

Pulmonary Sarcoidosis in HIV Patients: A Review

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Abstract

The status of the sarcoidosis outbreak, including the epidemiology, clinical presentation, radiographic findings, diagnosis and management of sarcoidosis were reviewed to present a better understanding of pulmonary sarcoidosis in HIV patients.

Keywords: Pulmonary Sarcoidosis; Human Immunodeficiency Virus (HIV)

Introduction

Sarcoidosis rarely develops in HIV patients. Studies from the last few decades described only a few cases of pulmonary sarcoidosis in HIV patients, mainly in hosts with relatively preserved immune systems. Currently, we observed some cases of newly diagnosed pulmonary sarcoidosis in HIV-infected patients, with the sarcoidosis developing after initiation of highly active antiretroviral therapy and coincident with partial immune reconstitution. Most of these patients had radiographic findings typical for sarcoidosis, including hilar and mediastinal lymphadenopathy and pulmonary nodules. Sarcoidosis diagnosis is never completely safe. If the clinical presentations are precise for the disease, then the diagnosis can rarely be made on clinical grounds without biopsy result. Otherwise, histological confirmation of granulomatous inflammation may require which is though not sufficient to make the precise diagnosis of this disease in HIV patients because this histological pattern is associated with other alternative diseases. Hence an assiduous effort (obtaining a detailed medical history as well as careful examination of the biopsied material) must be taken over to exclude such situation because it is a multisystem granulomatous disease of an unknown etiology [1,2]. In this review, we aim to discuss epidemiology, clinical presentation, radiographic findings, diagnosis, and management of pulmonary sarcoidosis in HIV patients.

Pathophysiology and Epidemiology

Sarcoidosis usually occurs in the lungs and lymph nodes, is a rare disease caused by inflammation, but it can also arise in almost any organ. Pulmonary sarcoidosis is sarcoidosis in the lungs which causes small lumps of inflammatory cells (non-necrotizing granulomas formation) in the lungs affecting the lungs' work, and its cause is still unknown. Due to these non-caseating epithelioid cell granulomas, the lung tissues remain inflamed, damaged and rigid which is called pulmonary fibrosis [1,2]. The non-caseating epithelioid cell granulomas formation in the lung is the main highlight. Typically clinical sarcoidosis indicates pulmonary involvement, intrathoracic lymph node enlargement, or some combination of these findings. Sarcoidal granulomas may involve in the lungs. Its lesions may differ depending on the various stages of the disease. In the earliest stage of the disease, mild alveolitis without granuloma formation has seen in the lung. Characteristic non-necrotizing epithelioid cell granulomas usually occur after that stage. The granulomas, which are microscopically reminiscent of epithelial cells, have a compact appearance with sharp circumscription from the surrounding lung. They are sporadically surrounded by lymphocytes and mostly composed of epithelioid cells which are firmly-assembled macrophages with spindle features [1,3,4].

Granulomas are typically followed by CD4+ T-lymphocytes in the middle (center) region and CD8+T lymphocytes in the periphery region, whereas B-lymphocytes are rarely observable within them. These observations are compatible with the hypothesis that cell-mediated immunity causes granulomas and CD4+T-lymphocytes are the basal cells that recruit other T lymphocytes and macrophages.

Epithelioid cells, alveolar macrophages in the lung and sinus histiocytes in the lymph nodes are immunohistochemically positive for CD68, which is a marker for pan-macrophages. In contrast, macrophages within pulmonary sarcoidosis granulomas are selectively positive for angiotensin-converting enzyme (ACE) by immunohistochemistry (IHC) in both sarcoidosis and sarcoid reactions and probably in other disease associated granulomas. ACE was selectively expressed in macrophages with particular differentiation including those with the epithelioid formation [5,6]. A unique histological feature is lacking in pulmonary sarcoidosis cases. So an exclusion of other granulomatous disorders is necessary for its diagnosis. The characteristics of sarcoidosis have gradually emerged due to the recent advances in the fields of immunology and IHC. It is apparent that pulmonary sarcoid granuloma has been formed through antigen presentation by DCs and sequential Th1 immunoreactions. Due to the recruitment of blood monocytes by Th1-associated cytokines may cause the granuloma formation. In between sarcoidosis and other granulomatous disorders including the expression of ACE and the contribution of mature DCs, the immunohistochemical characteristics of cells constituting granulomas seem to be universal. However, the causative antigens are still unknown. Environmental factors in addition to genetic susceptibility may associate with not only the onset of but also the predisposition to pulmonary sarcoidosis [7,8]. *Propionibacterium acnes* (*P. acnes*) may not be indicated as a causative agent even if they are vastly detected in pulmonary sarcoidosis lesions. Instead, it may be the supporting evidence that other antigens enter through the skin along with *P. acnes* that is indigenous to the skin. Further experimental researches are needed to confirm this possibility, such as testing the skin reaction by topical application of various environmental factors on the pulmonary sarcoidosis patient's skin to identify the antigen [9,10].

