A First Report of Paediatric Sarcoidosis in Thailand*

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SUMMARY **A case of sarcoidosis was described in a 12-year-old Thai boy with the presentation of generalised massive lymphadenopathy for 6 years. He had strongly positive tuberculin test and had been treated with antituberculous drugs without improvement. Diagnosis of sarcoidosis was made by the presence of the typical bilateral hilar node enlargement on the chest radiograph, characteristic histological appearance in lymph node biopsy, positive Kveim's test, and elevated angiotensin-converting enzyme level. Immunological studies revealed hypergammaglobulinaemia with elevated IgG level, normal intracellular killing activity of phagocytes, normal delayed hypersensitivity skin test to recalled antigens but impaired blast transformation of peripheral blood lymphocytes to phytohaemagglutinin in vitro. Study of the subpopulation of T lymphocytes showed decreased total T cells (OKT_3), and suppressor/cytotoxic T cell (OKT_8). He responded well to steroid treatment with complete resolution of enlarged lymph nodes within 3 months and is now in good health.**

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Sarcoidosis is a chronic multisystem granulomatous disease of undetermined aetiology and pathogenesis, characterised histologically by epithelioid cell granulomas. Since the initial clinical reports by Besnier in 1889[1] and by Hutchinson in 1898[2] it has been observed in many parts of the world. The incidence seems to be high in certain countries, especially among some northern European groups (e.g. Scandinavian), the United Kingdom, the south-eastern part of the United State of America, Australia and Japan.[3] Japan and the USSR are the only Asian countries in which a sizable number of cases of sarcoidosis has been observed.[4] The disease is seldomly encountered in Southeast Asia. In Thailand, after the first two cases of sarcoidosis reported by Bovornkitti and Kangsadal in 1959,[5] only 13 additional cases have heen reported upto 1982.[6-13] All of these cases were adults, ranging in age from 17 to 72 years. Since sarcoidosis is predominantly a disease of young adults, most incidents occur between the ages of 20 and 40; the disease appears to be relatively rare in children. In this report, we describe sarcoidosis in a 12-year-old Thai boy, the first case reported in Thai children, who presented with massive generalised lymphadenopathy and responded well to steroid therapy. The details of immunological work-up in this patient are also presented.

CASE REPORT

A 12-year-old Thai boy, from Surin province in northeastern Thailand, was admitted to the Department of Paediatrics, Siriraj Hospital on June 2nd 1983 with the history of generalised lymphadenopathy for six years. The illness began about six years prior to admission when small masses were noticed on both sides of his neck. These masses were slowly enlarged with new masses appearing in the inguinal, axillary and cubital regions. Neither pain and tenderness at the masses nor systemic symptoms were observed. He was diagnosed and treated as tuberculosis at the provincial hospital for six months without improvement. One year prior to admission, there was progressively enlargement of the masses and biopsy of the left axillary lymph nodes was performed at the provincial hospital. The diagnosis of malignant lymphoma was notified to his parents who refused further treatment and resorted to traditional herbal medications. After several trials without improvement, he was referred to the Siriraj Hospital in Bangkok where he was admitted. He had no history of BCG vaccination. His grandfather, living in the same house, died of tuberculosis when he was 3 years old. All other members of his family, however, were in good health.

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On examination he appeared healthy and was afebrile. Generalised peripheral lymph node enlargement were detected at the cervical, axillary, epitrochlear, and inguinal regions, ranging in size from 2x3 cm to 6x8 cm (Fig. 1). The masses were discrete, firm in consistency and not tender. The liver edge was palpated 2.5 cm below the costal margin, firm and not tender. There were large black nevi at the anterior abdominal wall, but no other skin lesions were observed. Other systems gave findings within normal limits. The haematocrit was 36 per cent; white-cell count $17.0x10^9/1$, with 45 per cent polymorphs, 28 per cent lymphocytes, 2 per cent monocytes, and 25 per cent eosinophils; platelet count was $335x10^9/1$. Stool examination showed *Enterobius* ova and *Strongyloides* larvae. Chest radiograph showed enlargement of right paratracheal and bilateral hilar nodes (Fig. 2A). Intracutaneous test with 5 TU of purified protein derivative (PPD) tuberculin was strongly positive (40x50 mm). Laboratory studies disclosed the following values: serum albumin, 4 g/dl; globulin, 3.2 g/dl; SGOT, 31 Sigma units; alkaline phosphatase, 40 international units; blood urea nitrogen, 14 mg/dl; creatinine, 0.9 mg/

