

SARCOIDOSIS: A review and report of three cases

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Abstract :

3 male patients with cutaneous sarcoidosis are reported. Systemic involvement has not been detected and they are periodically checked for possible future systemic spread. The first case was a male patient who presented with wide spread multiple cutaneous nodules affecting forehead, nostrils, upper arms, thighs and trunk. The nodules were asymptomatic and had a violaceous color and erupted over a period of 2 years. The second patient had nasal rim lesions of 7-8 months duration. The third patient had papular lesions of the face of 6 months duration. All cases were diagnosed on histopathological findings. The treatment given and the patient response is discussed.

Report of 3 cases :

First case:

(J.Z.) a 34 years old male Palestinian patient came to the dermatology clinic because of multiple asymptomatic cutaneous nodules affecting forehead, both nostrils, upper arms, thighs and trunk

(Fig 1,2,3,4,5,6). The lesions began to appear 2 years ago in June 1997, 2 months after returning from Mecca after pilgrimage. The patient also lived in India for four years (1982-1986). The nodules were violaceous in colour, subcutaneous, raised and fixed to the skin, and most of them had a diameter of 10-12mm. The forehead and nostril lesions were papular. The patient had no lymph gland, liver or spleen enlargement. Sensations, lacrimal and salivary glands were normal. Investigations done were normal except for a raised ESR.

The investigations included complete blood count, blood biochemistry profile, serum protein electrophoresis, complement estimation, 24 hour urine calcium, serology for hepatitis and HIV. Tuberculin test was negative. Fundoscopy and slit lamp examination for the eyes were normal. ENT examination showed normal upper respiratory tract. X-ray chest showed slight prominence of right hilum and normal heart and lungs. The diagnosis was sarcoidosis or cutaneous lymphocytoma and biopsy of one nodule showed sarcoid granuloma (Fig 7 & 8). Patient was put on systemic steroid 1 mg/kg daily plus cryotherapy once every 3 weeks and he began to improve. Some lesions cleared and some got smaller (Fig 9 & 10).

The patient is followed up for evidence of systemic sarcoidosis that may develop and body gallium scan has been requested.



Fig. 1 Forehead papular lesion- case one.



Fig. 2 Nasal rim and both cheeks papular lesions- case one

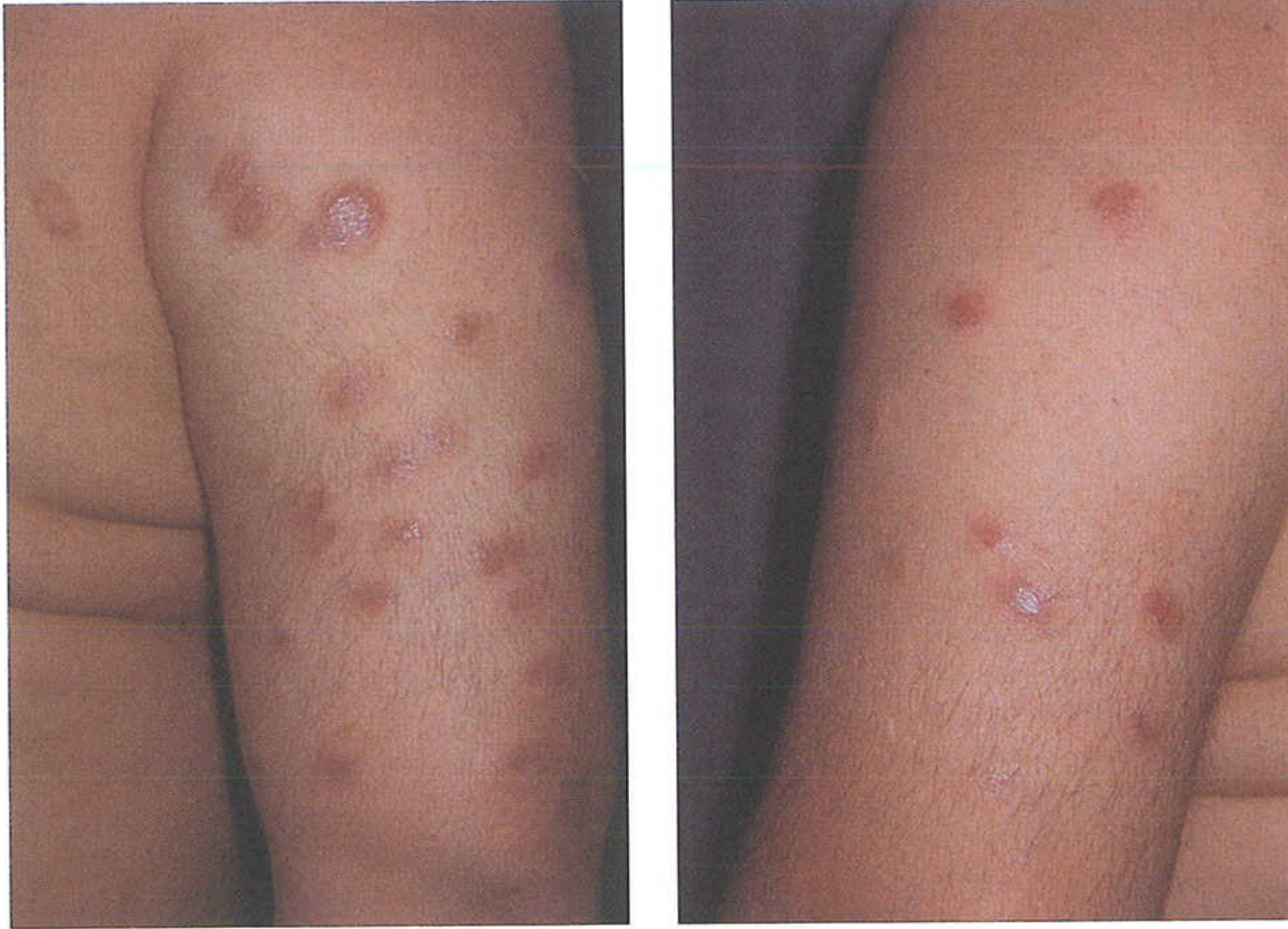


Fig. 3-4 Upper limb nodular lesions-case one



Fig. 5 Nodules of the back (case one)



Fig. 6 Nodules of the back (case one)