Pulmonary sarcoidosis is a worldwide distributed disease, affecting all races, ages and both sexes of HIV infected persons. Precise epidemiologic studies have hindered by the imprecise disease definition, variable presentation, under-diagnosis, and lack of systematic epidemiologic investigations. Nonetheless, current estimates of the prevalence of pulmonary sarcoidosis worldwide vary from 1 to 40 per 100,000 population/with a certain age, race, gender, and geographic predilections. The disease is most common in adults under the age of 50, with the highest incidence in 20- to 35-year-olds. Japan and the Scandinavian countries show a second peak in women over the age of 50. World rates of sarcoidosis are highest in Denmark (7.2/100,00), Sweden, and the United States. Disease rates in the United States reveal a slightly higher rate in women (6.3 per 100,000) than in men (5.9 per 100,000) and a higher age-adjusted annual incidence in African Americans (35.5/100,000) compared with Caucasians (10.9/100,00). In a metropolitan population in the United States of America, the age-adjusted annual incidence ranked from highest to lowest, was African-American females (39.1/100,000), African-American males (29.8/100,000), Caucasian females (12.1/100,000), and Caucasian males (9.6/100,000). Pulmonary sarcoidosis is rare in children. One study reports an incidence of 0.27 per 100,000 in children in Denmark and a peak age of diagnosis at 13 to 15 years [2,11,12].

Clinical presentation

Considerable variation in clinical presentation for pulmonary sarcoidosis is notable. According to the American Thoracic Society consensus statement, the principal organs involving sarcoidosis are the lungs, lymph nodes and skin. The primary site of sarcoidosis involvement is lung in 95% cases. Moreover, 90% of pulmonary sarcoidosis patients present with systemic symptoms including malaise, weight loss, fatigue, and fever. The prognosis is excellent. African-Americans who have a higher likelihood of HIV disease, are usually present with more severe symptoms than people of other races. Among Caucasians, acute and self-limiting pulmonary sarcoidosis is more typical. 'Lofgren's Syndrome' is a benign form of pulmonary sarcoidosis found in acute disease found in 20% to 55% of HIV patients. Pulmonary sarcoidosis in HIV infected patients may present with bilateral hilar adenopathy, fever, erythema nodosum, and arthralgias. However, any organ can affect it in HIV patients because of their weak immunity. The clinical symptoms of pulmonary sarcoidosis in HIV patients include a dry cough, chest pain and dyspnea, cutaneous anergy, peripheral lymphopenia, and a rise in polyclonal gamma globulin level, low CD4+ cell count, and variable rise in CD8 + cell count. The sequestration of CD4+ lymphocytes in the lungs and other sites are responsible for the peripheral quantitative defects in sarcoidosis. HIV-related depression of CD4+ lymphocyte function is due to a total reduction of this population and qualitative defects [11-13].

Radiographic findings

Chest radiograph (X-ray) showing bilateral hilar adenopathy suggests the diagnosis of pulmonary sarcoidosis especially if the patient has no fever, night sweats, or weight loss. X-ray indicating concomitant enlargement of the right paratracheal lymph nodes as well as bilateral enlargement the hilar lymph nodes which have described as the "1, 2, 3 signs". The findings on high-resolution chest computed