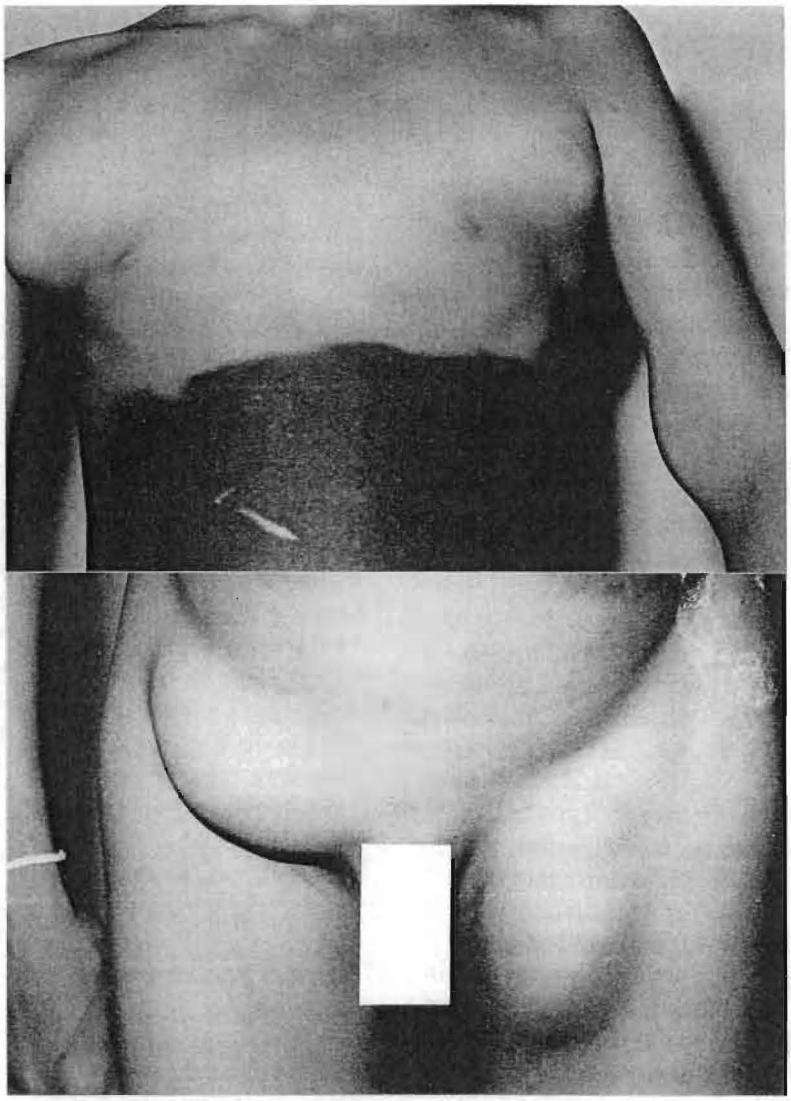

Fig. 1 Showing markedly enlarged axillary and inguinal lymph nodes bilaterally.

