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A COMPREHENSIVE REVIEW ON THE PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT OF SARCOIDOSIS

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ABSTRACT: Sarcoidosis is a rare autoimmune inflammatory disease, which is difficult to diagnose due to a lack of approved clinical tests. It has been observed in each race, and highest among the Scandinavia, African-American but Asians are less vulnerable to it. It affects most prominently adults from the age group of 20 to 60. The main characterized symptom of this disease is non-caseating granulomas, specifically in the lungs and lymph nodes progressing to lungs impairment to pass oxygen, and finally total failure of lungs as well as heart. The main cause of sarcoidosis is immune irregularities in genetically predisposed individuals which manifests antigen(s) like microorganism or their products, due to an ex-aggregated immune response. There is no specific treatment available, although corticosteroids help in disappearing its symptoms. While more than 50 percent of the patients don't require any treatment and illness goes on its own, only 10% require treatment in which severe symptoms developed and last long. The current review enlightens the pathogenesis of the disease, clinical indications, diagnostic evaluation, and various therapies for the treatment.

INTRODUCTION: Sarcoidosis is an evasive multisystem disorder characterized by granulomas of non-caseating giant cells with no significant reported cause. In 1877, English doctor Jonathan Hutchinson described this disease as a mimic of sarcoma (sarcoid-sarcoma-like) as a painless skin lesion [1]. The most common organs affected with the disease are lungs, lymph nodes, and less commonly the heart, skin, central nervous system, eyes, spinal, and liver [2].

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The lungs are the most commonly affected organ (90% of the patients), followed by skin, eyes, and heart. Sarcoidosis can occur at any stage of life, but it primarily affects young adults between the ages of 30 to 60 years and the highest incidence between 20–29 years. The occurrence rate is slightly higher amongst women than men; across racial and ethnic groups, as per reports [3]. The sign and symptoms of sarcoidosis, the infected organ might varies. Sarcoidosis develops slow and steadily, but the symptoms of the disease last for years. The most common symptoms of sarcoidosis include cough, dyspnea on exertion, chest pain, wheezing, fever, weight loss, arthralgia, musculoskeletal symptoms, and general weakness. Fatigue has been reported as a major problem for patients suffering from sarcoidosis.

The symptoms of the disease have a negative influence on patients' quality of life (QOL) which is an important consequence of treatment concerning chronic diseases [4].

Stages of Sarcoidosis: The sarcoidosis progresses through the following five stages according to the development of granuloma in various organs:

Stage 0: No signs and symptoms of granuloma shown in chest radiography

Stage 1: Granuloma developed in lymph nodes (Lymphadenopathy).

Stage 2: Granuloma of both lymph nodes and lungs (Lymphadenopathy and Parenchymal Lung Disease).

Stage 3: Granulomas developed in the lungs (Parenchymal Lung Disease).

Stage 4: Scarring of the lung tissue which leads to permanent damage (Pulmonary Fibrosis) [5, 6].

Etiology: Sarcoidosis is a systemic granulomatous disease that involves the development of non-caseating granulomas of multiple organs in the body. Though there are scientific and technological advances, the etiological cause of sarcoidosis has not been unraveled. The immune irregularities have been found to be the main cause of sarcoidosis in genetically predisposed individuals, elicited by the antigen(s) like microorganisms or their products, pollens, viruses, bacteria, and borrelia, due to an ex-aggregated immune response.

There are many shreds of evidence that suggest that the extrinsic antigens, environmental conditions, and genetic factors play a crucial role in the development of sarcoidosis through an exaggerated immune response. Although the exact mechanism has not yet been proved, numerous evidence studies support the Th1 lymphokine prevalence and involvement in sarcoidosis [7].

Etiological Factors: In the treatment and diagnosis of sarcoidosis, the etiological factors are required to be considered for a better understanding of pathophysiology. Some of these factors have been discussed as follows:

The Infectious Agents; a Trigger Factor in the Development of the Disease: Several studies have been carried out to identify the involvement of infectious agents like viruses, bacteria, and fungi, that could trigger sarcoidosis, and *Propionibacterium acne* and *Mycobacterium tuberculosis* are widely studied microorganisms. Antibodies in patients suffering from sarcoidosis, have been found to be heat shock proteins (hsp70, hsp65) and mycobacterial proteins (p36).