tomography (HRCT) may be more specific for the diagnosis of sarcoidosis than those found on X-ray. Typical HRCT findings that suggest sarcoidosis include parenchymal nodules and opacities that represent conglomerations of these nodules. Moreover, these nodules have a perilymphatic distribution along the bronchovascular bundles as well as in subpleural locations [14,15]. In a case report of 10 HIV infected patients with pulmonary sarcoidosis demonstrated that the X-ray findings included bilateral mediastinal and hilar lymphadenopathy in seven, pulmonary nodules in seven, focal consolidation in three, reticular opacities in three, granular opacities in two, and cysts or cavities in two (Figure 1). No patients had fibrosis on chest radiographs. Chest CT findings in the eight patients included hilar and mediastinal lymphadenopathy in six, nodules in seven (peri bronchovascular and subpleural in all seven), thickened interlobular septa in four, focal opacities in five, linear opacities in three, ground glass opacities in four, and cysts or cavities in two. One patient who was judged to have lymphadenopathy at chest radiography was found not to have it at CT. No patient had evidence of fibrosis at CT. No trend emerged for zonal predominance on chest radiographs or CT images. No relationship between the radiographic features of sarcoidosis and the CD4 cell count was found (Figure 2) [16-18].

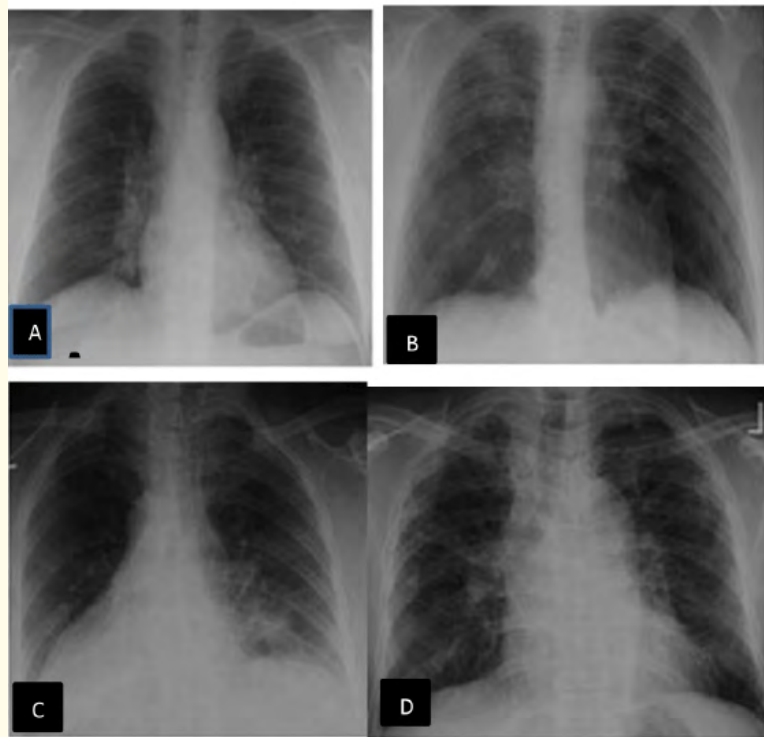


Figure 1: (A) A 32yr old female with hilar and right paratracheal lymphadenopathy. (B) A 61yr old male with bilateral hilar adenopathy and parenchymal opacities. (C) A 54yr old female right lower lung with parenchymal opacities. (D) A 51-year-old female with great increased interstitial markings[15-17].

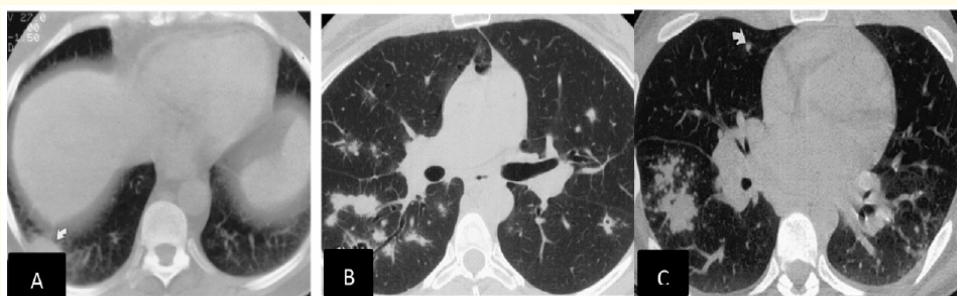


Figure 2: (A) A 43-year-old woman Chest, CT scan at the level of the dome of the diaphragm, demonstrates a 2.5-cm nodule (arrow) in the right lower lobe. (B) A 37-year-old woman Chest CT scan at the level of the hila demonstrates nodules and confluent opacities with a predominantly peribronchovascular distribution. There are small bilateral thick-walled cavities (arrow). (C) A 32-year-old woman Chest CT scan at the level of the inferior hila demonstrates small bilateral nodules in the lower lobes, with confluent opacity in the right lower lobe. There is a 5-mm nodule (arrow) in the right upper lobe abutting the minor fissure [15,17,18].