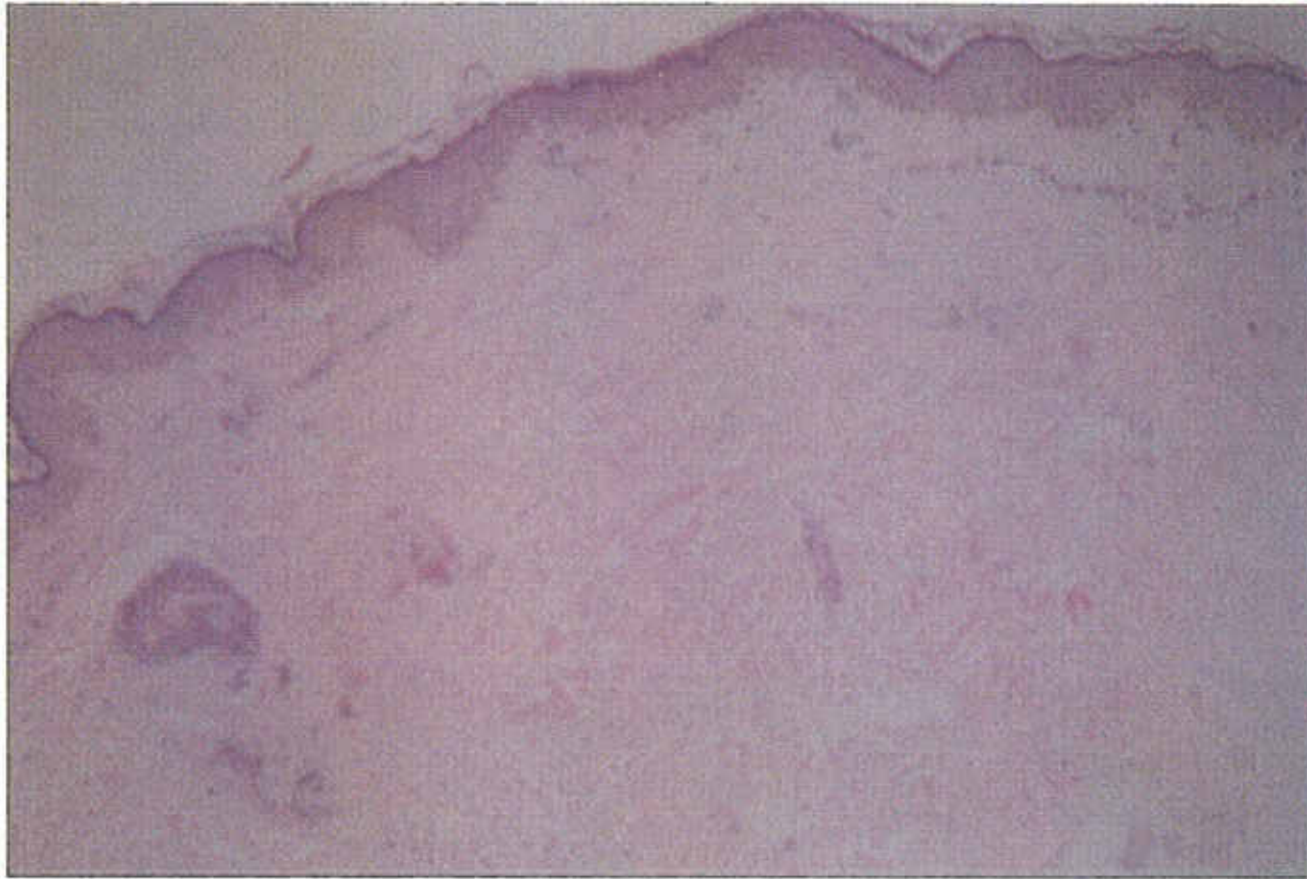


Fig. 7 Histopathology case one

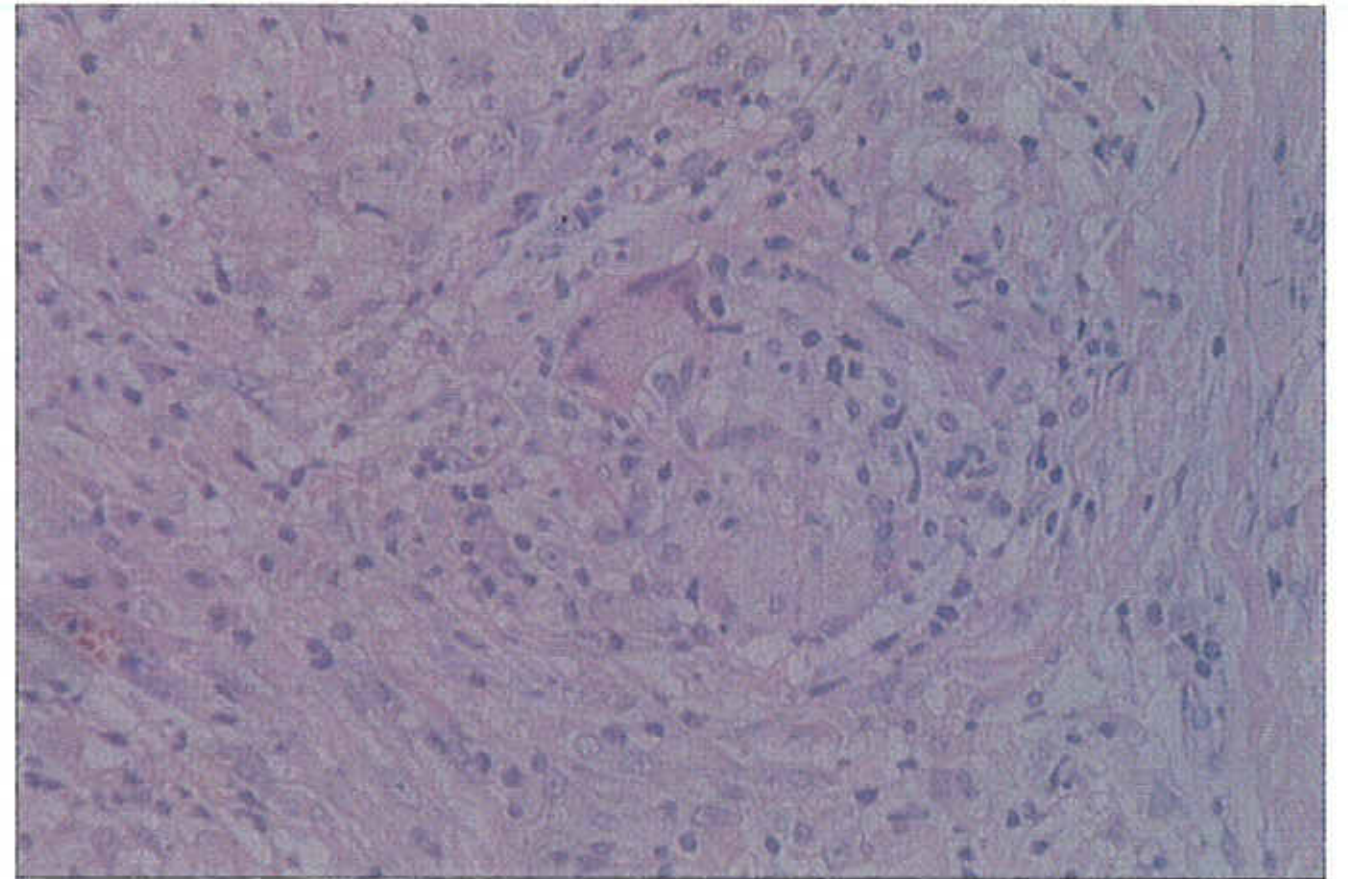


Fig. 8 Histopathology case one



Fig. 9&10 Result of liquid nitrogen treatment of sarcoid nodules of upper arm case one

Second case:

(J.D.) a 40 years old Sudanese male attended the clinic showing asymptomatic dark reddish brown skin papules at the rim of nasal nostrils, thighs and knees varying in size from 2 to 8 mm (Fig 11,12,13,14,15). The lesions were of 7-8 months duration. Clinically the differential diagnosis was sarcoidosis, cutaneous leishmaniasis, lupus vulgaris, rhinoscleroma, deep fungus infection and kaposi sarcoma. Investigations done included CBC, ESR, blood biochemistry profile and all were normal. Skin biopsy showed non caseating granuloma consistent

with the diagnosis of sarcoidosis (Fig 16,17) - chest x-ray showed prominent hilar shadows ? vascular, ? lymphoid enlargement. Both lungs were expanded and clear, cardiac size was normal. X-ray hands showed no articular or bony pathological changes.

On 15.4.98 patient was put on intralesional triamcinolone aqueous suspension 0.2 ml (8mg) diluted in 0.6 ml xylocaine solution and 2 weeks later there was dramatic improvement (Fig 18,19). Patient was referred to medical outpatients department for further evaluation of systemic involvement and for gallium scan.