Ang *et al*., reported a cross-reaction between proteins of Schaumann bodies (vimentin, desmin, tubulin) and mycobacterial antigens. Although the reports suggested a link between the rise in the prevalence of sarcoidosis and the presence of fungi in the dust, but the role of infectious agents in the progression of granuloma has yet to be proven.

Exogenous Triggers: As per epidemiological studies, the role of dust in granuloma development has not been demonstrated, but the collapse of the world trade center in September leads to an increase in the number of incidences of sarcoidosis. After the collapse of the Centre, it was found that the presence of concrete components, including gypsum, anhydrite (anhydrous calcium sulphate), and fiberglass, increased in the environment. The data obtained from various clinical studies show the positive effect of anaerobic triggers like silicates, talc, *etc*., in the development of sarcoidosis. Moreover, there are many evident studies that prove the positive effect of printer or copier toner ink.

Vimentin (Autoantigen): Vimentin, a type III intermediate filament protein involved in the intercellular interactions and functioning of the immune system, may act as autoantigen of sarcoidosis. Though the level of vimentin increases in granulomas but there is no evident study for autoimmune response against this protein till 2007; Wahlström group has studied cellular and humoral responses of body in disease and detected antibodies and specific T-cells towards vimentin as representatives of the HLA-DR-B1_0301 genotype. However, both vimentin and granulomas have shown the highest intensity for lysosomal proteins of CD68 and muramidase [8].

Pathophysiology: Sarcoidosis is an inflated immune response recognized by non-necrotizing granulomas. Non-caseating granulomas are composed

of CD163-positive (Cluster of Differentiation 163) macrophages. Upon the intrusion of unidentified infectious agents or organic or inorganic particles into the body, antigen-presenting cells (APCs) chiefly dendritic cells or macrophages phagocytize it. The APCs presents infectious agents to T-cell receptors via human leukocyte antigen (HLA) class II molecule [3]. The attachment of the CD41T-cell receptor with the antigen-APCs complex results in the release of various chemokines and cytokines, involving TNF-α (Tumor Necrosis Factor-alpha), (interleukins) IL-12,-15,-18, MCP-1 (Monocyte chemoattractant protein-1), MIP (macrophage inflammatory protein), GM-CFS (Granulocyte-macrophage colony-stimulating factor), which leads to the formation of granuloma. The other cells like CD81T lymphocytes, fibroblasts, regulatory T cells, and B lymphocytes found in the vicinity of granuloma, cause the release of chemokines and cytokines which affect the aggregation of the macrophages. The TNF-α derivative of alveolar macrophage contributes to the induction and maintenance of granulomas developed in sarcoidosis. Moreover, in chronic disease, cytokines such as IL-12, IL-8, and TNF-α are associated while in case of acute disease, involvement of high proportion of CD4-positive lymphocytes has been reported [7].

There are many factors which alter the immune response especially CD41+ type1 helper-like cells (Th1-cells) which includes the hyper-activation of Th1-cells leads to increase in the level of Th1 cytokines that contribute to the activation, and polarization of CD41T cells during the development of sarcoidosis. The key effectors of the granulomatous reaction are macrophages and CD41T cells, which are responsible for inflammation associated with the development of granuloma [9]. The pathogenesis of sarcoidosis has been explained in **Fig. 1**.