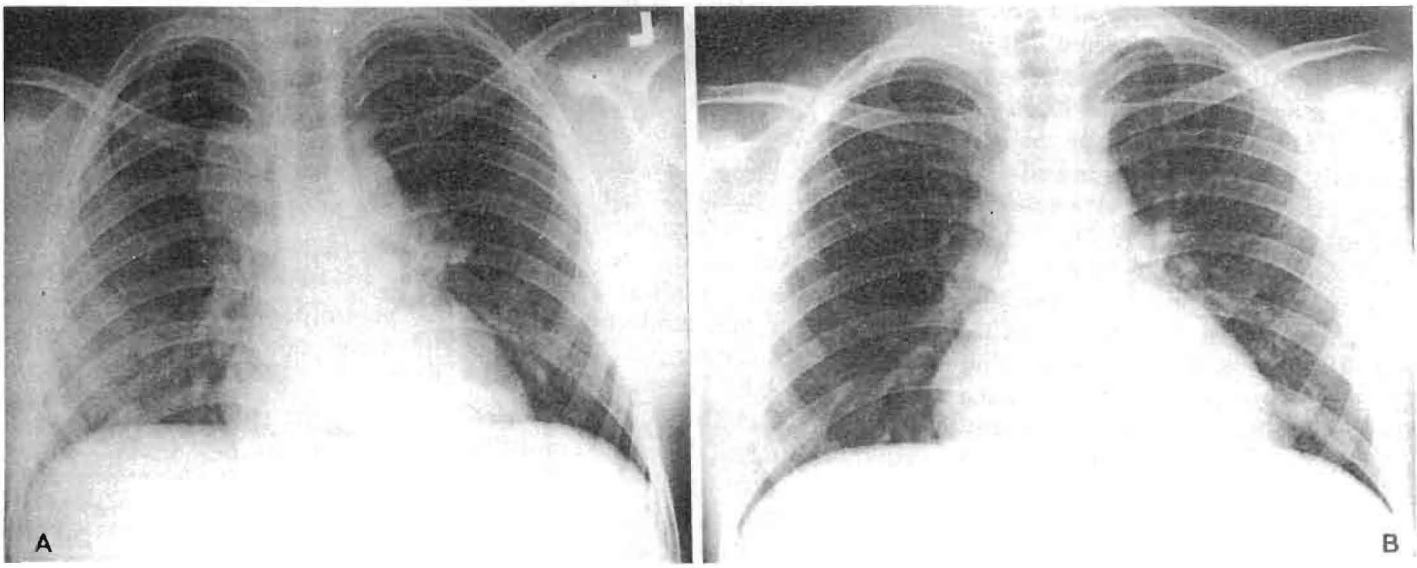

Fig. 2 A Chest radiograph on admission showing right paratracheal and bilateral hilar lymphadenopathies.
B. Following four weeks of corticosteroid treatment, there was a dramatic resolution of lymph node lesions.

dl; blood sugar, 64 mg/dl; calcium, 9.5 mg/dl; phosphorus, 6.4 mg/dl. The urine calcium and phosphate was 55 mg/dl and 89 mg/dl respectively. The bone marrow aspiration gave normal finding. Lymph-node biopsy from 2 sites (cervical and axilla) both showed epithelioid cell tubercles, with no caseation and without evidence of acid-fast bacilli or fungus (Fig. 3). Cultures for tubercle bacilli and fungus from the lymph node materials revealed negative results. A Kveim test gave a minute papule at 6 weeks after application with histology of sarcoid granuloma (Fig. 3D). The level of angiotensin-converting enzyme was 112.11 units/ml (normal value = 16.5±4 units).

The results of immunological work-up included: serum protein electrophoresis showed albumin 41.6 per cent, α_1 globulin 6.1 per cent, α_2 globulin 13.2 per cent, β globulin 12.8 per cent and γ globulin 26.3 per cent; the immunoglobulin levels were IgG 1,760 mg/dl, IgA 290 mg/dl, IgM 129 mg/dl. The intracellular killing activity of phagocytes as measured by the nitroblue tetrazolium dye reduction test (NBT) was normal. Beside the strongly positive tuberculin reaction, further delayed hypersensitivity skin test (DHST) with *Candida* and Mumps antigens were negative while positive result (8x9 mm) was observed with *Trichophyton* antigen. The blast transformation of the peripheral blood lymphocytes by phytohaemagglutinin