Fig. 11 Nasal rim lesions- case two

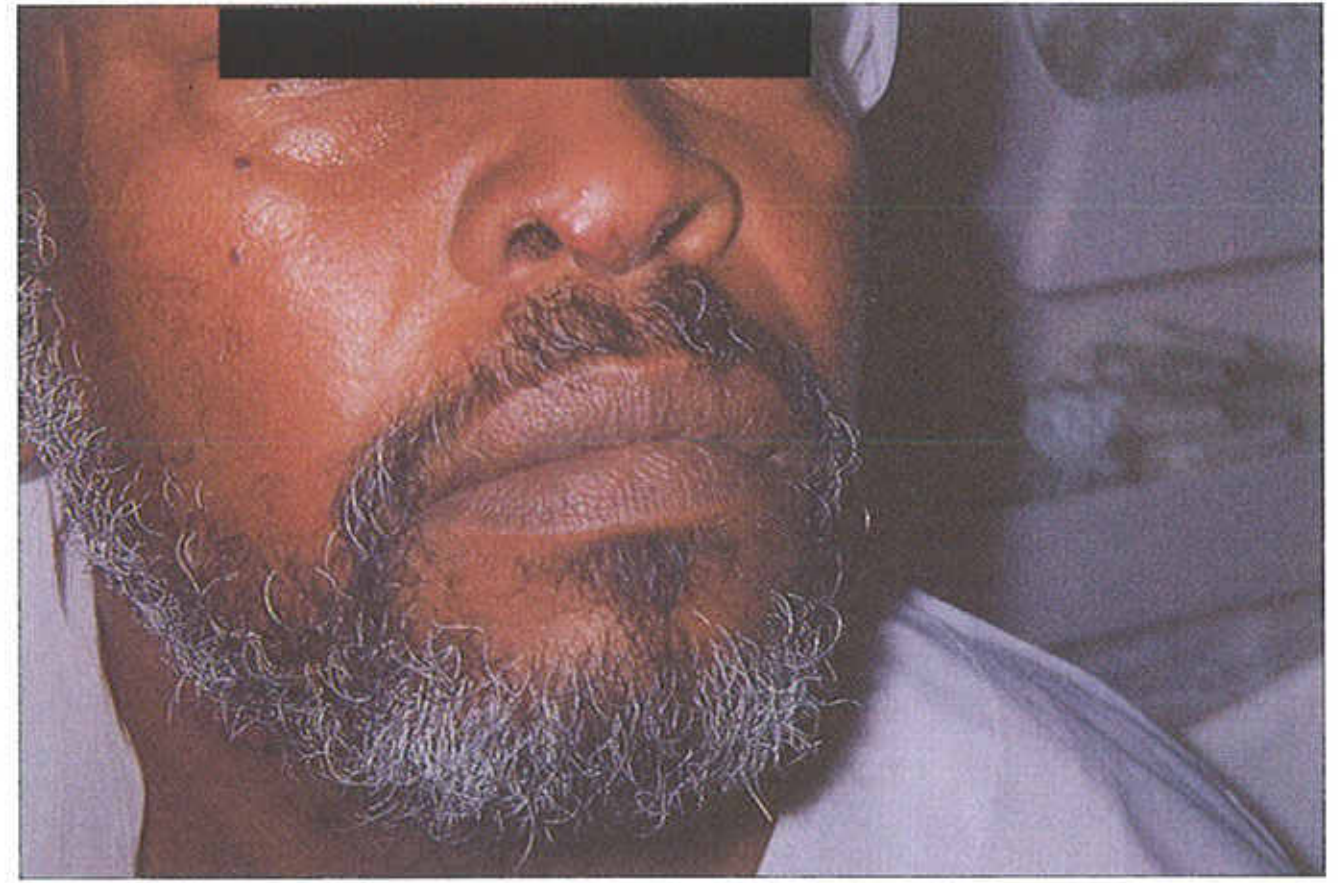


Fig. 12 Nasal rim lesions- case two



Fig. 13 Papular sarcoid of thigh, case two



Fig. 14-15 Papular sarcoid of knee, case two

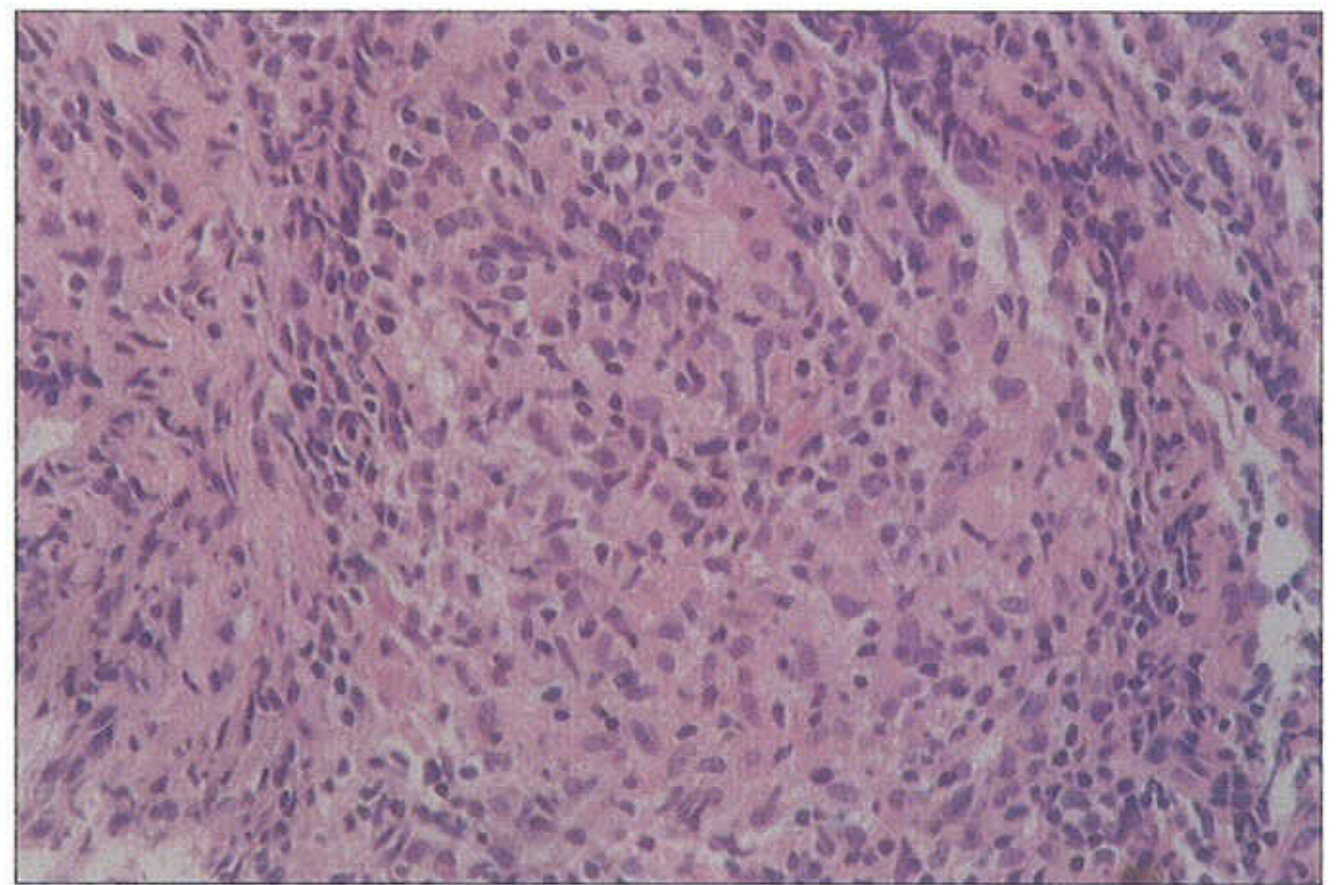
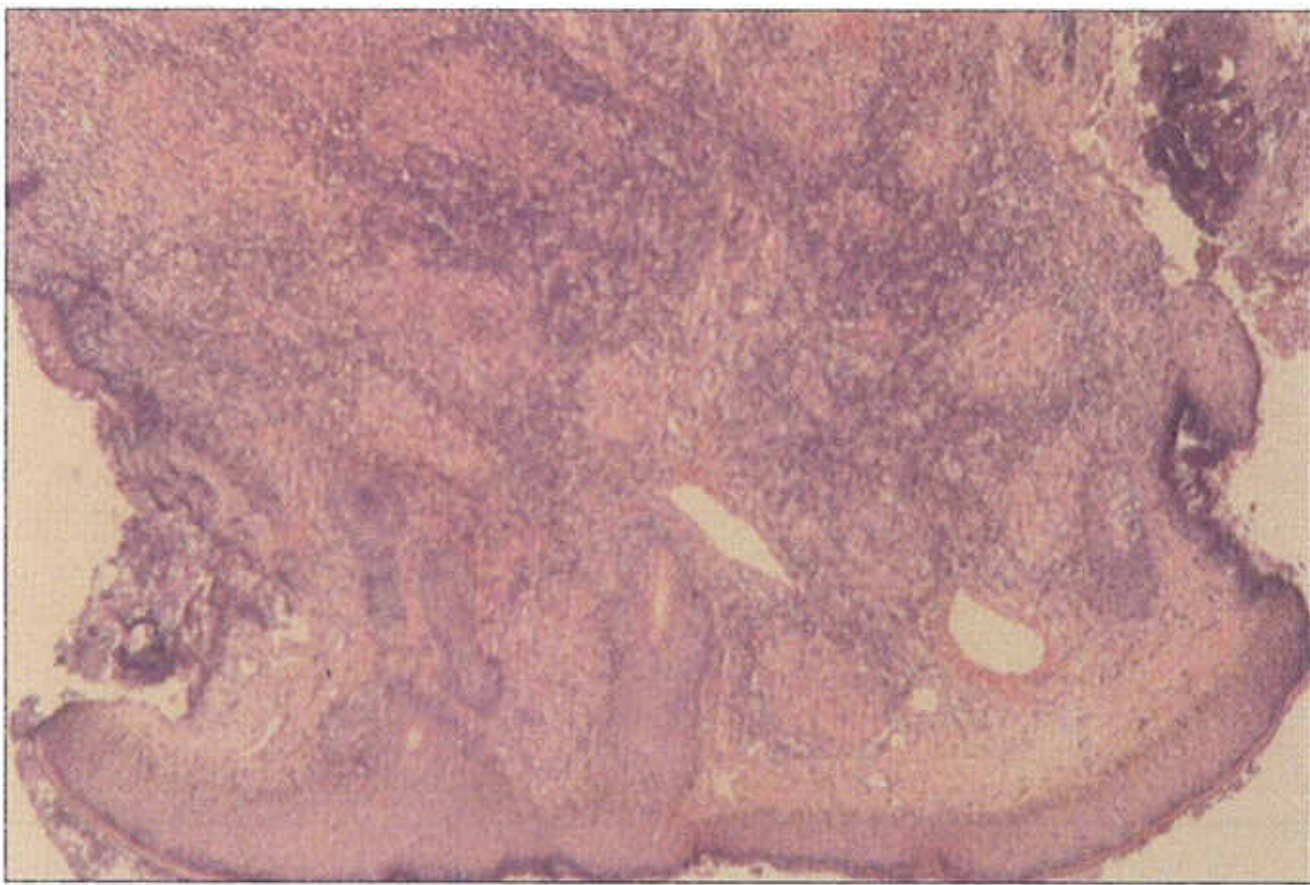


Fig. 16 &17 Non caseating granuloma with epithelioid cells in the dermis- no fungi or mycobacteria were detected, case two