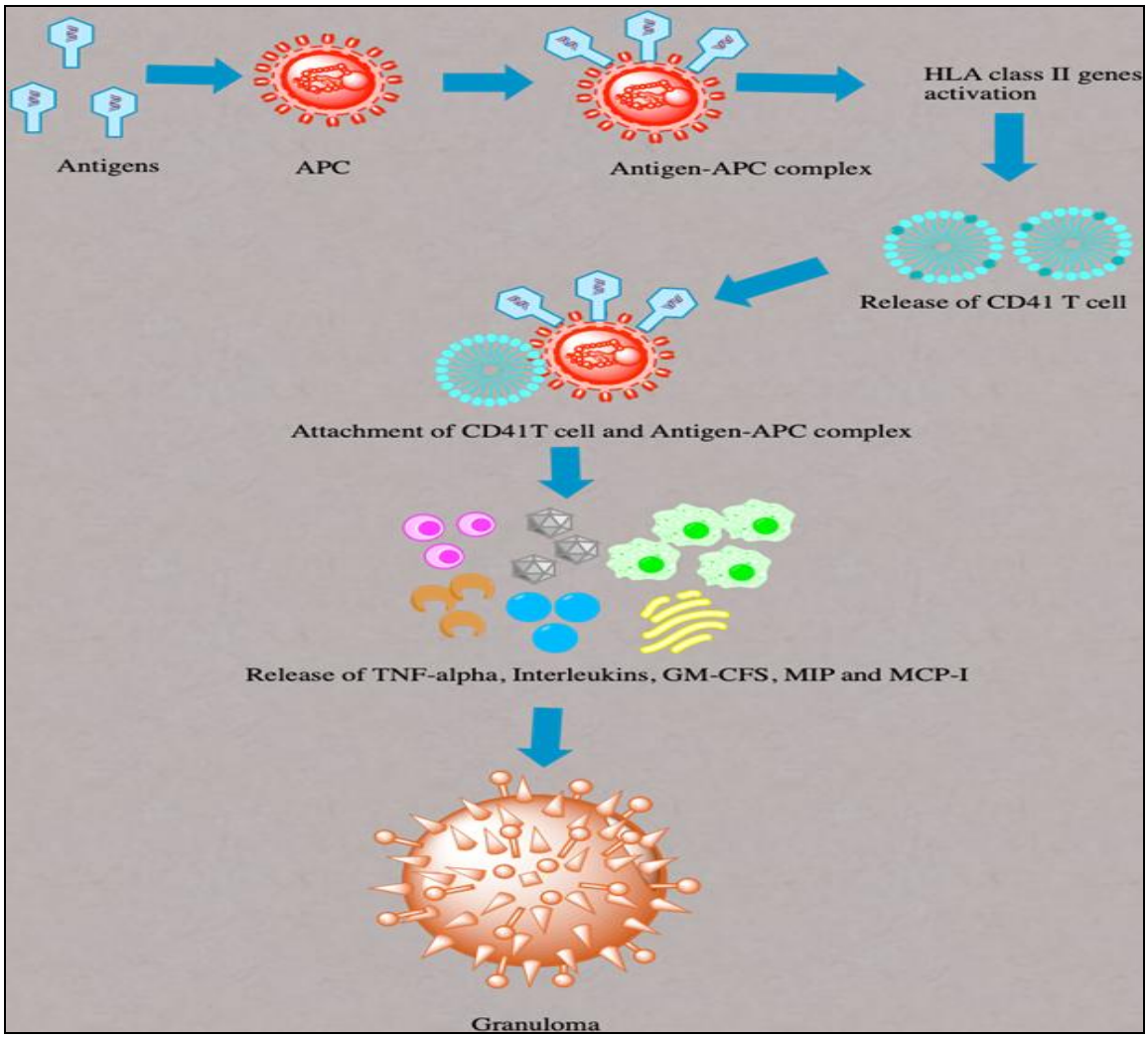

FIG. 1: PATHOGENESIS OF DEVELOPMENT OF GRANULOMA IN SARCOIDOSIS

According to Loke WSJ *et al.,* in the case of pulmonary sarcoidosis, there is an imbalance of Th1/Th2 and Th1-related cytokines, such as IL-2, IL-12, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) leading to an increased persistent inflammatory response of affected tissues. In susceptible individuals, both IL-2 and IFN-γ are the potent inducers of T cell proliferation. TNF-α involves in the differentiation of macrophages into giant cells and finally sarcoid granulomas [10].

Robert PB *et al.,* & Johnson J *et al.,* reported that CD41 T-cell receptor attaches to antigen-MHC (Major histocompatibility complex) and activates inflammatory cells to release cytokines and chemokines that involve IL-2 (interleukin-2) & finally leads to the induction of clonal proliferation of CD41 cells. However, the polarized T-helper cells that secrete proinflammatory cytokines *e.g.,* IL-1,-2,-6,-12,-15,-18, and interferon-gamma–inducing factor, facilitates the development of granuloma. The activation of tissue macrophages was also promoted by disseminating monocytes from blood vessels and disseminating monocytes induced by cytokines such as CXCL-8, selectins, integrins, and cellular adhesion molecules [7, 9, 11].