In 80% of pulmonary sarcoidosis patients, lymphadenopathy has commonly seen. Bilateral hilar lymphadenopathy is the characteristic pattern of involvement. Also, right paratracheal lymphadenopathy is also quite common. Commonly, hilar and right paratracheal lymph nodes are enlarged (Figure 3A). Lymph nodes also can see in different sizes ranging from subtle enlargement to conglomerate masses (as the disease progresses to a chronic state) (Figure 3B). In 25% pulmonary sarcoidosis parenchymal infiltration can be identified on radiographs. Reticulonodular opacities can also see in upper lung zones; it is also widespread. The primary CT findings of pulmonary sarcoidosis in HIV patients are symmetric lymphadenopathy, micronodules with the lymphangitic spread out, fibrotic changes, and bilateral perihilar opacities. The most usual pattern in patients with parenchymal involvement in pulmonary sarcoidosis is lymphangitic spread. It occurs due to the distribution of asymmetric bilateral perilymphatic micronodular. Peribronchovascular, subpleural, and interlobular septal distribution of the nodules had included in the lymphangitic spread (Figure 3C) [1,16,19].



Figure 3: (A) A 56-year-old female with hilar lymphadenopathy. (B) A 69-year-old female with calcified hilar lymph nodes. (C) A 56-year-old female demonstrates micronodules with peribronchovascular distribution [1,16,19].

Diagnosis

The actual incidence of sarcoidosis in HIV hosts are still unknown in the medical field. Some investigators have speculated the profound alteration in cellular immunity was associated with HIV infection to diminish the incidence of sarcoidosis without conscious reason. In one case study, newly diagnosed sarcoidosis occurred in HIV patients with CD4 cell counts of greater than 300 cells per cubic millimetre before the initiation of highly active antiretroviral therapy. Recent studies described that some HIV-infected patients had developed sarcoidosis or a sarcoidosis-like pulmonary disorder after beginning highly active antiretroviral therapy and coincidentally with an increase in the CD4 cell count. Bilateral hilar and mediastinal lymphadenopathy associated with pulmonary nodules ranging in size from < 5 mm to > 1 cm was the dominant chest radiographic and CT finding of newly diagnosed sarcoidosis in these HIV- infected patients. In these patients, infectious diseases such as tuberculosis, histoplasmosis, and cryptococcosis which having similar manifestations may be present. Such infectious diseases occur frequently in them and often demonstrate hilar and mediastinal lymphadenopathy associated with pulmonary nodules. These infections would be more likely to cause these radiologic findings than sarcoidosis because of their higher frequency of occurrence in these patients. HIV-associated neoplasms, such as lymphoma, Kaposi sarcoma, and metastatic cervical cancer, can also show a similar radiologic appearance but only very few. Radiologic changes support diagnosis like various examinations including tissue biopsy, bronchoalveolar lavage (BAL) for cytology or bacteriology investigation. These changes are not always sufficient to provide significant result. Metabolic activity at the site of the targeted lesions is essential for diagnosis, and two modalities may commonly use for this purpose: gallium isotope scanning or a positron emission tomography (PET) examination [18,20,21].

Biopsy play a vital role in diagnosis that without biopsy confirmation, the diagnosis will be inadequate. Also, granulomatous inflammation is mandatory to confirm the diagnosis of sarcoidosis in most cases. Meticulous histological examination with adequate staining of all biopsies should be performed to search for known causes of granulomatous inflammation, such as mycobacteria, fungi, parasites, and foreign material (e.g. talc granulomatosis). The sarcoid granuloma usually consists of an organised collection of mononuclear phagocytes (macrophages and epithelioid cells). Typically, there is no necrosis within the sarcoid granuloma; however, on occasion, there is a small to

moderate amount of necrosis. Commonly giant cells fuse within the sarcoid granuloma to form multinucleated giant cells. In the periphery, lymphocytes surround these granulomas. The crystal morphology and size are compatible with intravenously injected talc to ensure the diagnosis of talc granulomatosis (granulomatous inflammation). The atypical radiographic presentation will usually require histological diagnosis and correlation with other diagnostic methods decrease the diagnostic uncertainty. CT-guided biopsies of lung lesions have a very high sensitivity and specificity. In a study reveals that the cytologic diagnosis of CT-guided, fine-needle biopsy had confirmed in all 267 patients who underwent surgically or clinical follow-up (Figure 4) [4,22,23].

