Nodular Sarcoidosis

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Introduction:
Sarcoidosis is a systemic non-caseating granulomatous disorder of unknown origin. In Greek, sarcoidosis means a fleshlike condition (sarco means “flesh,” eidos means “like,” and osis means “condition.”) In contemporary times, sarcoidosis is a multisystem disorder of unknown origin, characterized by the accumulation of lymphocytes and mononuclear phagocytes that induce the formation of non-caseating epithelioid granulomas with secondary derangement of normal tissue or organ anatomy and function. Evidence of sarcoidosis lasting longer than two years designates it as chronic.

Sarcoidosis affects all races, both sexes, and all ages. Most commonly, it is present in winter and early spring. It usually peaks between the ages of 25 and 35 years; a second peak occurs in women aged 45 to 65 years. Cases affecting African Americans have a tendency to be more acute and severe than in other races, whereas cases affecting white persons have a tendency to be asymptomatic with a more favorable prognosis.

Case Report:
A 51 years old Canadian female patient presented to the clinic suffering from multiple asymptomatic bilateral erythematous nodules on the dorsum of both forearms of 1 year duration (Fig 1,2).
Our clinical impression was suspected clinically to be sarcoidosis or cutaneous T-cell lymphoma and investigations was done accordingly.
Investigations included CBC, ESR, Complete Blood Biochemistry, Tuberculin Test, Chest X ray, ANA, C3 and C4, Hepatitis B&C screening, RPR, and all are within normal limit.
A 3 mm punch biopsy showed non-caseating granuloma.
ACE inhibitor was not done because of the availability. So our diagnosis was Nodular Sarcoidosis and she was treated accordingly by superpotent topical corticosteroids which decreases the nodule height and the erythema.

Discussion:
Sarcoidosis is a systemic non-caseating granulomatous disorder of unknown origin. Many postulations abound as to whether the cause is multifactorial or due to a single antigen-driven disease that has not yet been determined. The cause has been thought to be elusive because sarcoidosis is a disease with the following characteristic flaws: polymorphic
disease presentations, overlap with other diseases, paucity of systematic epidemiologic investigations of cause, diagnostic access bias, misclassification of the disease because of insensitive and nondiagnostic testing, and its diagnosis is one of exclusion.  

**Immunologic pathogenesis**

The development of noncaseating granulomas is thought to be the result of the local presentation of an antigen by macrophages to T lymphocytes, CD4 T cells/helper T cell type 1 (Th1) phenotype. The CD4 T cells most likely act in a two-fold manner: in antigen recognition and in amplification of the local cellular immune response. The CD4 T cells in sarcoidosis express alpha/beta T-cell receptors and recognize antigens that are major histocompatibility complex (HLA) class II restricted (exogenous antigen presentation). T-cell activation is also dependent on the interaction of the B7:CD28/CTLA-4 costimulatory pathway.

A cellular redistribution from the peripheral blood and in situ proliferation account for the increased number of cells in tissues involved in the inflammatory process. There is CD4 T-cell compartmentalization, when lymphocytes recognize specific adhesion molecules (i.e., E-selectin) on endothelial cells. Once compartmentalized, the production of CD4 T-cell cytokines (interleukin 2 [IL-2], interferon gamma, IL-8, and tumor necrosis factor-a [TNF-a]), with other immune effector cells (macrophages, natural killer cells, and mast cells), enhance lymphocyte proliferation to induce granuloma formation. Thus a highly focused, antigen-driven, over-exuberant cellular immune response occurs within the target organ. Vaalamo et al. found that macrophage production of metalloelastase contributes to elastin degradation and aids in the macrophage migration occurring in granulomatous diseases. The granulomas become hyalized, then fibrotic, resulting in tissue scarring. This is believed to be a shift in cytokine profile to that of Th2 CD4 T cells (ie, IL-4), thereby causing a fibroproliferative phase. The recruitment of CD4 T cells from the peripheral blood causes the development of anergy. There is also resultant hypergammaglobulinemia from a nonspecific induction of polyclonal B-cell immunoglobulin production activated by the response of localized T cells.