Grunewald J *et al.,* reported the role of CD4 cells in granuloma development, involving epithelioid cells, giant cells [17], macrophages/mononuclear phagocytes, and CD41 T cells with a few CD81 T cells around the periphery. These cells are closely correlated with CD41 T lymphocytes, whereas immunoglobulin (Ig) A–producing plasma cells, CD41, Th17 cells, T_{reg} (T-regulatory cells), and B lymphocytes are involved in many inflammatory and autoimmune diseases.

Moreover, the role of T_{reg} cells in chronic sarcoidosis remains unknown, which regulate autoimmune reaction by controlling the growth of $CD4^+$ and $CD8^+$ T lymphocytes due to the secretion of immunosuppressive cytokines like transforming growth factor β (TGF-β) and IL-10 involving the mechanism of cell contact *via* the CD25 molecules present on their periphery of granulomas. The Tregs have also been reported in the mutations of BTNL2 (Butyrophilin like 2) and ANXA11 (Annexin A11), leading to the development of gene products with anti-inflammatory and immune regulatory properties. These lead to the development of an imbalance between regulatory T cells and Th17, responsible for autoimmune diseases [12].

Human Leukocyte Antigen (HLA) Genes: HLA class II cells are surface proteins, and the HLA alleles comprised of HLA class I (HLA-A, -B, and -C) and class II (HLA-DR, -DP, and -DQ), also HLA-DRB1 and DQB1 (human leukocyte antigen DQ beta 1) which are HLA class-II variants. These predominate the immune system and adapt to the antigens associated with development of disease.

In class II antigens, HLA-DR like HLA-DRB1∗01 and HLA-DRB1∗04, have been found to possess a negative association with sarcoidosis, but HLADRB1∗15, HLA-DRB1∗14, HLA-DRB1∗12, HLA-DRB1∗11, and HLA-DRB1∗03 lead to an increase in the incidence rate of sarcoidosis. The HLA-DRB1∗1501/DQB1∗0602 haplotype variants are reported to be associated with the development of severe and chronic pulmonary sarcoidosis [13].

Jolanda VD *et al.,* investigated the patients of sarcoidosis involved in a multicenter epidemiologic study in the United States and proved that the transmission of HLA-DRB1*1101 and HLADPB1 *0101 alleles are the main critical factors involved in the development of autoimmune diseases. The inter-relation study between families of black U.S. based patients clarified that predisposition or immunity associated with sarcoidosis involve certain HLA-DQB1 alleles while the study involve single nucleotide polymorphisms (SNPs) in non-HLA genes such as CCR2 (chemokine receptor type 2), CCR5, IL-1α, IL23R, NOD2 (Nucleotide-binding oligomerization domain-containing protein 2), FCGR (Fc gamma receptor), and TNF-α conducted in single population as above-mentioned, alleles increase the risk for sarcoidosis.

T-Helper 1 (T_H1): The $CD4^+$ T cells activate the development of granuloma and oppose T_H1 cells. In the $CD4^+$ T cells, once the TCR (T-cell receptor) gets activated, Tbx21 (T-box genes encode transcription factors), and IFN-γ (Interferon) assistance with interleukin-12 (secreted by dendritic cells) become more pronounced. The IFN-γ binds to IFN receptors which stimulate STAT1 (Signal transducer and activator of transcription 1) leads to nurturing of Tbx21 (T box transcription factor),

gene expression of Tbx21, finally enhances IFN-γ gene transcription competence leading to an increase in the IFN-γ production. Tbx21 also controls IL-12 β receptor (IL-12βR) and antagonizes Gata3, a transcription factor which regulates the separation while IL-18 up-regulates IFN-γ and IL-12βR expression, whereas IL-12 increases the expression of IL-18 receptor on $CD4^+$ T cells [3, 14].