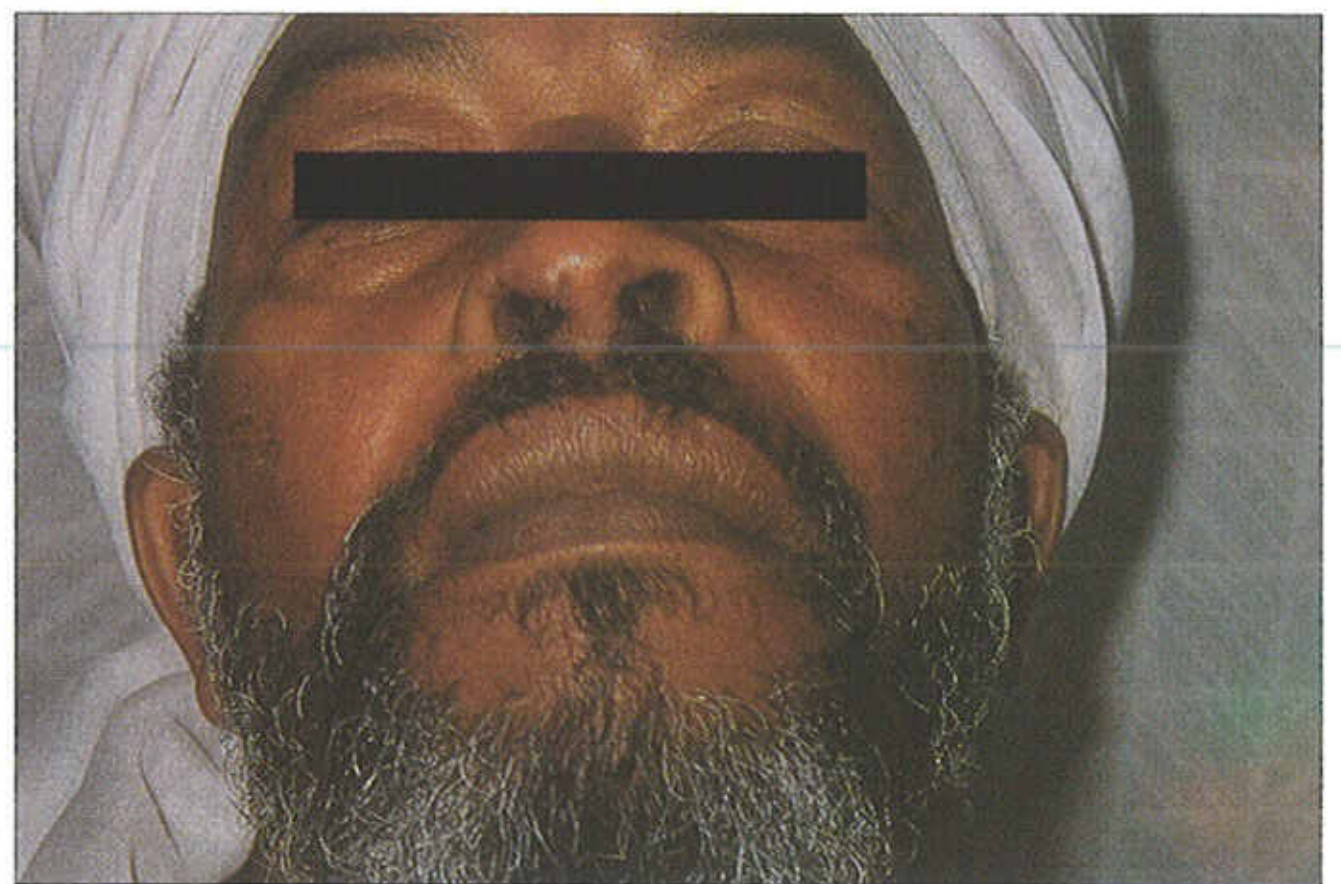
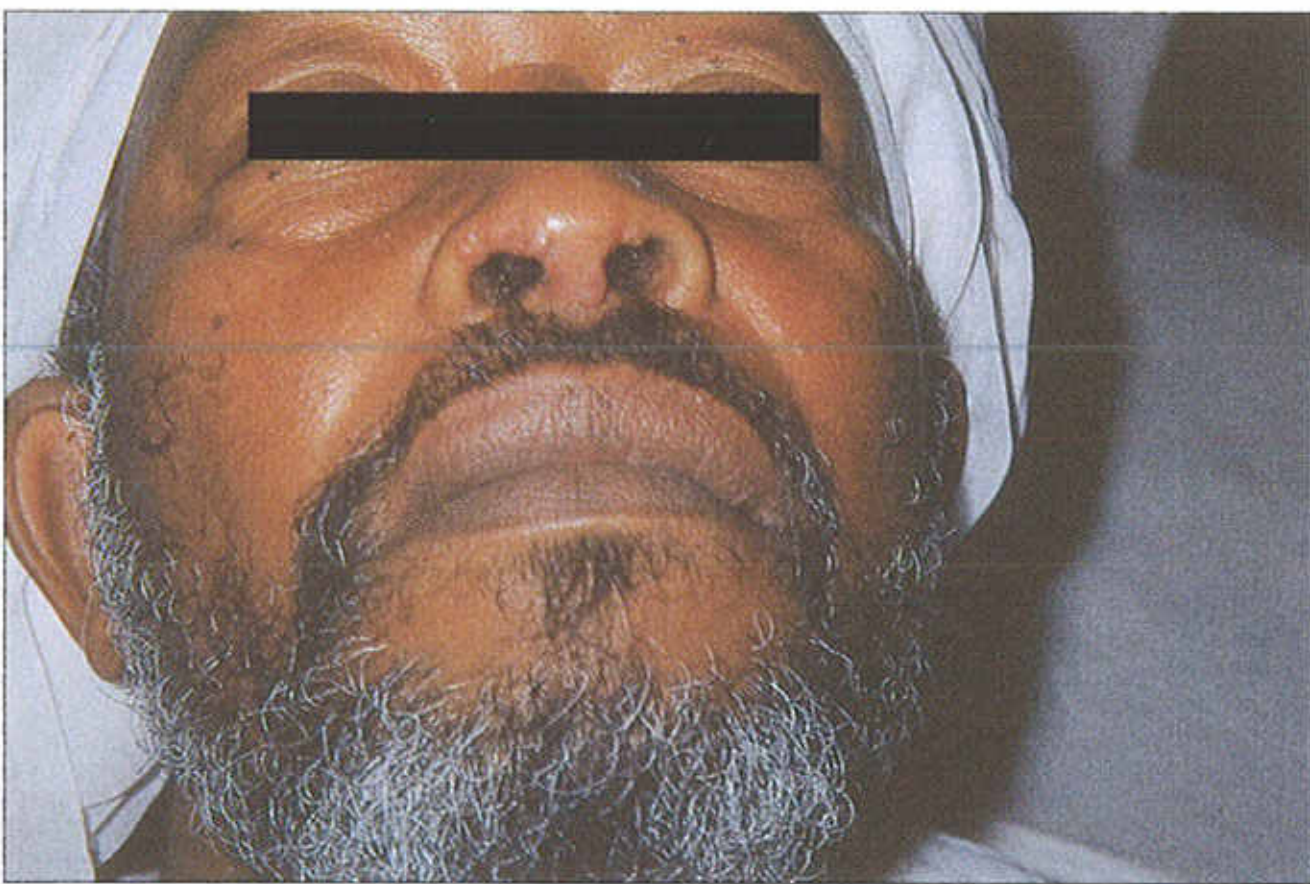


Fig. 18 & 19 Improvement after intralesional steroid, case two

Third Case :

(JA) a 20 years old Bangladesh male complained of a papular asymptomatic skin rash of the face of 5 months duration. The rash was slowly progressive. On examination, he had dark red papules varying in size from 1-3 mm in diameter affecting the forehead, right cheek, paranasal and perioral regions. (Fig20,21,22).

Clinically the diagnosis was sarcoidosis or acne agminata (lupus miliaris disseminatus faciei) Investigations done showed normal findings and included CBC, ESR, serum protein electrophoresis, blood biochemistry profile and urine for routine and microscopic examination. Serology for herpes simplex type I and II IgG antibodies were posi-

tive 1/100. Tuberculin test reading was 16 mm after 48 hours.

Skin biopsy showed epithelioid non caseating granulomatous inflammation consistent with sarcoidosis (Fig 23,24,25). Patient is investigated for systemic involvement. He is treated with cryotherapy once every 2 weeks.

DISCUSSION :

Sarcoidosis is a systemic disease of unknown aetiology characterized by a non caseating granuloma. The sarcoid granuloma is composed of epithelioid cells and occasional Langhans giant cells and may be surrounded by lymphocytes, macrophages and fibroblasts. Inclusion bodies are frequently