**Genetic pathogenesis**

A genetic origin is supported by the presence of positive familial clusters of sarcoidosis. In the United States familial clusters occur more commonly among African Americans. Genetic variations that promote susceptibility to the disease could reside in loci that influence immune regulation, T-cell function, or antigen presentation. Primary associations through serologic studies have shown patients with certain class I and II HLA alleles, found on chromosome 6, may have increased susceptibility to sarcoidosis. Martinetti et al. found that the heterogeneity of HLA polymorphisms mirrors the heterogeneity of the disease. Of 233 European patients with sarcoidosis, there was a positive association with HLA-1, -B8, and -DR3. There was also a positive association with HLA-B27 and disease limited to the lungs. There was a negative association with HLA-B12 and -DR4. HLA-B13 and -B35 were associated with early onset of disease, and HLA-DR3 was found to be associated with good outcome. With the use of polymerase chain reaction (PCR) restriction fragment polymorphism, pinpointed the HLA-DRB1 locus to determine susceptibility to sarcoidosis. Further genetic studies have found that angiotensin-converting enzyme (ACE) gene polymorphism might play a role in sarcoidosis.

**Infectious pathogenesis**

The association of tuberculosis and sarcoidosis remains controversial (TB or not TB). Because of the use of PCR, *Mycobacterium* has re-emerged as a possible transmittable agent in sarcoidosis. They demonstrated *M paratuberculosis* or a closely related *M avium*, but no *M tuberculosis*. Vokurka et al. using PCR, found no detectable *M tuberculosis* in 15 cases of lung and lymph node sarcoidosis. Di Alberti et al. suggested a viral origin of sarcoidosis, when they demonstrated a high detection rate of human herpes virus-8 ORF 26 DNA in sarcoidosis tissue.

**Environmental pathogenesis**

Some inorganic antigens suggested in the origin of sarcoidosis have included clay, talc, pine pollen, oxalosis, and beryllium. Occupational environmental associations have been health care workers, firemen, and navy personnel on aircraft.
Carriers.5 Sarcoïdosis is found to be more common in nonsmokers than in smokers.2

**Cutaneous manifestations**

On average, 25% of sarcoidosis cases have cutaneous involvement that can occur at any stage; however, most often cutaneous involvement occurs at onset of the disease.2,12,15,53 In general, specific skin lesions have no prognostic significance. It does not show any correlation with the extent of systemic involvement, and do not indicate a more serious form of sarcoidosis.2,12,13 This is with the exception of erythema nodosum (EN), which has been shown to have a good prognosis because of its association with sarcoidosis that resolves spontaneously.53,156 The dermatologist will often be the first to consider a diagnosis of sarcoidosis because of the cutaneous manifestations of the disease. Any granulomatous skin lesion without apparent diagnosis, screening for systemic sarcoidosis is indicated.2,53,56 Sarcoidosis cutaneous lesions, especially those that are chronic, tend to be asymptomatic.53

Sarcoidosis lesions are classified as specific and nonspecific; specific lesions contain granulomas, and nonspecific lesions are reactive processes.3 Common specific sarcoidosis skin lesions manifest as maculopapules, nodules, plaques, subcutaneous nodules, infiltrative scars, and lupus pernio.2,12,16,54,55 Maculopapular lesions are the most common cutaneous manifestation of granulomatous involvement in sarcoidosis (Fig 1).2,56,161,166

1. **Maculopapular sarcoidosis**

   They are usually red to purple papules and measure less than 1 cm.56 They are commonly found on the face, lips, nape of the neck, upper back, extremities, and rarely in the oral cavity (which often gets confused with Fordyce spots).2,12,16,54,161 They may be associated with acute forms of sarcoidosis with simultaneous parotid, ocular, lymph node, or pulmonary involvement.156,162 Diascopy of the lesions gives the appearance of an “apple-jelly” color, but this change is not specific to sarcoidosis.61 Nodular lesions occur more frequently on the torso or extremities, but may occur on the face.62

   **Nodular sarcoidosis**

   Skin plaques are round to oval red-brown lesions, which are generally elevated with induration, and occur on the face, scalp, back, shoulders, arms, and buttocks.2,15,164 Annular plaques can occur on the forehead and lead to scarring and alopecia.56 Skin plaques of the head and neck are seen in association with chronic sarcoidosis.156,162 Subcutaneous nodules are painless, firm, mobile nodules measuring from 0.5 to 2 cm without epidermal involvement.56,164,168

   **Subcutaneous sarcoidosis**

   The number of nodules can range from 1 to 100 and most frequently the nodules appear late in the course of the disease.2,56,168 They can be associated with lung, liver, and spleen sarcoidosis.156