T Regulatory (T_{reg}) Cells: In the development of granuloma, T_{reg} cells play an essential role in the regulation of expression of CD4 and CD25 T cells and suppress the proliferation and production of activated T cells. Moreover, the co-expression of CD25 and CD27 leads to activation of FOXP3-positive T_{reg} cells, which inhibit autoimmune diseases in mice. It has been reported that mice and humans in which production of FOXP3 was inhibited, could not survive due to severe autoimmune disorders [15].

Serum Amyloid A: Serum amyloid A (SAA) proteins regulate the granuloma formation and cytokine production in patients with lung inflammation and sarcoidosis. SAA stimulates granuloma formation and cytokine production, causing granulomatous lung inflammation mediated through Toll-like receptor-2 (TLR2) in the case of patients infected with the disease [10, 14].

Natural Killer T (NKT) Cells: The natural killer T (NKT) cell can produce a good amount of Th2 (IL-4) cytokines and Th1 (IFN-γ), which are CD4 positive and express an invariant T-cell receptor (TCR). The glycolipid (galactosylceramide), is a potent NKT-cell used for the staining of CD1d-restricted NKT cells in CD1d-tetramers. The level of NKT cells has been found to be low in BALF (bronchoalveolar lavage fluid) and blood fluid in sarcoidosis. Patients infected with Lo ¨fgren's syndrome have reported normal levels of NKT cells in blood [13,] while the reduction in the level of regulatory NKT cells has been found with an exaggerated T-cell response in the infection [16].

T Cell Receptor (TCR) Genes: The sarcoidosis has been characterized by the presence of TCR genes $\gamma\delta$ or $\alpha\beta$ at inflammation site. The presence of Vα, Vβ, or $\gamma\delta$, TCR genes in lungs and blood, especially at the site of Kveim-Siltzbach skin reactions showed that it is an antigen-driven disorder. Moreover, the amount of AV2S3+ BALF T in the granuloma cells of sarcoidosis has been positively related to prognosis. The presence of AV2S3+ T cells has been found to offer a protective action against the granuloma of disease [4, 17].

Organ Involvement in Sarcoidosis: The prevalence of organ involvement in the progressive stages of sarcoidosis has been detailed in **Table 1** below [7, 18, 19].

TABLE 1: LIST OF PREVALENCE OF ORGANS INVOLVED IN PROGRESSIVE STAGE OF SARCOIDOSIS

S. no.	Organ involved	Prevalance
1	Lungs	89-95%
2	Skin	16-32%
3	Eyes	12-23%
4	Liver	12-20%
5	Lymph nodes	12-15%
6	Spleen	7%
7	Bone marrow	4-8%
8	Calcium irregulation	4-7%
9	Upper respiratory tract	3-10%
10	Nervous system	3-9%
11	Parotid glands	3-4%
12	Heart	2-5%
13	Bone joints	1-7%
14	Kidney	1%
15	Muscles	0.4-1%

Diagnosis: The diagnosis of sarcoidosis is extremely difficult because there is not a single test that would be able to diagnose the signs and symptoms of the disease. In case of sarcoidosis, before precluding the disease, a complete medical history including occupation, medication, and environmental exposures, a physical examination must be done [13, 20].

The diagnostic tests which are used to diagnose the disease are as follows:

Chest X-rays: A chest X-ray can locate granulomas in the lungs and heart. Stages of sarcoidosis cannot be determined with the help of this technique. The chest radiograph in an asymptomatic patient, Lo 'fgren' syndrome or Heerfordt syndrome, shows uptake in the lacrimal and parotid glands shown with Panda sign while uptake in bilateral hilar and right paratracheal represents with Lambda sign [2].

Stages of Chest Radiography:

0 stage = Represents the normal chest X-ray

I stage = Bilateral hilar lymphadenopathy (BHL): In this stage, X-ray manifests a similar extent of growth of lymph nodes at the "root" across the lungs.

II stage = BHL plus pulmonary infiltrations: The X-ray manifests a disease with enlargement into additional lung tissue.

III stage = Pulmonary infiltration only (without BHL): The X-ray manifests a disease process that metastasizes all along with the lung tissue (without enlargement of lymph nodes).