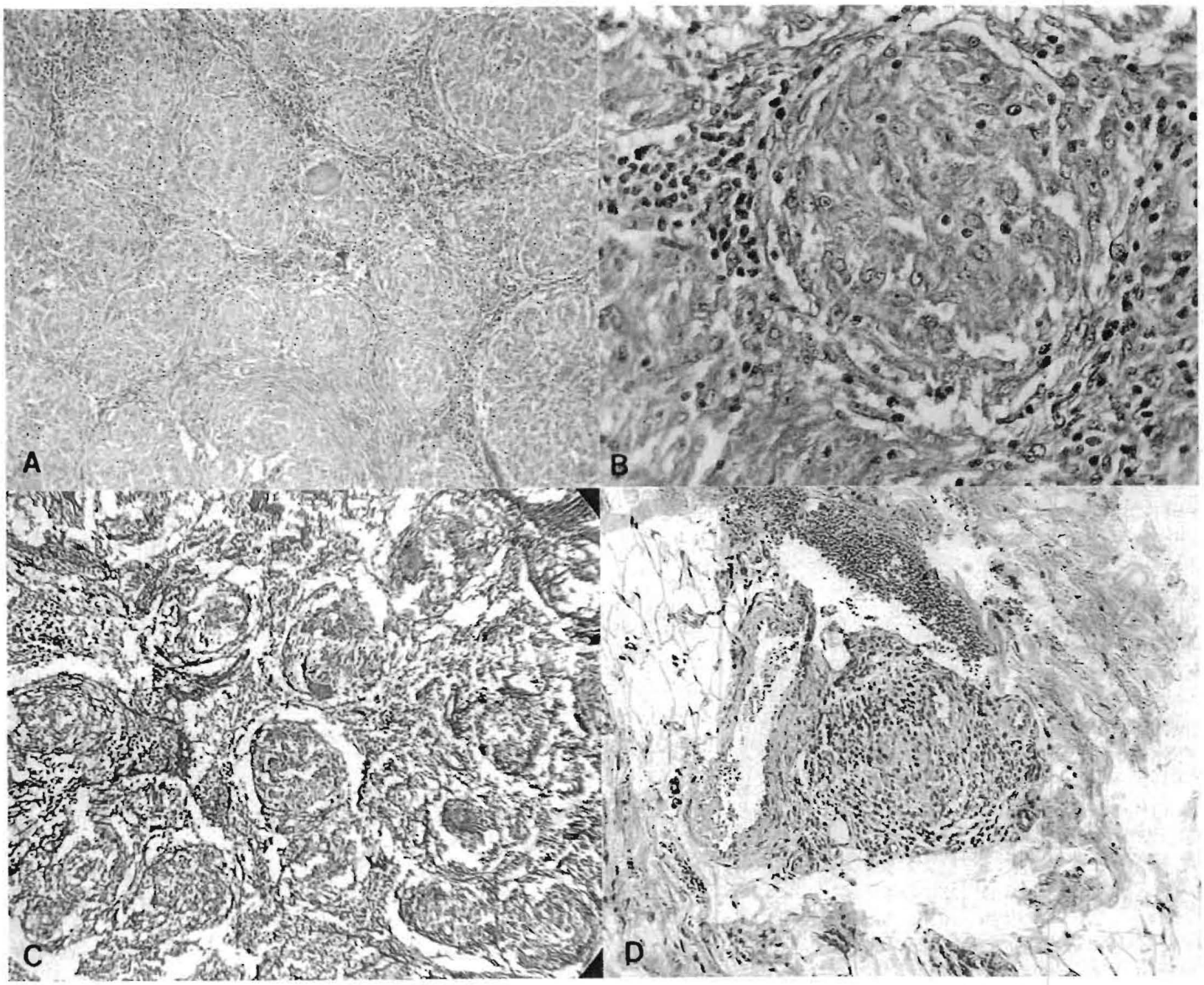

Fig. 3 A Section of biopsied lymph node showing replacement of normal architecture with packed epithelioid tubercles; multinucleated giant cells were present in some places (H & E, x 35).

B Showing clear separation between each epithelioid tubercle (H & E, x 100).

C Showing individual tubercles surrounded by reticulin frameworks (Reticulin stain, x 100)

D Section of skin at the site of Kveim's test showing an epithelioid tubercle in the dermis (H & E, x 100).