   In active scars that have been quiescent for years that become infiltrated with sarcoidosis develop a red or purple hue with induration.156,164,168

   **New-onset redness and fullness to a previously quiescent traumatic scar. Infiltrating scar sarcoidosis.**

   They may appear early in the disease before the onset of pulmonary disease or parallel chronic systemic findings.2,12 Patients with sarcoidosis in remission with whom changing scars develop show possible reactivation of their sarcoidosis.121 The pathogenesis of infiltrative scar sarcoidosis is unknown.121

   **Lupus pernio**

   Lesions of lupus pernio can be disfiguring.122 Lupus pernio coexists with chronic fibrotic sarcoidosis of the upper respiratory tract, with nasal, pharyngeal, and laryngeal involvement, pulmonary fibrosis, chronic uveitis, and bone cysts.164,165,166

   Multiple manifestations in the skin with underlying granulomatous changes (specific) have been reported, to some extent mimicking syphilis with its protean manifestations.

   **Atypical erythematous exfoliative sarcoidosis.**

   Acquired ichthyosis is a specific sarcoid cutaneous finding but not a common presentation.65,174

   **Sarcoidosis ichthyosis**
The differential diagnosis includes sarcoidosis, lymphoma, solid malignancies, HIV and mycobacterial infection, medication-induced connective tissue disease, malnutrition, and parathyroid/thyroid disease. Some documented uncommon atypical specific presentations of sarcoidosis are ulcerative, psoriasiform, hypopigmented, faint erythema, verrucous, ichthyosiform, folliculitis, lichenoid, eruptive, erythrodermic, cicatricial alopecia, mutilating lesions, erythematous plaques of palms and soles, unilateral lower extremity edema, nodular fingertip lesions, penile (Fig 9), granulomatous cheilitis, scalp nodules, erythema annular centrifugum, annular elastolytic, palmar erythema, rosacea-like syndrome, vulvar, morpheaform, light-exposed papules, angiolupoid, perforating, lupus erythematosus-like, and umbilicated.

8. Scarring alopecia due to sarcoidosis.

Erythema nodosum. A reactive form of sarcoidosis.

When associated with bilateral hilar adenopathy with or without pulmonary fibrosis, migratory polyarthritis, fever, and iritis, it is called Lofgren’s syndrome.

Other nonspecific changes seen with sarcoidosis are calcifications, prurigo, and erythema multiforme. Nonspecific and specific nail changes that occur with sarcoidosis include clubbing, dystrophy with and without underlying bone cysts, subungual hyperkeratosis, and onycholysis (Fig 11).

Clinical polymorphisms of systemic sarcoidosis

In patients with sarcoidosis, one third can present with nonspecific constitutional complaints including fever, fatigue, malaise, and weight loss. Postsarcoidosis chronic fatigue syndrome may be difficult to separate from low-grade persistent sarcoidosis. Sarcoidosis is also in the differential diagnosis of a fever of unknown origin. Other symptoms can be associated with the specific organ system affected. Johns and Michelle noted that extrathoracic manifestations of sarcoidosis are more common in African American patients. Lung manifestations occur in nearly all cases (90%) of sarcoid. Lung disease is mainly granulomatous involvement of interstitial areas, affecting alveoli, blood vessels, and bronchioles. These pulmonary changes lead to dry chest, restricted lung volumes, and abnormal gas exchange. In 10% to 15% of patients, there is irreversible fibrosis and severe disability. Pleural effusions with infiltration of pleura are documented, but rare. Symptoms of lung disease include dyspnea, cough, chest pain, and rarely hemoptysis. Radiographically, sarcoidosis of the lung is staged. Stage 0 is normal; stage I is bilateral hilar and/or para tracheal adenopathy; stage II is adenopathy with pulmonary infiltrate (Fig 12); stage III is pulmonary infiltrates only; stage IV is pulmonary fibrosis. The stages are not chronologic in nature.

Bone marrow and hematologic changes of sarcoidosis are seen in up to 40% of cases, manifesting as leukopenia, lymphocytopenia, and an elevated erythrocyte sedimentation rate.