Fig. 20 Papular sarcoidosis affecting forehead and right cheek, case three

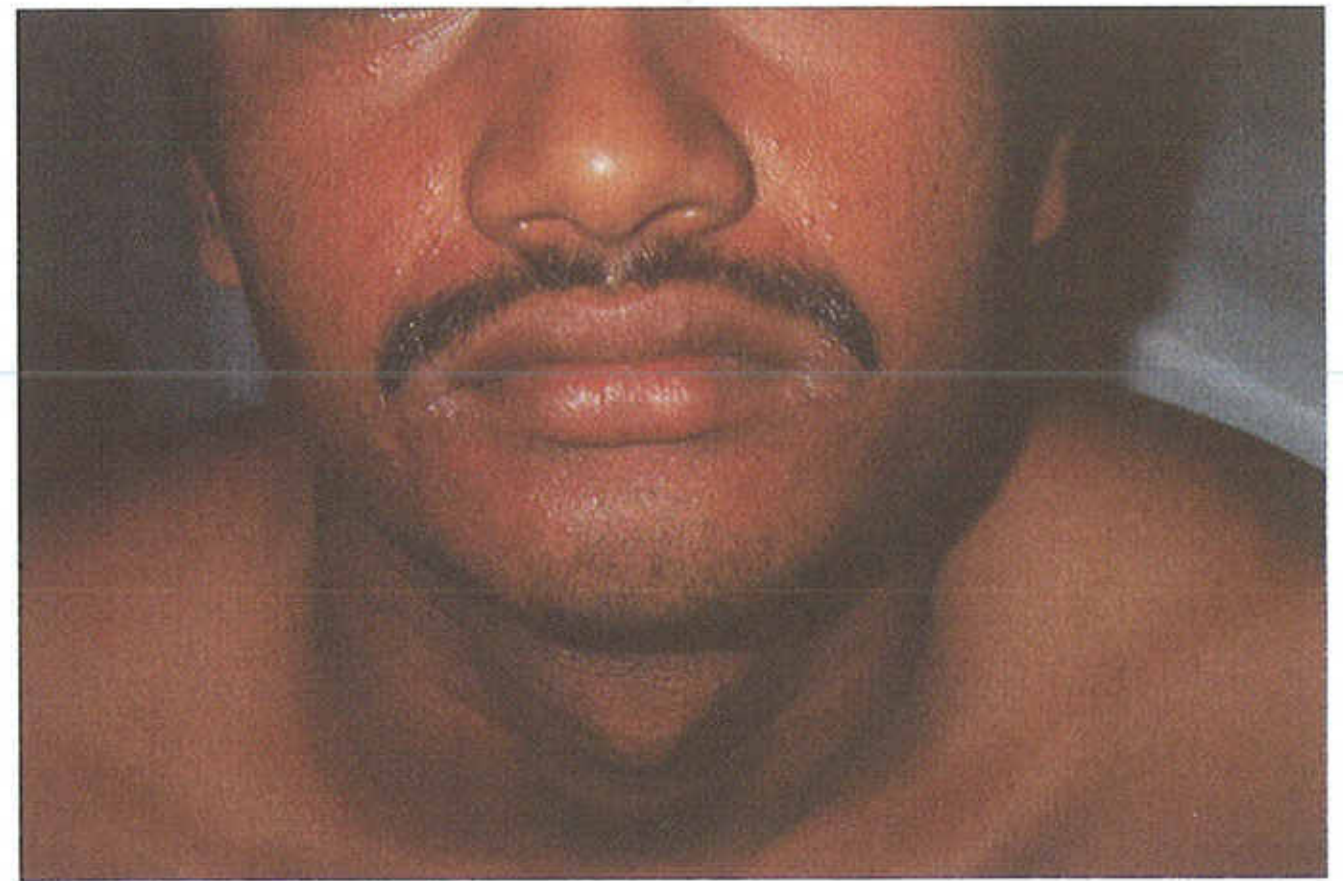
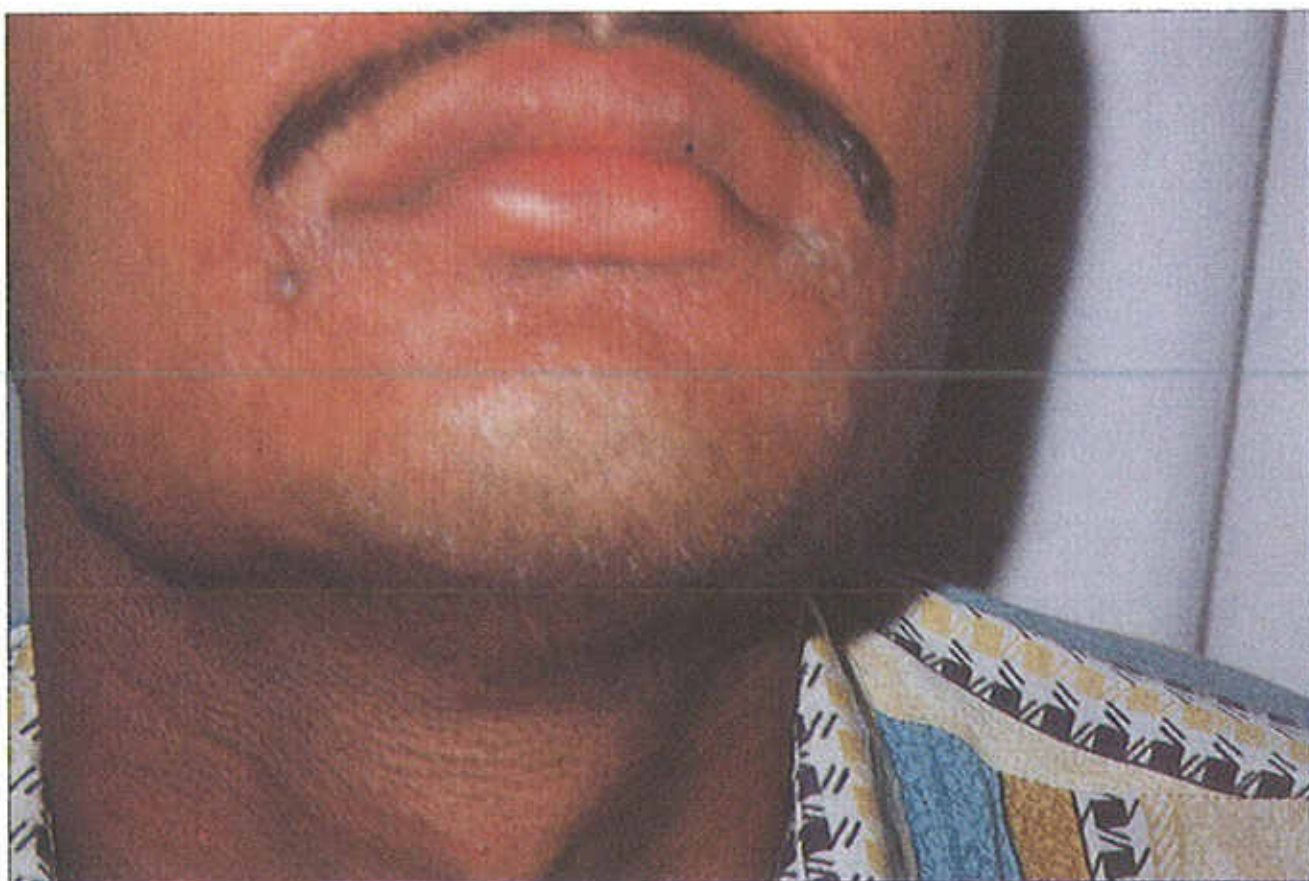