IV stage = Pulmonary fibrosis: The X-ray shows scarring, small lung fields, and "retraction" of both hila, which represents the area at the "root" of the lung" [19].

Bronchoscopy: This test is used to examine the bronchial tubes, perform a biopsy (a small tissue sample), to check the presence of granulomas, and preclude infection [3].

Pulmonary Function (Breathing) Tests: Spirometer is a device used to record the variation in airflow while the patient inhales and exhales as well as the overall volume of air exhaled. The sarcoidosis patients may have normal PFTs but can show a restrictive or obstructive pattern with reduced diffusing capacity, which can be due to parenchymal involvement or because of the presence of pulmonary hypertension. There has been a significant difference observed in all parameters of PFTs amongst the patients of sarcoidosis. Technically, the gas transfer ability of the lungs (gas transfer factor, DLco) drops to 50% in the patient.

Blood Tests: Blood analysis evaluates the types, number of blood proteins and cells in the body. In a blood test, if calcium level rises, as well as abnormality in liver function, is observed, this can follow sarcoidosis. The blood test is performed to evaluate a substance called angiotensin-converting enzyme (ACE), and an increase in the level of ACE enzyme is an indirect measurement of the soluble interleukin 2 receptor levels (sIL2R) [9].

Pulse Oximetry: A pulse oximeter is used to measure the amount of oxygen in the blood. If the oxygen level is low, then supplemental oxygen is recommended [21].

Electrocardiogram (EKG or ECG): Electrocardiogram (ECG or EKG) is used to identify the electrocardiographic abnormalities and to detect the type and frequency of electrocardiographic pattern differences between the patients of pulmonary sarcoidosis and non-patients [22, 23].

PET Scan (Positron Electron Tomography): The severity of inflammation can be identified by this scan by the use of a radioactive material F-fluorodeoxyglucose (iv) [12, 24].

Gallium Scanning: Gallium scanning has been used to estimate the serum ACE (Angiotensin-converting enzyme) activity in the inflammation of eyes or lymph nodes, to diagnose sarcoidosis, using radioactive agent gallium-67 [25].

The Tuberculin Skin Test (TST): TST is used to differentiate the conditions of granuloma. If TST is negative in the general population, then the population could be sensitive to sarcoidosis, and the positive reports would indicate tuberculosis in sarcoidal population.

Slit-lamp Examination: The slit-lamp examination is done to verify and detect the vision-related problems associated with sarcoidosis.

Transbronchial Lung Biopsy (TBLB): Mediastinoscopy, and video-assisted thoracoscopic surgery (VATS) have been reported to be advantageous in procuring lung as well as intrathoracic lymph nodes material. Non-caseating epithelioid cell granulomas in tissue biopsy specimens confirm the diagnosis of sarcoidosis. The endobronchial ultrasound-guided transbronchial needle aspiration (EBUSTBNA) technique involves the diagnostic yield to 75% in pulmonary sarcoidosis. The diagnostic yield is calculated by combining EBUS-TBNA with endobronchial mucosal and transbronchial lung biopsy [15].

Neurological Tests: Neurological tests like electromyography, spinal taps, evoked potentials, or nerve conduction tests are performed to identify the nervous system-related problems associated with sarcoidosis.

High-Resolution Computed Tomography (CT) Scan: The CT scan is used to identify the granulomas. High resolution computed tomography (HRCT), modified scanning technique, has a more

sensitive modality to identify fibrotic changes in patients to establish a better correlation with pulmonary function in comparison with chest x-ray [7, 9, 18].

The basic pattern of HRCT in sarcoidosis-related pulmonary fibrosis are bronchial distortion, diffuse linear, and honeycombing. Moreover, the bronchial distortion is characterized by angulation and bronchial dilatation [9].

In diffuse linear fibrosis, the presence of scattered peripheral lines, or septal reticulation and translobular lines, represents the HRCT pattern that results from sarcoid inflammation within the lymphatics through interlobular septa. However, the honeycombing fibrosis-associated with PF, shows the formation of cyst at the distal airway and alveolar level. This honeycomb pattern has been noted in less than half of patients with sarcoidosis-associated PF [24].