(PHA) in vitro was found to be impaired twice (22 per cent blasts and 17 per cent blasts on August 1st and 22nd 1983 respectively; normal = 81.2±17 per cent). Study of T-lymphocyte subpopulation from the peripheral blood showed total T lymphocytes (OKT_3/dl) 1,026 (normal 2,240), T-helper/inducer lymphocytes (OKT_4/dl) 701 (normal 1,426), T-suppressor/cytotoxic lymphocytes (OKT_8/dl) 312 (normal 654) and the ratio $T_4:T_8$ was 2.25 (normal 2.18).

After the diagnosis of sarcoidosis was established, prednisolone 2 mg/kg of body weight was instituted for 4 weeks. The enlarged lymph nodes were markedly decreased while the chest radiograph returned to normal (Fig. 2B). The dosage of prednisolone was then gradually reduced and ultimately tapered off within 3 months when all lymph nodes had disappeared completely. Presently the patient enjoys an excellent health and is in good physical condition.

DISCUSSION

Sarcoidosis is rare in children, and the actual incidence is unknown. In a review of the world literature, McGovern and Merrit[14] found only 104 cases of sarcoidosis in children under 15 years of age while over 3,000 cases were reported in adults between the years 1875 and 1953. To this total they added 9 cases which were diagnosed in Washington, D.C. In 1968, Jasper and Denny[15] reviewed 86 more cases in children with sarcoidosis reported since the world review by McGovern and Merrit, and added 25 cases from their own institution. In these series, cases were reported from U.S.A.,[15-18] Hungary,[19] Germany,[20] and Japan.[21] Since that time, few more reports of sarcoidosis in children has appeared in English literature.[22-28] Among children, most cases of sarcoidosis occur in the 9-to-15-year age group; the youngest patient reported was a 2-month-old boy.[14] Both sexes are equally affected and it has generally been found that blacks are more often affected than whites. The age of onset in the present case report lies in the common age group for childhood sarcoidosis. According to the authors' knowledge, this is the first case reported in Thai children. Furthermore, the presenting symptom and sign with massive peripheral lymphadenopathy in this patient is rather unusual for clinical manifestation of sarcoidosis in children. Although generalised lymphadenopathy is a common finding, occurring in 60-70 per cent of children with sarcoidosis, the lymph nodes are not markedly enlarged.[25,26,29] Among 15 cases of sarcoidosis reported in Thiland, multiple, slow growing lymph nodes, scattered around the neck for about 2 years were noted only in a young man aged 17 years from the northern part of Thailand.[12] The size of enlarged lymph node in this patient, however, was only 0.5-1 cm., and no generalised superficial lymphadenopathy was observed. Similar to sarcoidosis in adults, pulmonary involvement can be demonstrated in the vast majority (90-97 per cent) of older children by chest radiography.[14,15,29] The characteristic bilateral hilar lymph adenopathy (BHL) as demonstrated in this patient is common. Pulmonary parenchymal infiltrates may occur in about half of the patients. The parenchymal pattern is classically reticulonodular with fine linear densities and small nodules. Occasionally large nodules simulating lymphoma are present. Pulmonary function tests will reveal a restrictive pattern with decreased forced vital capacity and diffusion capacity.[30] In the present case, there was no parenchymal involvement and the pulmonary function test was not done. Hepatomegaly or splenomegaly may be present in approximately 40 per cent of patients. In this case reported, there was enlarged liver but the spleen was not palpable. Other manifestations such as arthritis,[23,31] eye involvement,[32] parotitis,[15,25] central nervous system involvement,[33] cardiac involvement[34] and skin rash as well as constitutional symptoms (fatique, lethergy, malaise, fever) were absent in this patient.

The abnormal laboratory tests in the present case include eosinophilia which is found in about 50 per cent of children with sarcoidosis.[29] However, intestinal parasites may be responsible for the finding in our case. Hypergammaglobulinaemia which can be seen in nearly 75 per cent of children with sarcoidosis, was also demonstrated in this patient and was confirmed by the elevated IgG level. Hypercalcaemia and hypercalciuria were absent. The former is seen in less than 20 per cent of paediatric patients, but the latter may be present even when serum calcium is normal.[29]