Fig. 21,22 Papular sarcoidosis of perioral region, case three

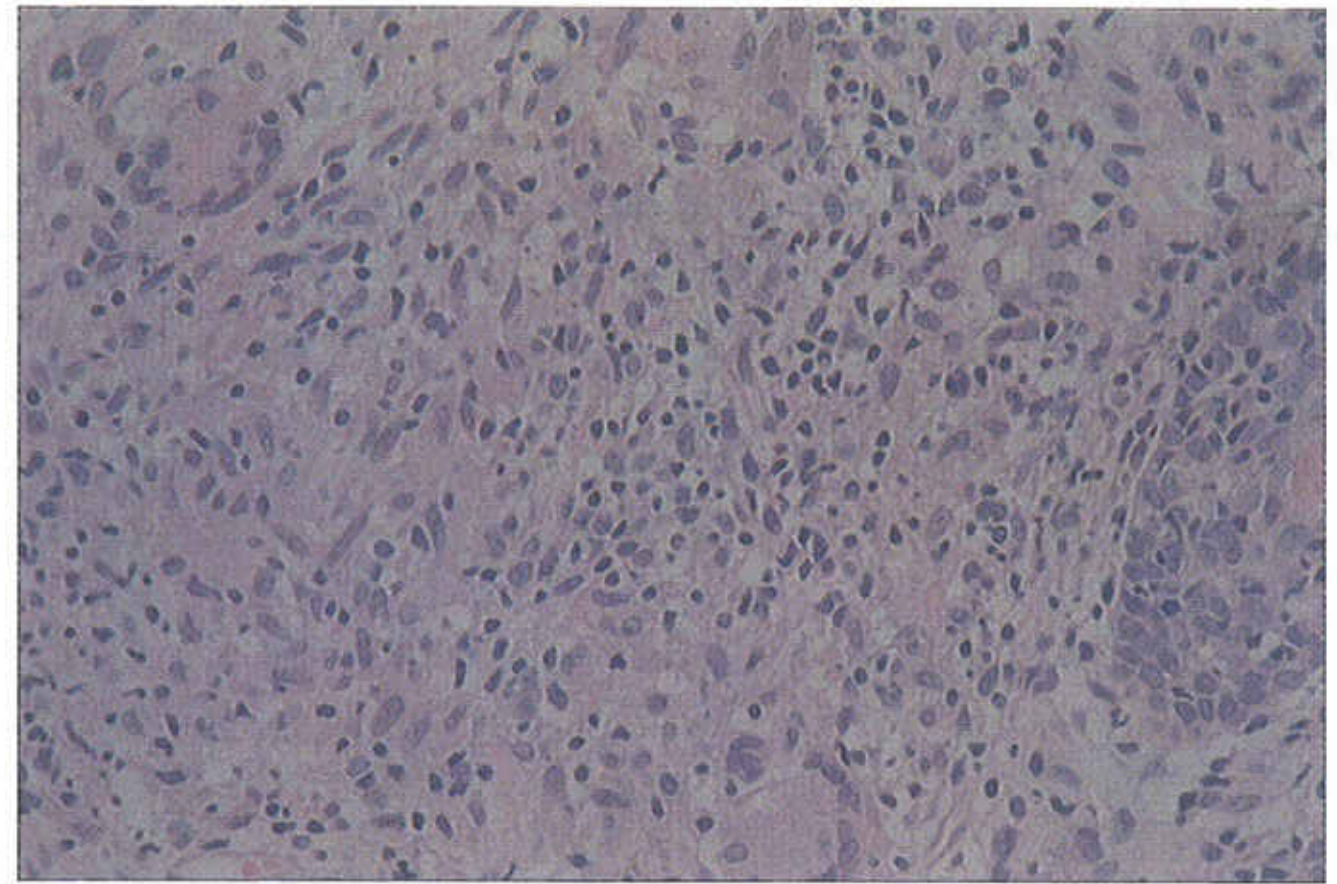


Fig. 23,24 Light microscopy showing sarcoid granuloma

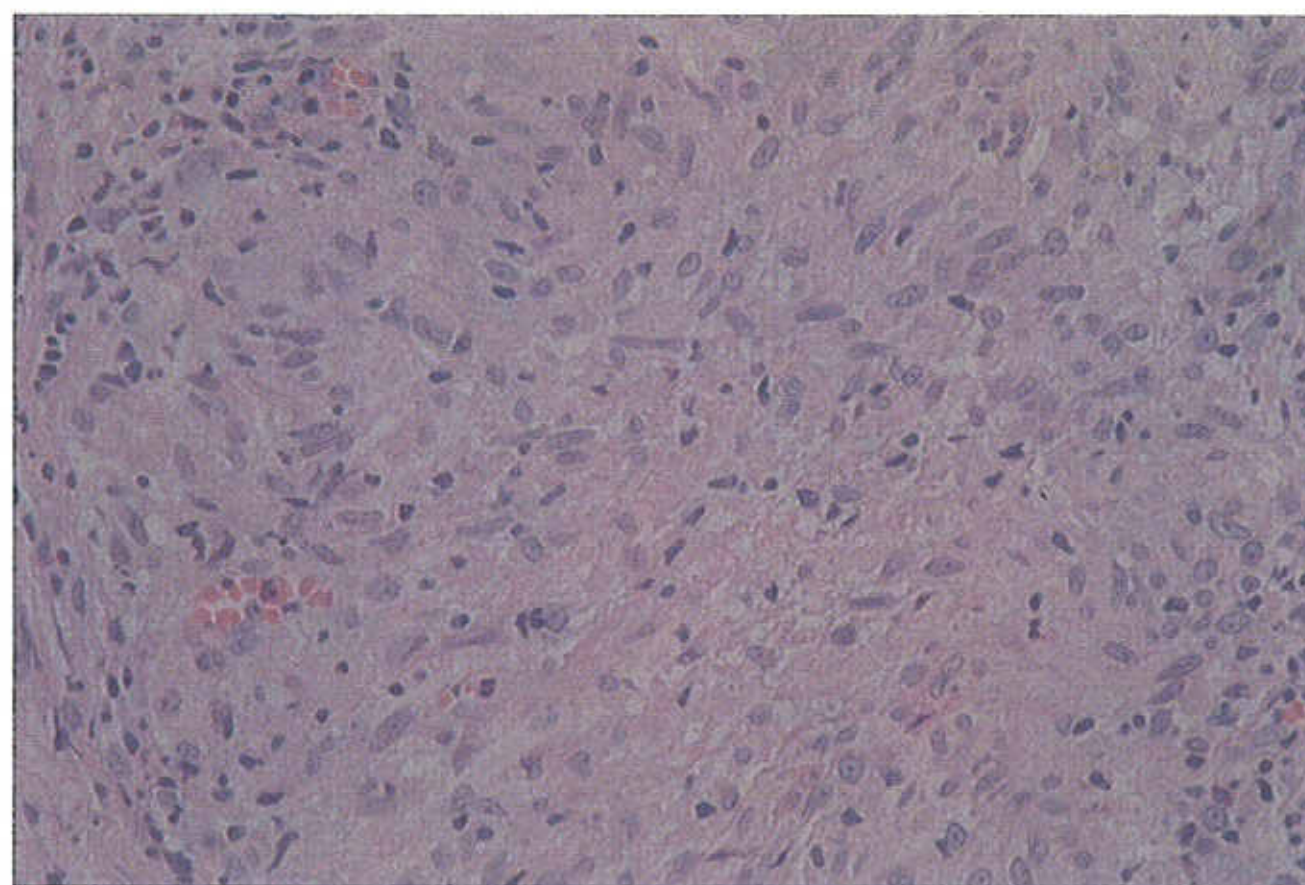


Fig. 25 Light microscopy showing sarcoid granuloma

found in macrophages, as a nonspecific finding. Three types of inclusion bodies are described : Schaumann body which consists of calcium carbonate, phosphate and iron. The asteroid body which is made of lipoprotein and the residual body which probably represents lipo-mucoprotein granules. There is deposition of IgG and C-3^(1 & 2). Because the histopathology of sarcoidal tissue is nonspecific and may be seen in tuberculosis, deep fungal infection, berylliosis, zirconioses, cutaneous leishmaniasis and tuberculoid leprosy, it is important to do specific stains and cultures routinely and also to polarize the specimen to determine the presence of foreign body and to rule out the possibility of an underlying neoplasm exhibiting an associated sarcoidal reaction^(3 & 4)

Sarcoidosis may affect any system of the body and can be associated with polyclonal hyperglobulinemia, hypercalcemia, hypercalciuria, circulating immune complexes and cutaneous anergy⁽⁵⁾. The main organs affected in sarcoidosis are lungs, mediastinal and peripheral lymph nodes, skin, eyes, lacrimal glands^(5,6,7), parotid gland⁽⁷⁾, liver, spleen, central nervous system, heart, upper respiratory tract, bones, kidneys⁽⁸⁾ genital tract⁽⁹⁾, thyroid and pleural effusion and multiple bronchial stenosis^(10,11,12).

Sarcoidosis was reported to have a prevalence that varied between 20-200 per 100,000.

The disease mainly affects adults and is commoner in women of childbearing age and 70% of patients were under the age of 40^(13,14,15). It is exceedingly rare under the age of 4^(16 & 17).

The acute forms of the disease tend to resolve spontaneously whereas the chronic forms rarely involute⁽⁵⁾. Sarcoidosis at its onset is frequently clinically manifested as erythema nodosum (EN), hilar lymphadenopathy, ocular symptoms or other skin lesions⁽¹³⁾. High frequency ultrasound can provide a reliable morphologic representation of skin lesions. The high frequency probes up to 2 MHz are used to monitor disease course and efficacy of treatment in sarcoidosis⁽¹⁸⁾.

The skin lesions in sarcoidosis are classified into specific lesions which show the characteristic granuloma and nonspecific lesion represented mainly by EN.

The specific sarcoidal lesions are seen in 9-37% of patients⁽¹⁹⁾ and include lupus pernio, infiltrated plaques, maculopapular eruption, subcutaneous nodules and infiltrations of old scars. Different skin lesions may occur in the same patient. The overall skin involvement in sarcoidosis is 25%. The specific cutaneous lesions in sarcoidosis may occur at any stage in the course of the disease and are often seen at its onset. The specific lesions resolve in 80% of patients without scarring⁽¹⁾ while a small percentage progress to fibrosis⁽²⁰⁾.

In a published series of 37 patients⁽⁶⁾, 73% presented at the onset of the disease with specific cutaneous lesions and 70% of them had associated systemic manifestations and 30% showed the systemic manifestations after 6 months to 3 years. In the same series the 27% who had no specific skin manifestations at time of examination developed them 6 months to 9 years after the initial diagnosis of sarcoidosis⁽⁶⁾.

This finding clearly points out the need to do periodical screening of patients with specific skin lesions for systemic manifestation of sarcoidosis particularly in any patient who has nasal rim specific lesions as such patients are likely to develop sarcoidosis of the upper respiratory tract⁽²¹⁾. The systemic involvement is assessed by careful general history, physical examination, chest x-ray, CT scan of chest⁽²²⁾, whole body gallium 67 scanning⁽²³⁾, pulmonary function tests, tuberculin test, ophthalmologic examination including slit lamp and funduscopy, blood and urine calcium, serum angiotensin converting enzyme (SACE) level. SACE level is increased in 60% of patients but normal SACE level in patients with skin sarcoidosis does not rule out systemic disease. In some patients with skin sarcoidal granuloma SACE may be increased while

the patient does not show systemic affection⁽²⁴⁾. The specific skin lesions may be associated in 41% with respiratory symptoms and in 38% with splenomegaly and 32% with hepatomegaly and 31%⁽²⁵⁾ with lymphadenopathy and in 8% with ocular lesions.