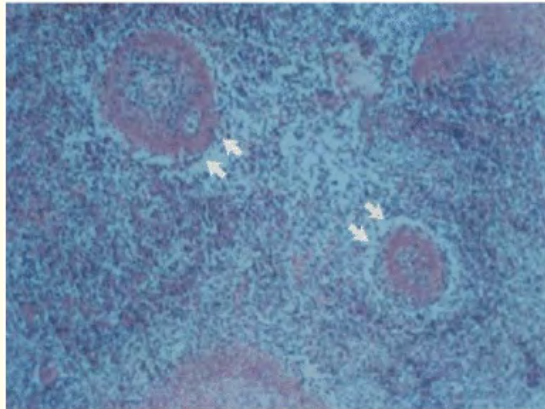


Figure 4: CT-guided, fine-needle biopsy showing signs of aseptic inflammation and necrosis (arrows) with extensive infiltration of lymphocytes and neutrophilic granulocytes [23].

Gallium isotope scanning is one of the oldest radionuclide imaging techniques used for sarcoidosis diagnosis. Gallium 67 (^{67}Ga) is the mostly used for the detection of pulmonary sarcoidosis in HIV infected hosts as it cause fabricating an expanded blood flow in lesions having an inflammatory or infectious. Sensitivity of ^{67}Ga ranges from 70 to 90%. Abnormal results appears as “lambda pattern” and “panda pattern” indicating sarcoidosis, which occurs when chronic inflammatory cells form nodules on multiple organs. The presence of these both patterns is highly specific for sarcoidosis in HIV hosts. However, it is a time-consuming procedure as it took 48-72 hours to complete and to get a diagnosis [24,25].

The FDG-PET (fluorodeoxyglucose positron emission tomography) is widely used in the evaluation of active metabolic malignancy. FDG-PET aids for both the diagnosis and therapeutic response in sarcoidosis. However, PET-CT scans are not universally available and are expensive. A small retrospective study compared the clinical utility of FDG-PET/CT and ^{67}Ga scanning in biopsy-proven sarcoidosis and found out that FDG-PET frequently displayed positive activity in areas with active granulomatous inflammation from sarcoidosis. Also FDG-PET can provide a complete morpho-functional mapping of the active inflammatory areas and follow therapy response in patients with sarcoidosis. Different tracers had used for the differentiating malignant lesions from the sarcoid lesions and inflammatory lesions. A study shows that the fluorine 18 alpha methyl tyrosine tracer was used in PET scanning and was able to differentiate malignancy from sarcoidosis. In PET scan positive result may be the result of malignancy or an alternative inflammatory condition. So it cannot take as definitively diagnose of sarcoidosis in HIV patients. Also, it is costly. Therefore, PET scans have not usually used in the diagnostic evaluation of sarcoidosis in HIV hosts [24,26,27].