Since this patient had the presenting clinical manifestion of massive generalised lymphadenopathy, the definite diagnosis is chiefly one of exclusion of malignant lymphoma and other granulomatous diseases such as tuberculosis, histoplasmosis, and coccidioidomycosis, which should be based on biopsy material. The characteristic lesion for sarcoidosis was found in the lymph node biopsy in this patient. It is a well-outlined follicle composed chiefly of epithelioid and giant cells, usually surrounded by lymphocytes, with no caseation. The Kveim-Siltzbach test has been used as an adjunct to diagnosis, and was positive in this case.[35] This test is positive in 80-90 per cent of adult patients and it was suggested that the Kveim reaction may be a specific T-lymphocyte-mediated immune reaction that caused epithelioid cell granulomas.[36] Recently, serum angiotensin-converting enzyme (ACE) was found to be useful in confirming the diagnosis of sarcoidosis in childhood as well as a sensitive indicator for following the activity of the disease.[37] In the present case, definitely elevated ACE level was observed and it was decreased after

steroid therapy. However, more recent evidence suggests that ACE is neither specific nor sensitive in practice. False-positive increases of ACE levels have been reported in tuberculosis, chronic active hepatitis, berylliosis, asbestosis and other diseases; and changes in ACE level seem to reflect steroid treatment rather than changes in disease activity.[38] The unusual laboratory finding in the present case reported was the strongly positive skin test to purified protein derivative tuberculin, since patients with sarcoidosis frequently are anergic to skin test antigens. Tuberculosis was excluded in this patient by the clinical settings, histological appearance of the lymph node biopsy, failure to demonstrate tubercle bacilli in the affected lymph nodes both by staining and culture and no improvement after antituberculotic therapy.

The immunological abnormalities in sarcoidosis have been extensively studied.[39] A mixture of depressed cell-mediated immunity and increased humoral immunity was observed. These abnormalities are characterised by lymphopenia associated with a low percentage of circulating T lymphocytes, anergy to skin-test antigens, particularly tuberculin and hypergammaglobulinaemia. In addition, analysis of the subpopulations of circulating T lymphocytes has suggested an imbalance between the suppressor T cells and the helper T cells.[40,41] The increased activity of T suppressor cells is probably mediated by circulating immune complexes present in 60 per cent of sera from patients with sarcoidosis.[42] Although *in vivo* delayed hypersensitivity skin reaction to recalled antigens in this patient was normal and normal peripheral lymphocyte count, *in vitro* studies of lymphocyte function as well as the determination of lymphocyte subpopulation confirm the previous findings. The recognition that sarcoidosis is not an anergic disease has been stressed.[43] In contrast to the systemic immune response, the local pulmonary response is totally different, for both the proportion and the number of T lymphocytes in bronchoalveolar lavage fluid are significantly greater than in normal controls and other chronic pulmonary diseases.[44,45] A three-to fourfold increase in ratio of helper: suppressor T lymphocytes in lavage fluid of patients with active sarcoidosis has been observed.[46] It has been demonstrated that monocyte chemotactic factors and various other lymphokines are produced from activated T cells, and as a result, epithelioid-cell granulomas are formed.[45] The aetiology of sarcoidosis remains obscure despite extensive investigations of bacteria, viruses, fungi, parasites, nontuberculous mycobacteria or foreign bodies as possible causes.

Sarcoidosis is a self-limited disease that can be resolved over two to three years, and for most cases no therapy is required.[29,46] In the present case, however, massive generalised lymphadenopathy persisted over the period of six years, so requiring intervention. Corticosteroids are the drug of choice for sarcoidosis, and the lymphadenopathy resolved completely after steroid treatment within 3 months in the present case report. Other indications for therapy in sarcoidosis include (1) progressive pulmonary impairment, (2) uveitis, (3) myocardial disease (conduction defect), (4) central nervous system disease and (5) hypercalcaemia, hypercalciuria or renal impairment.[29] It was uncommon for the disease to recur after corticosteroids were discontinued. However, in those with serious extrapulmonary manifestations (such as the involvement of the eye, CNS, heart, liver), treatment should be continued for years, perhaps even for life. Although the majority of patients with sarcoidosis recover over the years, 10-20 per cent will have long-term sequelae especially blindness and severe restrictive lung disease. Long term follow-up of the case reported here is required.

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