The most common sarcoidal specific skin lesions are maculopapules⁽²⁶⁾, which are red brown to purple and are less than one centimeter in diameter. They are commonly seen on the eye lids, around orbits, nasolabial folds and may involve the neck, trunk and extremities. They may coalesce to form annular lesions or plaques⁽²⁷⁾. They are commonly associated with hilar lymphadenopathy, acute uveitis, lymph node enlargement or parotid enlargement⁽²⁸⁾. They are a sign of good prognosis and usually disappear in less than two years⁽²⁸⁾. Infiltration of old scars is a characteristic finding in sarcoidosis and is often associated with long standing systemic affection of lungs, mediastinal glands, peripheral lymph glands, eyes, parotid gland and bones^(29,30). Old scars that result from surgery, trauma, acne, venipuncture become reddish purple, infiltrated and indurated and tend to persist according to the activity of sarcoidosis⁽¹⁴⁾.

Subcutaneous nodules appear as non tender, firm, mobile subcutaneous nodules 0.5 - 2 centimeters and may range in number from 1-100⁽³¹⁾. They may occur early associated with EN and bilateral hilar lymphadenopathy but they occur more frequently late in the disease associated with more systemic forms and they do not have prognostic significance^(31,32).

Skin plaques are usually associated with chronic forms of sarcoidosis but seem not to be associated with uveitis and bone cysts⁽³⁰⁾ skin plaques appear as round or oval brownish red infiltrated patches most commonly located on limbs, face, scalp, back and buttocks⁽²⁶⁾.

The most typical specific sarcoidal skin lesion is lupus pernio which appears as reddish purple or violaceous indurated lesions of the skin of the nose, cheeks, ears, lips, forehead. Lupus pernio may be associated with extensive involvement of nasal cavity and maxillary sinus. Patients may give a long history of nasal obstruction⁽³³⁾ Lupus pernio may co-exist with sarcoidosis of the upper respiratory tract and may be associated with pulmonary fibrosis, chronic uveitis and bone cysts. The sarcoidal skin lesions run an indolent often benign course⁽³⁴⁾, When the nose is affected, there is frequently in-

involvement of the nasal mucosa and bone and in some cases ulceration with septal perforation⁽²⁶⁾. Lupus pernio with or without pulmonary infiltration usually follow a chronic course from 2 to 25 years⁽³⁰⁻³⁵⁾.

Atypical granulomatous lesions are described in sarcoidosis and include, extensive ulcerative lesions⁽³⁶⁾ psoriasiform plaques⁽³⁷⁾ hypopigmentation in black patients⁽³⁸⁾ verrucous and papillomatous lesions⁽³⁹⁾ Ichthyosiform lesions⁽⁴⁰⁾ pustular folliculitis⁽⁴¹⁾ papules in light exposed areas⁽⁴¹⁾, lichenoid eruptions⁽⁴²⁾, erythrodermic eruption⁽⁴³⁾, cicatricial alopecia⁽⁴⁴⁾, lupus erythematosus like lesions⁽³⁷⁾, mutilating lesions⁽⁴⁵⁾, erythema and plaques involving palms and soles⁽⁴⁶⁾, pruritus caused by granulomatous skin lesions⁽⁴⁷⁾ and rare forms of cutaneous sarcoidosis with diffuse skin plaques associated with uveitis and arthritis seen in children younger than 4 years.⁽⁴⁸⁾

The most important nonspecific skin lesion in sarcoidosis is erythema nodosum. when EN is associated with hilar lymphadenopathy and or right paratracheal lymphadenopathy with or without pulmonary infiltration is known as Lofgren's syndrome⁽²⁵⁾. The presence of EN is predictive of good prognosis^(49 & 50)

Lofgren's syndrome usually follows a chronic course 2-25 years but more than 80% resolve within less than 2 years⁽⁵¹⁾. Lofgren's syndrome has an incidence of 17%⁽⁵²⁾. It usually affects young adults (30 years of age)⁽²⁸⁾ and may be associated with fever, arthralgia, and anterior uveitis and some may get swelling of ankles⁽⁵³⁾. x-ray chest must be done routinely in EN and it was found that serum angiotensin converting enzyme levels are increased in 55% of Lofgren's syndrome patients⁽⁵⁴⁾. Whole body gallium 67 scanning may show the typical λ pattern resembling the Greek letter lambda produced by gallium uptake of right paratracheal and bilateral hilar lymph nodes which may or may not be associated with image of the face of a panda bear produced by symmetrical lacrimal gland and parotid gland gallium uptake⁽²³⁾.

The bilateral hilar adenopathy in combination with evidence of pulmonary parenchymal involvement is the most frequent manifestation of the disease⁽³²⁾.

Pulmonary fibrosis has been shown to correlate with the presence of chronic plaque-like skin lesions as well as lupus pernio⁽⁵⁵⁾. Sarcoidosis causes interstitial pulmonary fibrosis in which the bronchoalveolar studies show elevated fibronectin

level and macrophage neutrophil exudate in lavage fluid⁽⁵⁶⁾. Recently, the developed epidemiologic, immunologic and molecular biology techniques are useful to study the syndrome of interstitial lung disease which has more than 200 causes including sarcoidosis⁽⁵⁷⁾.

Although sarcoidosis is a multisystem disease mortality from sarcoidosis is usually due to respiratory failure⁽⁵⁸⁾ 20% of patients with pulmonary parenchymal sarcoidosis develop local or diffuse fibrosis and this is possibly due to an insulin like growth factor-1 (IGF-1) which enhances fibrogenesis and development of fibrosis. This IGF-1 is produced by the alveolar macrophages⁽⁵⁹⁾. They found increased tissue concentration of hyaluronan (HYA) in sarcoidosis and idiopathic pulmonary fibrosis⁽⁶⁰⁾. This increase in (HYA) leads to increased accumulation of water and increased presentation ligands for receptors on inflammatory cells⁽⁶⁰⁾

IgG/albumin ratio is increased in bronchial lavage in interstitial lung disease in sarcoidosis with an increased production of IgGI 2+4. Analysis of Ig in bronchoalveolar lavage is useful to assess sarcoidosis activity⁽⁶¹⁾. Sarcoidosis is reported to be accompanied by pleural effusion and multiple bronchial stenosis⁽¹²⁾. Pseudo-tumoral manifestations in thorax is an unusual presentation of sarcoidosis and surgical biopsy may be required to eliminate the possibility of tumoral proliferation or another granulomatous cause⁽⁶²⁾

Neurosarcoidosis develops in 5-16% of patients^(63 & 64) The main manifestation in neurosarcoidosis are cranial nerve palsy, diabetes insipidus, lymphocytic hypophysitis and destruction of anterior pituitary⁽⁶⁵⁾, chronic aseptic meningitis and sometimes as intracranial mass. Brain biopsy may be necessary if no peripheral histologic evidence of sarcoidosis was obtained. Sequential magnetic resonance imaging is a useful means for follow up of neuro sarcoidosis⁽⁶⁶⁾.

Multimodality evoked potentials can detect sub-clinical neurosarcoidosis and are an important adjunct to neuroradiology in the diagnosis of neurosarcoidosis⁽⁶⁷⁾

MRI is useful to detect cranial nerve lesion of sarcoidosis⁽⁶⁸⁾.

A good chance for a successful treatment of neurosarcoidosis depends on early diagnosis which depends among other investigations on an early biopsy⁽⁶⁹⁾

Facial palsy is the most frequent neurological presentation of sarcoidosis. It occurs with equal frequency on the right or left side and equally unilateral or bilateral.

When bilateral facial palsy develops in young adult sarcoidosis is the most likely cause and resolution of facial palsy is complete in 80% of patients⁽⁷⁰⁾.

Sarcoidosis may be presented by isolated third nerve palsy⁽⁶⁸⁾ or with stroke or with focal neurological deficit as episodic non-fluent dysphasia⁽⁷¹⁾. Demyelinating optic neuritis may occur in sarcoidosis patients who may show Uhthoff phenomenon which is visual loss lasting 24 hours after exposure to heat⁽⁷²⁾.

Sarcoidosis may cause granulomatous hepatitis⁽⁷³⁾ which presents with pyrexia and hepatosplenomegaly. Focal hepatic and splenic lesions of sarcoidosis can be detected by multiple image modalities including CT and MRI⁽⁷⁴⁾.

Sarcoidosis may be associated with IgA nephropathy⁽⁷⁵⁾. Pseudotumoral sarcoid granulomatous nephritis is a very uncommon complication of sarcoidosis⁽⁸⁾. Also granulomatous nephritis and renal failure which is usually the result nephrocalcinosis have been described in sarcoidosis^(76 & 77)

Thyroid gland is one of the organs that could be affected in sarcoidosis^(10,11). Cardiac sarcoidosis may present with dilated cardiomyopathy and a high incidence of grave conductive disturbances and poor prognosis compared with those with idiopathic cardiomyopathy⁽⁷⁸⁾. The incidence of cardiac sarcoidosis is estimated to be 25%⁽⁷⁹⁾. It is estimated that 67% of 89 patients with cardiac sarcoidosis had sudden death and the commonest arrhythmia was ventricular tachycardia and the commonest conduction defect was complete heart block⁽⁸⁰⁾. Other cardiac presentations were congestive heart failure, pericardial effusion and acute myocardial infarction. Sudden death without prior warning occurred in 17% of patients with cardiac sarcoidosis and other studies correlated sudden death with wide spread disease^(79,81)

Muscle involvement in sarcoidosis is rare⁽⁸²⁾. Some patients show asymptomatic nodules which has sarcoid granuloma histopathologically^(83,84). Sarcoidosis has been reported associated with acute and chronic myositis secondary atrophy or hypertrophy^(85,86). Random muscle biopsy is a reliable procedure for histologic confirmation^(86,87).