Treatment: The pharmacological treatment is not required in all the patients as the majority of them recover from the disease with the course of time [20]. The severity and extent of the diseased condition will determine whether and what type of treatment is required to suppress the immune system and the organ damage. The main reason to start treatment is "to avoid danger or improve quality of life". Therapeutic treatments are provided to reduce the inflammation of the affected tissues, an impact of granuloma development, and to prevent the progression of lung fibrosis as well as irreversible organ damage.

Therapeutic Management of Sarcoidosis: The current guideline, dating from 1999, states that "the appropriate treatment has not been well-defined for all patients" [26]. The medications which are prescribed for symptomatic treatment of sarcoidosis have been summarized below **Fig. 2**.

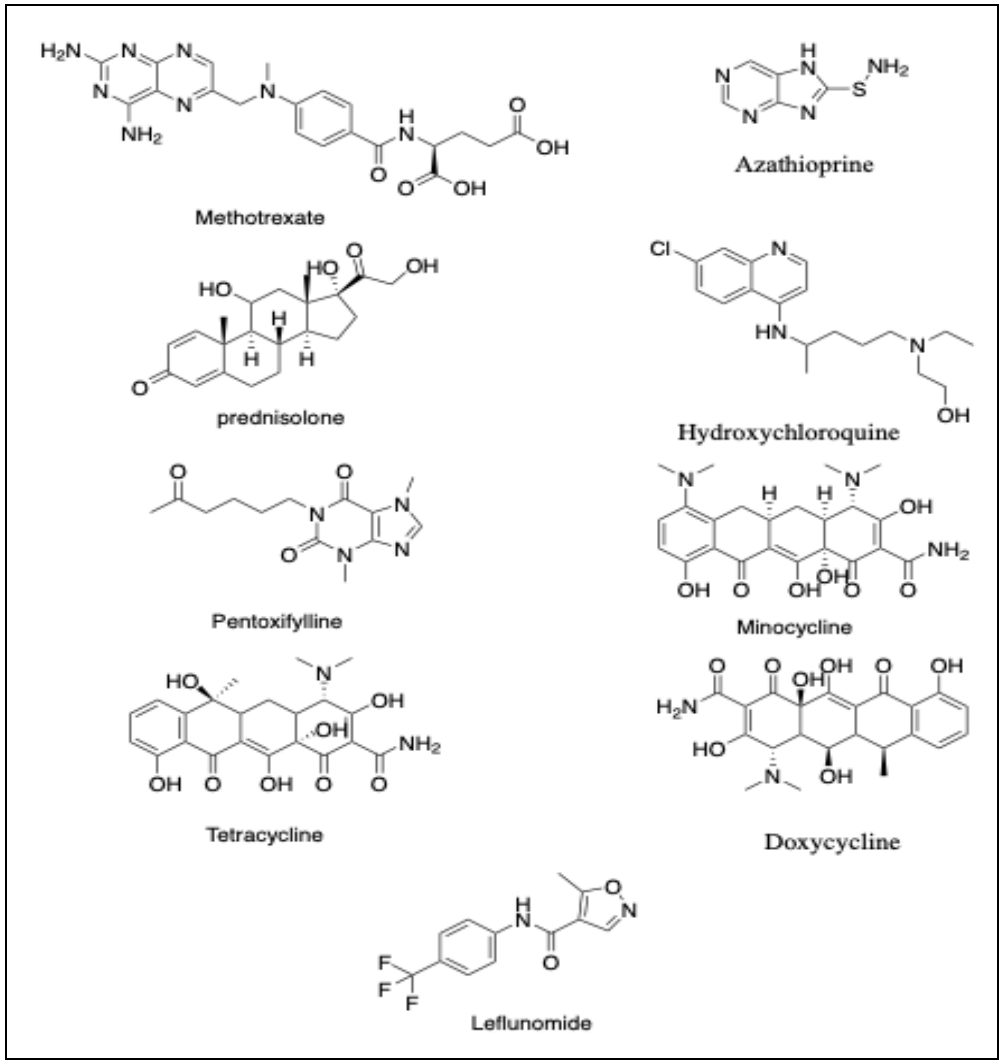

FIG. 2: STRUCTURES OF DRUGS PRESCRIBED FOR SARCOIDOSIS

First-Line Treatment: Corticosteroids are powerful anti-inflammatory agents, especially prednisone is the most commonly used corticosteroid for the treatment of sarcoidosis in the form of pills, injections, inhalations, or as eye drops or other topical forms. The serious adverse effects of corticosteroids are hypopigmentation, telangiectasias; acne-folliculitis with long-term use. Moreover, as the daily dose is concerned, for topical corticosteroids, it is twice daily, and for oral corticosteroid, the initial dose is 0.5–1mg/kg/d of prednisone equivalent, which may be gradually increased to a maximum safe dose of 6.5mg/kg/d while the lowest effective dose of the drug is 200–400mg daily [27-29]. The major use of corticosteroids in sarcoidosis is to improve liver function, especially in patients with liver dysfunctioning [30, 31,] and to prevent the progression of the disease [27, 32].

Second Line Treatment: Disease-modifying anti-rheumatic drugs (DMARDs are used to suppress the hyperactive immune system such as methotrexate, folic acid antagonist [33] (dose 7.5–25mg/week orally), azathioprine (daily dose of 50–200mg) and leflunomide (daily dose 20 mg/d) to reduce inflammation. Moreover, the potential side effects of using DMARDs include liver damage, gastrointestinal disturbance, hematologic abnormalities, and hypersensitivity skin reactions [13]. Methotrexate exhibits a significant steroid-sparing effect and improves the deteriorated functions of the lung [34, 35]. It is commonly used as a first-line agent in case of contra-indications for corticosteroids [33]. A second choice, second-line treatment, is azathioprine. A retrospective study reported that azathioprine and methotrexate are equally efficient, but azathioprine appeared to have more side effects [34]. Mycophenolate mofetil and leflunomide are other second-line alternatives [12].