Musculoskeletal involvement has been reported to occur in up to 39% of patients with sarcoidosis. Clinically muscular involvement may be evident because of weakness, pain, tenderness, and erythema with warmth of the overlying skin. Musculoskeletal manifestations include bone cysts and osteolytic lesions, chronic myopathy, muscle nodules, tumorlike lesions, arthralgias, arthritis, and tenosynovitis. Ocular manifestations are present in 30% to 50% of cases. There is a definite threat of blindness, and all patients need eye examinations, even if they have no symptoms. Sarcoidosis classically presents as acute anterior uveitis. There may also be blurred vision, photophobia, and excessive lacrimation. Other ocular lesions include posterior uveitis, conjunctival nodules, scleral plaques, lacrimal gland enlargement, and iritis cardiac manifestations occur clinically in 5% of cases and may cause serious sequelae. In comparison at autopsy, 10% to 20% in the United States and 67% in Japan were found to have cardiac muscle granulomatous infiltration. Sudden cardiac death can be the initial manifestation of cardiac sarcoidosis in 5% to 10% of cases. Electrocardiographic abnormalities such as complete heart block and other arrhythmias may also exist. Patients can also have papillary muscle dysfunction, infiltrative cardiomyopathy with congestive heart failure, and pericarditis. Myocardial scintigraphy with thallium 201, echocardiography, 24-hour...
Holter monitor, and gallium 67 scan may be helpful in evaluating the extent of cardiac disease. Neurologic sarcoidosis manifests in 5% to 10% of sarcoidosis cases. The most common is self-limited cranial nerve VII palsy, but all cranial nerves can be affected. Other manifestations are aseptic meningitis, sudden hearing loss, seizure, psychiatric changes, arachnoiditis/perivasculitis, space-occupying masses, peripheral neuropathy, stroke, and myasthenia gravis. Neurologic manifestations are associated with a higher mortality rate and can be either chronic or relapsing. There is a case reported of neurosarcoidosis occurring after breast silicone implantation and of the Uthoff phenomenon (visual loss after exposure to heat) with sarcoidosis.

Hypercalcemia is an endocrine manifestation of sarcoidosis occurring in up to 17% of cases. Alveolar macrophage secretion of 1,25 dihydroxy-vitamin D, independent of a feedback mechanism, induces increased calcium levels. Johns and Michelle noted anorexia, nausea, and vomiting from hypercalcemia caused by exposure to sunlight or ingested vitamin D. Supplemental oral calcium does not suppress granuloma vitamin D production. Diabetes insipidus can result from pituitary involvement. Thyroid involvement can result in a diffuse or nodular goiter with hyperthyroidism. Hashimoto’s thyroiditis with elevated circulating thyroid autoantibodies can be seen in sarcoidosis.

Renal sarcoidosis involvement can result in diffuse interstitial nephritis often without identifiable granulomas. These patients are at risk of renal insufficiency; however, patients with sarcoidosis have a 20% greater risk than the general population for the development of nephrolithiasis and nephrocalcinosis due to hypercalcemia. There has been a report of bilateral hydronephrosis due to obstruction from a sarcoid retroperitoneal mass. Sarcoidosis of the urethra can cause obstructive symptoms. Gastrointestinal sarcoidosis is rare. Involvement most commonly presents in the stomach as an ulcer or mass as well as pancreatitis, acute appendicitis, and duodenal obstruction. Sarcoidosis granulomas may infiltrate virtually all organs including the breasts, uterus, fallopian tubes, ovaries, testicles, epididymis, and prostate gland. Pearce and Nolan reported a case of postmenopausal bleeding from endometrial granulomas.

**Sarcoidosis syndromes**

Because of the many polymorphisms of sarcoidosis, there are several syndromes incorporating specific manifestations of the disease. Lofgren’s syndrome, frequent in Irish, Scandinavian, and Puerto Rican female patients, consists of acute sarcoidosis, EN, migratory polyarthritis, fever, and iritis. It usually has a good prognosis with a self-limiting course and resolution without therapy. Sarcoïdosis, Darier-Roussy type, is the presence of subcutaneous nodules of the trunk and extremities. Heerfordt-Waldenstrom syndrome is the combination of fever, parotid enlargement, anterior uveitis, and facial nerve palsy. Some complications of this syndrome can include lethargy, hypereleasip, papilledema, meningism, and other bizarre neurologic manifestations. Mikulicz’s syndrome is bilateral sarcoidosis of the parotid, submandibular, sublingual, and lacrimal glands.