The bone changes are found in 15-20 % of cases^(85,88,89). The bone changes tend to be cystic and favor terminal phalanges of hands and feet⁽⁸⁵⁾ and are often associated with pulmonary changes⁽⁹⁰⁾ and lupus pernio⁽⁵⁵⁾.

In order to diagnose sarcoidosis when suspected in a patient, it is essential to take complete history, clinical examination including ophthalmologic evaluation, x-ray chest, ECG, SACE level, 24 hour urine calcium, serum protein electrophoresis, intradermal test to evaluate anergy, and biopsy from skin lesions which is the most accessible organ and is affected in 20-35 % of cases⁽⁹¹⁾, because the histopathology is nonspecific and may be seen in tuberculosis, deep fungal infection, berylliosis, zirconiosis, cutaneous leishmaniasis and tuberculoid leprosy, it is important to do specific stains and cultures routinely⁽²⁴⁾.

A radiolabelled somatostatin analogue scintigraphy shows that it accumulates in extrathoracic granulomatous lesions in sarcoidosis from which a biopsy may be attempted⁽⁹²⁾ as well as from peripheral lymph glands, which are affected in up to 75%⁽¹³⁾, salivary glands, which may be involved in 50% of patients. A Kveim Siltzbach test may be done. A suspension is prepared from sarcoid spleen or sarcoid tissue.

This heat sterilized sarcoid tissue is injected intradermally and a biopsy is taken from the tested site 4-6 weeks later. In positive cases a sarcoid granuloma is seen in 70 - 90 % of patients^(94,95) with 2% false positive^(13,96). It is rarely positive in normal individuals or patients with other granulomatous disorders⁽⁹⁷⁾.

Neurosarcoid may be detected by skull x-ray, brain scan, EEG, lumbar puncture and computed tomography of the head⁽⁹⁸⁾.

Aetiology :

The cause of sarcoidosis is still not clear. HLA typing showed that HLA-B8 carriers possibly have an overall risk to get sarcoidosis⁽⁹⁹⁾. HLA-B8 was found in chronic sarcoidosis⁽¹⁰⁰⁾ while HLA-A1B8 was associated with acute sarcoidosis especially Lofgren's syndrome⁽¹⁰¹⁾. One of the major genetic factors controlling development of sarcoidosis is located within DRB1 locus of the HLA class II region⁽¹⁰²⁾.

Multiple infectious agents such as bacteria, fungi, viruses, protozoa and non infectious agents as plants

and chemical substances have been implicated in causing sarcoidosis but none of these have been substantiated⁽¹⁰³⁾.

L-form of mycobacteria were described as a possible cause of sarcoidosis but needs to be confirmed⁽¹⁰⁴⁾. It has been noted in one study that 40% of cases of sarcoidosis had been in contact with cases of tuberculosis before onset of sarcoidosis compared with 1.2% of the controls⁽¹⁰⁵⁾. Tuberculosis and sarcoidosis were concomitantly reported in a Chinese patient and mycobacterial DNA was identified by polymerase chain reaction (PCR) in the sarcoidal lesion. This finding is another repetition of what is said about the possibility that mycobacteria or some of its components may be capable of inducing the pathologic changes in sarcoidosis⁽¹⁰⁶⁾.

Sarcoidosis was once held to be a variant of tuberculosis although no acid fast bacilli were detected. It is known that pathogens may exist in forms without cell wall and cause slow bacterial infection in which the organism will not be easily cultured⁽¹⁰⁷⁾. Mycobacterial cell wall deficient spheroblasts have been detected but this finding was generally difficult to reproduce⁽¹⁰³⁾.

Mycobacterial DNA was found by PCR in 50% of pulmonary and intrathoracic lymph node biopsies⁽¹⁰³⁾, acid fast bacteria without cell walls and tuberculostearic acid^(108,109) have been isolated from lesions of sarcoidosis patients. The advent of PCR to detect DNA in clinical samples may clear the debate about the role of mycobacteria in aetiology of sarcoidosis.

Identification of mycobacterial DNA in samples from sarcoidosis by PCR gave widely divergent results⁽¹¹⁰⁾. Some studies report either no positive or very few positive results, false positive and false negative results cannot be ruled out⁽¹⁰³⁾. Sequence capture PCR procedure is 100 times more sensitive than PCR and can detect mycobacterial DNA from samples of patients with paucibacillary active tuberculosis including samples that were smear negative and culture positive and samples that were smear negative and culture negative. This sequence capture PCR could not detect mycobacterial DNA in 15 biopsies from patients with sarcoidosis and this supports prior studies suggesting that mycobacterium tuberculosis does not play a pathogenic role in sarcoidosis in most patients⁽¹¹⁰⁾. Antituberculous treatments in sarcoidosis have discouraging results and this may be because the mycobacteria are present

in static form and fail to grow in culture and have no wall, so drugs that act on the bacterial wall such as INH will not be effective⁽¹⁰⁷⁾.

There is a possibility that another unidentified organism may be involved⁽¹⁰⁷⁾.

There are some immunologic findings in sarcoidosis such as polyclonal hyperglobulinemia⁽⁸⁵⁾, circulating immune complexes^(111,112) and depressed cell mediated immunity often manifested by skin anergy⁽¹¹³⁾.

Peripheral anergy in sarcoidosis was investigated and it was found that serum levels of soluble CD23 (SCD23) and interleukin 10 (IL-10) were significantly elevated in patients with sarcoidosis than in control group⁽¹¹⁴⁾, suggesting an increase in peripheral humoral immunity. Also vitamin D3 was significantly higher in sarcoidosis and is related to alteration in calcium metabolism in sarcoidosis. Ionized calcium level may be considered a useful index of sarcoidosis activity⁽¹¹⁵⁾. It is suggested that IL-10 and vitamin D3 may contribute to the peripheral anergy in sarcoidosis. Factors that are capable of activating monocytes and macrophages namely IL-8, IFN γ , GM-CSF and TNF α were not elevated in peripheral blood in sarcoidosis⁽¹¹⁴⁾. The study of sarcoid tissue showed large number of activated T-lymphocytes mainly T-helper cells^(116,117,118,119). The large number of T-helper cells in the affected sites may secondarily decrease the number of peripheral circulating T-helper cells (1) thus producing a relative increase of T-suppressor cells in blood^(120,121). This alteration of T-helper to T-suppressor ratio may partly explain the anergic state often encountered in sarcoidosis patients⁽¹²⁰⁾.

In the affected organ the activated T-cells and macrophages release a number of cytokines that provide the stimulus for granuloma formation⁽⁶⁾.

Recent advances support the hypothesis that sarcoidosis is an antigen T-cell mediated response and it has been suggested that sarcoidosis represent an abnormal host response to non specific antigen⁽¹²³⁾. It has been also hypothesized that sarcoidosis and other skin disorders as lichen planus, alopecia areata, psoriasis and vitiligo are cell mediated autoimmune diseases⁽¹²⁴⁾.

Therapy and prognosis :

Systemic corticosteroids are used in treatment of sarcoidosis⁽¹²⁵⁾, particularly in ocular involvement or central nervous system disease⁽⁹⁸⁾. Corticoster-

oids possibly influence T-cell effector function and affect the response of mononuclear phagocytes to lymphokines produced by T cells. ^(126,127). High dose methyl prednisolone was given to treat autoimmune thrombocytopenia in sarcoidosis ⁽¹²⁸⁾.

Deflazacort appeared to be as effective as prednisolone in treatment of sarcoidosis and may have fewer side effects especially on bones ⁽¹²⁹⁾. Chloroquine and hydroxychloroquine may influence cutaneous sarcoidosis ⁽¹³⁰⁾ and were reported to control neurological sarcoidosis ^(130,131,132).

Thalidomide may have therapeutic use in sarcoidosis. It has an immunomodulatory effect and suppresses IL-12 production ^(134, 133). Thalidomide is a

useful drug for long term monotherapeutic or steroid sparing agent in the treatment of sarcoidosis ⁽¹³⁵⁾. The role of colchicine in treatment of sarcoidosis remains to be determined ⁽¹³⁶⁾. Methotrexate 10-15 mg per week is helpful in treatment of cutaneous sarcoidosis ⁽¹³⁷⁾. Lupus pernio was successfully treated with topical steroid ⁽¹³⁸⁾ and with plastic surgery ⁽¹³⁹⁾.

The presence of EN in acute sarcoidosis is predictive of good prognosis ^(74,50). Sarcoidosis may result in blindness, shortness of breath, fatigue, renal failure, disfiguring cutaneous lesions, but mortality has been reported in 3-6% ⁽¹³⁾.

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