Hydroxychloroquine is used to prevent malaria and is considered a disease-modifying anti-rheumatic drug. It can decrease the swelling of arthritis, pain, and long-term disability. Hydroxychloroquine suppresses the immune system and is used to treat sarcoidosis of the skin, lungs, and nervous system. The daily dose of hydroxychloroquine is 200–400mg, and the maximum safe dose is 6.5mg/kg/d. It is used in case of cutaneous involvement or hypercalcemia [35, 36, 37].

Third Line Treatment: In refractory sarcoidosis, TNF-alpha inhibitors can be prescribed as a third-line agent. TNF-alpha inhibitors such as pento-xifylline are used in the treatment of peripheral vascular disease. By decreasing TNF-alpha signaling, pentoxifylline reduces the immune response and thus granulomas formation in the lungs [37].

Moreover, monoclonal antibodies like infliximab, adalimumab, rituximab, and golimumab which are mostly prescribed to treat overactive immune systems may also be the drug of choice in many cases where a specific antibody is required to treat a specific antigen. Infliximab has been studied in randomized controlled trials and reported to possess beneficial effects on both pulmonary and extra-pulmonary sarcoidosis in a subgroup of carefully selected patients [38, 39, 40].

The INBUILD study has shown the efficiency of nintedanib in reduced forced vital capacity in patients with fibrotic interstitial lung disease in sarcoidosis [41]. Recently, inhibition of the JAK-STAT signaling pathway has been reported as a new promising treatment in sarcoidosis; future research is underway (NCT03910543, NCT037-93439). The efficacy of pirfenidone in progressive fibrotic sarcoidosis has also been studied (NCT03260556) [42].

Several reports have proven the efficacy of colchicine derivatives in sarcoid arthritis, and good responses have also been observed in the case of lúpus pernio. This medicine is the first-line treatment in gout to treat joint pain associated with sarcoidosis. The major adverse effects related to the use of this drug are nausea, vomiting, diarrhea, and stomach cramps or pain [38].

CONCLUSION: However, sarcoidosis is a rare autoimmune inflammatory disease; an improvement in the cases of sarcoidosis has been seen in recent years, much research is unknown and going on. With the increased use of modern diagnostic tools, the findings so far are considered. Raising the awareness of rare manifestations will facilitate better management of these patients. At the very least, it is likely to get more recognition in the future concerning pathogenesis and therapeutic research.

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