver granulomas typically present in four histologic variants: caseous, caseous with fibrin ring, and lipogranulomas. Non-caseating epithelioid granulomas are typical of sarcoidosis, whereas caseous granulomas are associated with tuberculosis. Fibrin ring granulomas occurs in various infections, for instance hepatitis A and Q fever. Lipogranulomas are common in individuals who use mineral oil but can also occur in hepatic steatosis patients, or patients with hepatitis C, and fatty liver disease.

The characteristic of granulomas is the accumulation of epithelioid histiocytes and giant cells, along with lymphocytes and fibrin deposits predominantly located on the periphery. The lesions are distributed within the liver parenchyma, and at the same stage of maturity. In a few cases, there may be small areas of necrosis [14]. In the late stages, the granulomas lesions usually contain reticular fibers, or with prominent fibrotic sleeves. Large confluent granulomas can result in clear scar formation. In combination with chronic intrahepatic cholestasis, these changes can lead to mild nodular biliary cirrhosis.

Histologically, hepatic sarcoidosis with intrahepatic cholestasis is similar to lesions seen in primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). However, in most cases of PBC, the degree of granulomatous infiltration is less severe than in sarcoidosis [15]. Hepatic sarcoidosis granulomas are swollen and well-demarcated, not pointing to bile ducts. (Figure 5) In some cases, the granulomas may fuse to form large swollen nodules. Swollen lymph nodes in the hepatic portal vein can cause external compression on the hepatic duct, leading to extrahepatic cholestasis and occasionally cholangitis. Other histologic changes include sinusoidal expansion and nodular regenerative hyperplasia.

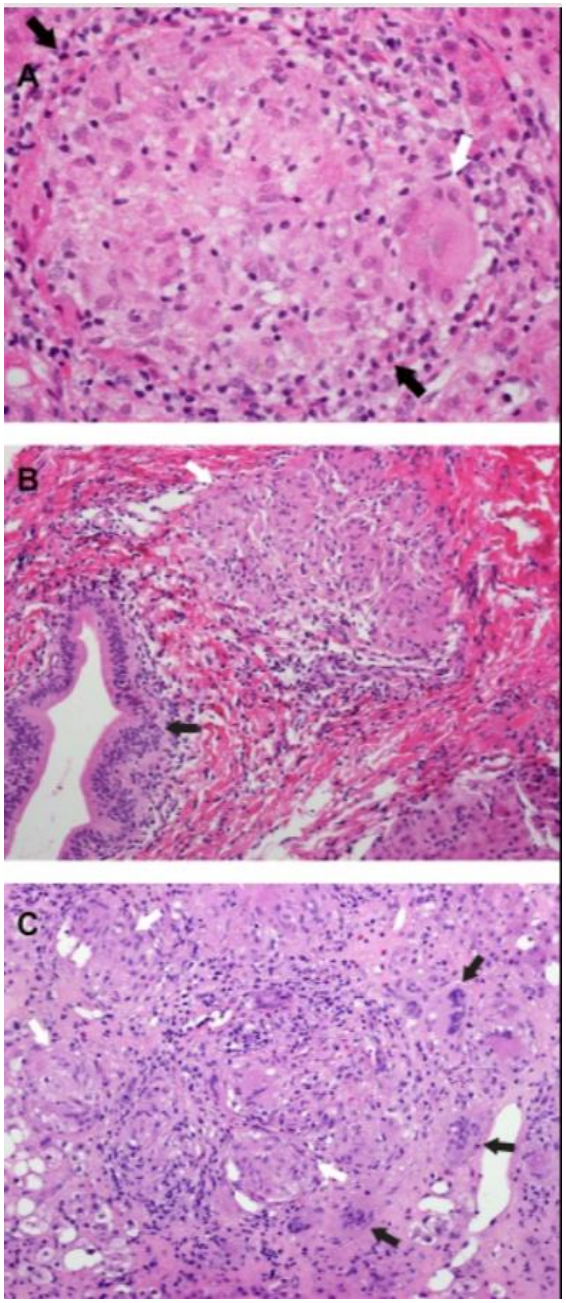

Figure 5. (A) Compact, morphologically distinct nodular noncaseating epithelioid granulomas. Lymphocytes (black arrow) and Langerhans giant cells (white arrow) appear. (B) Compared with PBC, the epithelioid granulomas (black arrow) of sarcoidosis are well shaped and usually do not point to the bile duct. (C) Epithelioid granulomas fused into enlarged nodules. Large numbers of giant cells (black arrow) are seen.

3. Discussion

3.1. Organ-Specific Variations

Although the commonality of granulomas, the histopathological form of sarcoidosis can vary significantly between different organs, reflecting the unique microenvironment and functional context of each tissue.

a. Lungs: The characteristic feature of pulmonary sarcoidosis is the form of granulomas in the peri lymphatic areas. In advanced stages, some patients may display fibrosis, resulting in a honeycomb lung. Granulomas can impact both the alveolar and interstitial compartments, potentially resulting in restrictive lung disease.

b. Skin: Cutaneous sarcoidosis occurs a wide variety of lesions, from maculopapular eruptions to plaques and nodules. From a histological perspective, these abnormalities show the presence of granulomas in the dermis, frequently accompanied by a perivascular infiltration of lymphocytes. Erythema nodosum, a reactive condition associated with sarcoidosis, shows a different histological pattern of septal panniculitis without granulomas.

c. Breast: Breast granulomas are rare compared with other organs. Typical epithelioid cell granulomas with mild lymphocytic infiltration and fibrosis are found in the interlobular stroma of breast sarcoidosis.

d. Liver: Hepatic sarcoidosis is usually asymptomatic and the occurrence of granulomas in the portal triad is the typical characteristic. Granulomas can occasionally be detected in the parenchyma. Although sarcoidosis commonly affects the liver, severe liver failure is uncommon, highlighting the mostly asymptomatic nature of hepatic sarcoidosis.

3.2. Diagnostic Challenges

The variation in histological characteristics among different organs highlights the diagnostic difficulties presented by sarcoidosis. Sarcoidosis must be distinguished from other granulomatous disorders, such as tuberculosis, fungal infections, and granulomatosis with polyangiitis, due to the non-specific character of granulomas. An extensive clinical assessment, such as imaging and laboratory examinations, is crucial to corroborate the histological presentations and establish a diagnosis of sarcoidosis.

3.3. Progress in Histopathological Techniques

The development of histological techniques such as immunohistochemistry, molecular pathology, and digital pathology has improved our capacity to diagnose sarcoidosis and provide insight into its pathology. Immunohistochemical staining is a useful technique for determining the cellular makeup of granulomas and distinguishing sarcoidosis from other disorders characterized by the formation of granulomas. For instance molecular methods polymerase chain reaction (PCR) and next-generation sequencing, can exclude infectious etiologies and ascertain genetic predispositions. Digital pathology and whole-slide imaging enable the exchange and examination of histological data, fostering collaborative diagnosis and research.

3.4. Significance for Clinical Practice and Future Directions

Accurate diagnosis and therapy planning for sarcoidosis heavily rely on comprehending the histological characteristics of the disease in various organs. Subsequent investigations should prioritize the identification of biomarkers capable of forecasting the advancement of diseases and the efficacy of treatments. Furthermore, investigating the molecular pathways that contribute to the development of granulomas in sarcoidosis may uncover new potential targets for therapeutic intervention.

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