Bronchoalveolar lavage (BAL) is useful in the staging and diagnosis of pulmonary sarcoidosis in HIV. In characterising lymphocytic alveolitis with high CD4+/CD8+ ratios (such as sarcoidosis and berylliosis) or low CD4+/CD8+ ratios (such as hypersensitivity pneumonitis), a flow cytometric analysis of lymphocyte subsets is beneficial. In the staging of sarcoidosis into high- and low-intensity lymphocytic alveolitis to determine those patients who will require corticosteroid therapy, the BAL role is very needy. Recently BAL studies in HIV-infected patients have defined a lymphocytic alveolitis with a CD8+ lymphocyte predominance. The potency of this alveolitis may represent a spectrum of lung disease from minimal lymphocytic infiltration to fulminant lymphoid interstitial pneumonitis (LIP). Lymphocytic alveolitis has been found in early and advanced HIV infection in as much as 80% of patients without an opportunistic infection or associated malignancy. It may be asymptomatic, but is often associated with respiratory symptoms. The accumulation of CD8+ lymphocytes within the lung in HIV alveolitis may represent either an in situ clonal proliferation or a migration of CD8+ lymphocytes in response to the infected alveolar cells. In sarcoidosis, the BAL reveals a significant lymphocytosis with an increase in the CD4+ T cells so that the CD4/CD8 ratio is 10: 1 rather than 2: 1, the ratio has seen in healthy lungs. These T helper cells are thought to release cytokines, such as IL-2, IL-2R, TNF- α , and IFN- γ , which may also measure at increased levels in the BAL of sarcoidosis patients. The use of BAL as a diagnostic test had debated. Some believe that the CD4/CD8 ratio is too variable among sarcoidosis patients to be helpful, while others believe that BAL alone may be sufficient to diagnose sarcoidosis. Decreases in both the lymphocytosis and CD4/CD8 ratio in the BAL are indicators of decreased disease activity and favourable treatment effect. Given this, it is probable that the BAL from patients with sarcoidosis is most useful as a measure of disease activities or treatment effect, or as supportive evidence for a clinical diagnosis of sarcoidosis [14,28,29].

The granulomas are the major histopathologic feature of sarcoidosis. It is an organised inflammatory response consisting of activated epithelioid histiocytes. Through a proinflammatory cytokine network directed by T-helper cells (CD4+), epithelioid histiocytes form tight nodules surrounded by a border of lymphocytes. The granulomas in sarcoidosis typically range in diameter from 15 to 30 μm . Less commonly, the granulomas may constitute smaller, ill-formed clusters of histiocytes. In general, the granulomas from a single patient with pulmonary sarcoidosis have a uniform appearance and are all of a similar histologic stage (Figure 5). The central necrosis that has commonly seen in infectious granulomas is uncommon. One large series that examined over 300 cases of sarcoidosis found necrosis in 39% of the cases; however, it was usually minimal rather than the extensive necrosis found in infectious granulomas. Because if any necrosis in sarcoid granulomas, connective tissue stains show a delicate reticulum in these granulomas, confirming the absence of tissue destruction is there is a few. Cytokines, INF- γ , and IL-2, had implicated in HIV-related sarcoidosis. Both of these chemical messengers are affiliated with granuloma formation and secreted by CD4+ helper T cells. In one study of 11 HIV patients that were diagnosed with sarcoidosis and concluded that the cause of sarcoidosis in this patient population is due to the late resurgence of memory and naïve CD4+ lymphocytes through the use of highly active antiretroviral therapy [3,11,30].

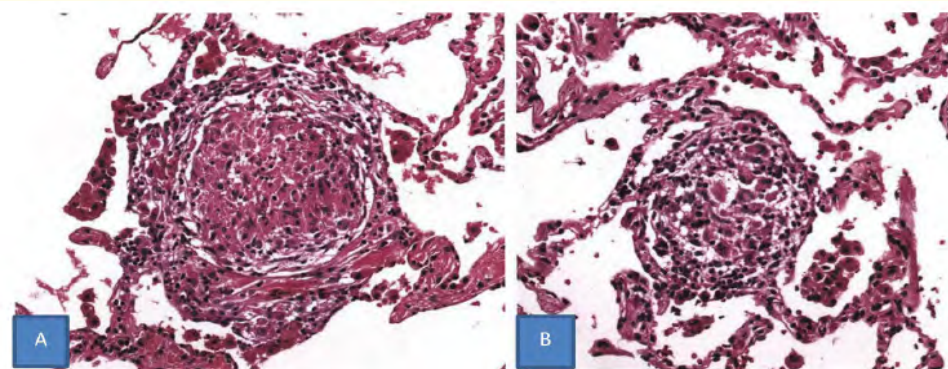


Figure 5: A) Epithelioid histiocytes surrounded by scattered lymphocytes. B) Epithelioid histiocytes with lymphocytes surrounding the aggregate of histiocytes [30].