**Diagnostic evaluation**

There is no diagnostic test for sarcoidosis. Hence it is a diagnosis of exclusion. It is important to obtain a complete history with emphasis on occupational and environmental exposure. The emphasis during physical examination should be placed on the skin, lungs, eyes, nerves, and heart. If there are any abnormal findings suggestive of sarcoidosis, a biopsy (skin, peritracheal nodes, or salivary glands) should be performed to obtain histologic confirmation of noncaseating granulomas, polarization for foreign body evaluation, and tissue culture to rule out a bacterial, mycobacterial, and fungal origin. Bronchoscopy with transbronchial lymph node biopsy is often performed in patients without cutaneous involvement. At the time of bronchoscopy, bronchoalveolar lavage for evaluation of leukocyte differential counts may also be performed. A CD4/CD8 ratio higher than 3.5 is suggestive of sarcoidosis. Histologic examination of sarcoidosis shows well-demarcated islands of epithelioid cells with occasional giant cell formation and no necrosis. Ga scan from patient shown in Fig 1.
demonstrating the panda and lambda signs. The panda appearance is the image of a face of a panda bear produced by parotid and lacrimal gland sarcoidosis granuloma gallium uptake. The lambda sign is absorption by the bilateral hilar lymph node involvement and forms the Greek letter lambda. Lesions of nodular cutaneous sarcoidosis may be observed on gallium 67-labeled scanning with a differential diagnosis of cutaneous deep fungal and mycobacterial infections as well as cutaneous lymphomas.

Laboratory evaluation of a suspected patient with sarcoidosis includes liver and renal function tests, complete blood cell count, erythrocyte sedimentation rate, and determination of serum calcium and ACE levels. Other tests based on the clinical presentation may include rapid plasmin reagin and antineutrophil cytoplasm, antinuclear, antimitochondrial, and antithyroid antibodies. Additional clinical evaluation should include pulmonary function tests, electrocardiography, slit-lamp eye examination, and tuberculin/energy testing.

**Measurement of disease progression**
ACE is normally produced by endothelial cells in the kidney and in sarcoidosis by T-cell-stimulated epithelioid cells at the periphery of the granulomas. ACE is not specific for sarcoidosis and is elevated in leprosy, alcoholic liver disease (cirrhosis), alpha-1-antitrypsin deficiency, diabetes mellitus, Kaposi's sarcoma/HIV, Melkerson-Rosenthal syndrome, silicosis, hypersensitivity pneumonitis, Gaucher's syndrome, primary biliary cirrhosis, histoplasmosis, and asbestosis.

**Treatment**
The indication for treatment of systemic sarcoidosis depends on disabling symptoms, organ derangement or dysfunction, and laboratory and ancillary study results. Glucocorticoids are the first-line treatment. In chronic disease, nonsteroidal immunosuppressive agents are used to avoid long-term corticosteroid-induced side effects. The agents most often used are antimalarials, methotrexate, azathioprine, chlorambucil, cyclophosphamide, and cyclosporine. Nonoral therapies reported for limited cutaneous sarcoidosis have included superpotent topical corticosteroids, topical steroid with hydrocollloid occlusive dressing, topical hydrocortisone 5% powder in hydrophilic ointment with phenophoresis, intralesional triamcinolone (5-10 mg/mL repeated monthly), intralesional chloroquine (50 mg/mL monthly), and carbon dioxide or pulsed dye laser for lupus pernio. Oral therapies for cutaneous sarcoidosis can be used for large disfiguring lesions, generalized involvement, or lesions that have proven refractory to localized nonoral therapies. Recently reported oral therapies that have been successful with cutaneous sarcoidosis include prednisone, hydroxychloroquine, chloroquine, methotrexate, allopurinol, thalidomide, isotretinoin, PUVA, tranilast, melatonin, and prospidine.

**Prognosis/mortality**
Up to 60% of patients with sarcoidosis experience spontaneous resolution, and an additional 10% to 20% of patients have resolution with corticosteroid use. Patients with EN and acute inflammatory manifestations of sarcoidosis appear to have a high rate of spontaneous remissions (80%). The prognosis of cutaneous sarcoidosis depends on systemic involvement. Relapses as treatment is withdrawn are frequent, especially in African American patients, who tend to have more severe and more prolonged symptoms than white patients.
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