The CD4+ cell plays a vital role in the initiation and maintenance of the immune system. Sarcoidosis has a likelihood to improve spontaneously. However, the selective destruction of CD4+ lymphocyte leads to spontaneous remission or stabilisation of the sarcoidosis. In one *vitro* study demonstrated an increased susceptibility of the activated CD4+ lymphocyte, presumably through its Surface receptors, to HIV infection. The natural history of sarcoidosis complicated by HIV infection may depend upon the number of activated CD4+ lymphocytes present. Active CD4+ lymphocytes present in the different stages of sarcoidosis may provide receptors for attachment by HIV and selective destruction of CD4+ lymphocytes. Other examples of CD4+ lymphocyte-modulated immune disease complicated by HIV infection with spontaneous remissions have been reported in the literature and include one case of Crohn's disease and two cases of systemic lupus erythematosus. Complete remissions may not be possible because some CD4+ populations retain the ability to expand on HIV infection clonally. In all but one of the patients reported, the sarcoidosis remitted or remained quiescent [11,29,31].

Through pulmonary function tests, all varieties of abnormalities can see in sarcoidosis such as obstructive, restrictive, diffusion impairment, or combinations. In pulmonary sarcoidosis patients, a decreased diffusion capacity and a restrictive ventilatory defect have most often seen. Almost 50% of patients also have obstructive airway disease. Although, hyper bronchial responsiveness is seen in up to 20% of patients and had associated with the presence of microscopic non-necrotizing granulomas in the endobronchial mucosa. During bronchoscopy, typical lesions in the trachea as well as in the bronchi are erythema, thickening of the mucosa, and a "cobblestone appearance" which yields a high number of granulomas on biopsy (Figure 6) [32,33].



Figure 6: A 57-year-old sarcoidosis patient is showing "cobblestone" appearance in the endobronchial Biopsy proved multiple non-necrotizing granulomas [33].

Pulmonary disorders are prevalent in HIV-infected patients. Recently, cases of symptomatic sarcoidosis in patients with HIV infection on highly active antiretroviral therapy has reported. Pulmonary sarcoidosis should be considered in the differential diagnosis of patients with pulmonary symptoms while on highly active antiretroviral therapy. Comparison of the CD4 count and CD4/CD8 ratio in BAL versus peripheral blood may be useful in the diagnosis and management and of these patients. Typical BAL fluid cellular or findings of non-necrotizing epithelioid granulomas in endobronchial biopsy material confirmed the diagnosis of sarcoidosis in asymptomatic patients and patients with HIV infected. At least 65% of all sarcoidosis cases had diagnosed this way. If the BAL fluid cellular profile is non-typical and the non-necrotizing epithelioid granulomas had not found. Then lung biopsy should perform. The finding of non-necrotizing granulomas confirms sarcoidosis [34,35].

Management

Management of pulmonary sarcoidosis in patients with HIV infected population is controversial. Therapy of choice for these patients are corticosteroids. Corticosteroids are notorious for resistant depression; therefore, the use of such agents must outweigh the risks.

There have been reports showing a positive response to high-dose fluticasone inhalation therapy as well as prednisone. The patient should go through initial dosage of 20 - 40 mg prednisone or its equivalent for 12 - 24 months. In one study, without therapy for six months in HIV patients with pulmonary sarcoidosis, 20% of patients had natural enhancement of their chest roentgenogram without therapy, and 40% deteriorated and started on corticosteroids. If corticosteroid therapy has started, a large number of these patients may need long-term therapy. However, there is limited information about how to predict who will need long-term therapy. Lastly, the studies to date have not described that corticosteroids or any other therapy prevent pulmonary sarcoid progression in HIV hosts. The vital features of sarcoidosis are the presence of a T- cell, expressing the CD4+ protein. T- cell, trigger inflammation that results in the formation of granulomas (inflamed tissue) in lung, skin and lymph nodes. Patients infected with HIV have immune comprised of low levels of T-cells and a reduced incidence of autoimmune diseases. However, highly active antiretroviral therapy (HAART)- an HIV treatment – aims to regain the patient’s immunity, including CD4+ T-cell levels, which may eventually higher-up the incidence of sarcoidosis [30,36,37].

For active sarcoidosis, the decision to initiate corticosteroid therapy may have long-term complications in the HIV-infected patient. In one study of seven HIV patients, three of seven patients had treated with corticosteroid therapy without serious complications. One patient had a spontaneous improvement concurrent with HIV infection. Moreover, two others were able to be weaned from corticosteroid treatment as the HIV infection progressed. The decision to treat should reflect the type and activity of the alveolitis defined by BAL in sarcoidosis complicated by HIV infection. Evidence for potential infectious complications suggests corticosteroids and lack of a clear benefit for therapy of CD8+ alveolitis should reserve for patients with BAL-defined CD4+ high-intensity alveolitis. Sarcoidosis complicated by HIV is rare, management will require BAL with the determination of lymphocyte subset populations. As with other CD4+ lymphocyte-modulated diseases, sarcoidosis may stabilize or even improve with HIV infection as a result of the progressive loss of activated CD4+ lymphocytes; however, corticosteroids may still indicate for active sarcoidosis [34,38,39].

In HIV patients with sarcoidosis, the CD4/CD8 ratio in BAL fluid will be more variable with the immunological condition at diagnosis because of the activity of the disease and the assumption of highly active antiretroviral therapy. In common, the ratio may be less aloft or typical in of radiological signs of lung granulomas in non-HIV hosts. In HIV patients undergoing of highly active antiretroviral therapy(immune reconstitution) particularly during the first nine months, it is mandatory to figure out the possibility that the patient is affected by a chronic granulomatous disease such as sarcoidosis. It is not simple to start steroid therapy in a patient infected by HIV by clinicians because of the fear to harm the patient with iatrogenic immunosuppression in case of any causative agents. So, before the diagnosis of sarcoidosis and that all microbiological examinations for causative agents and atypical mycobacteria should be negatively contributed to increase the level of security for the patient when corticosteroid therapy had requested. Some relevant points extracted from some literature may aid for clinicians in the decision of starting immunosuppressive therapy and for the evaluation at follow up of pulmonary sarcoidosis (Table 1 and 2) [34,40,41].

- In early-stage Sarcoidosis have 50 % spontaneous resolution within two years and late-stage lasting ≥ 3 - 5 years.
- Refractory Sarcoidosis: progressing despite treatment toward fibrosis (pulmonary and extrapulmonary), pulmonary hypertension, persistent disabling symptoms, impaired QoL.
- Systemic therapy to 20 - 80% of patients.
- Indications for systemic therapy, progressive respiratory symptoms or demonstrated deterioration of lung function, hypercalcemia.
- Each 3 - 6 months: clinical examination, chest radiography, pulmonary function test, ECG and blood test (including calcium and creatinine blood concentrations, 24-hour urinary excretion of calcium)
- When corticosteroids had reduced or discontinued, then the patients have had exacerbation and relapse in about 35 - 80% of treated patients.
- After corticosteroids withdrawal, relapses may occur within two to six months, but it’s rare after three years without symptoms.

Table 1: Therapy and follow up of pulmonary sarcoidosis [41,42].

Corticosteroids	Cytotoxic drugs	Cytokine modulators	Antimicrobial drugs
Prednisone 2 - 3 months, then tapering for other 3 months	Methotrexate Azathioprine Leflunomide Cyclofosfamide Mycophenolate mofetil	Pentoxifylline Thalidomide TNF α antagonist (infliximab)	Antimalarial drugs (hydroxychloroquine) Tetracyclines (minocycline, doxycycline)

Table 2: Therapy and follow up of pulmonary sarcoidosis [40-42].

Conclusion

Although diagnostic strategies and management of sarcoidosis had improved over the past few years, much is still unknown. Identifying the causes and populations at risk for the disease would not only enhance the diagnosis and management but possibly aid in prevention. While on highly active antiretroviral therapy, Sarcoidosis should consider in the differential diagnosis of patients with pulmonary symptoms. Comparison of the CD4 count and CD4/CD8 ratio in BAL versus peripheral blood may aid in the diagnosis and management and of these patients. The fact in HIV patients was the cellular immunity is highly variable, following antiretroviral therapy start and discontinuation, with the chance of crossing the threshold of 200 CD4+/mmc several times. This fact mainly influenced by the clinical presentation and diagnosis of sarcoidosis in HIV-infected patients which is similar to that of other non-co-infected patients. Further studies have needed to evaluate the risk of pulmonary sarcoidosis in HIV patients after immunosuppressive therapy [8,36,41,42]. We hope this review can aid practitioners to evaluate accurate diagnosis and follow-up therapy at the right time. Early detection and treatment of sarcoidosis is mandatory to control the mortality rate of these HIV infected populations.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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