

Cases Report

Histopathologic Aid to Diagnosis of Sarcoidosis: Report of 8 Cases

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Sarcoidosis is a multisystemic disease of unknown etiology. The disease is common in blacks and is very rare in Thailand. It presents as one of the most variable manifestations usually affecting the lungs and intrathoracic lymph nodes. Other organs such as liver, spleen, joints and eyes including skin are also involved. The common cutaneous lesions are maculopapular, erythematous plaque, subcutaneous nodule, scar and lupus pernio. No reliable indicator is useful for diagnosis except the histopathologic change which is the only way for approaching this disease. Sarcoidosis is the disease of exclusion. Various infections producing granulomas should be excluded histologically. The ultimate diagnosis requires clinical correlation, laboratory investigations, chest X-ray as well as available tissue culture. Herein, the authors reported eight cases of sarcoidosis by retrospective study primarily diagnosed by histopathological findings at Siriraj Hospital from January, 1997 to December, 2004 with many different clinical presentations. Despite the diverse clinical pictures, interestingly, the presented patients almost had the same histopathologic findings as small, uniform, discrete naked granulomas usually without necrosis. These findings act as a hallmark for diagnosis of this disease.

Keywords: Sarcoidosis, Histopathology, Diagnosis

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Sarcoidosis is a multisystemic disease of unknown etiology and has many clinical presentations ranging from asymptomatic abnormal clinical findings on chest X-ray as lung infiltration or as mediastinal lymphadenopathy to progressive multiorgan failure in unfortunate minority. The illness can be self-limited or chronic, with episodic recrudescence and remissions. The lungs and thoracic lymph nodes are almost always involved with asymptomatic or insidious respiratory symptoms. Variable organs are also affected including skin, eyes, liver, spleen as well as cardiomyopathy. It affects persons of all races, all ages and females outnumber males^(1,2). It has a particular proclivity for adults under the age of 40 and in blacks. The diverse manifestations of this disease make it difficult to diag-

nose definitively. The authors reported 8 cases of sarcoidosis with different clinical presentations. The presumptive diagnosis was primarily based on histopathological change which acted as a clue for diagnosis of this disease

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The present retrospective study of eight patients diagnosed with sarcoidosis at the Department of Pathology, Faculty of Medicine, Siriraj Hospital between January, 1997 and December, 2004. The diagnosis of all patients was primarily guided by histopathological changes. After the initial diagnosis, the medical charts were used to obtain data about the patient's age, sex, disease stage according to chest X-ray, organs involvement, laboratory investigations, treatments, course of disease and outcome (Table 1, 2). Patients who responded to antituberculous drugs were excluded. Most patients had characteristic histopatho-

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Table 1. Detail of cases

Case	Sex	Age (years)	Organs involvement	Follow up
1	F	33	Mediastinal lymph node	S (9 months)
2	F	27	Skin	L
3	F	42	Skin	L
4	F	48	Skin	Back to provincial hospital
5	M	40	Mediastinal lymph node	S (6 months)
6	F	39	Mediastinal lymph node	S (2 months)
7	F	2	Skin, Eyes, Joints, lymph node, (cervical, axilla, inguinal), Liver, Spleen	P
8	F	35	Skin, Cervical lymph nodesLung (interstitial infiltration and hilar lymphadenopathy)	Improve without any treatment

F = female M = male L = loss to follow up S = stable P = Progression

Table 2. Skin manifestations

Case	Skin manifestations
1	-
2	Multiple, diffuse, ill-defined, fresh-color papules and on top of scars
3	Subcutaneous nodule on forehead, fixed to the underlying bone
4	Multiple papules, nodules on back
5	-
6	-
7	Generalised ichthyosiform, erythematous rash
8	Asymptomatic, multiple discrete erythematous papules, plaques on face, neck, forearm

logic findings as dense, discrete, small, uniform, non-caseating granulomas. Inclusion bodies as Schauman (Fig. 2) and asteroid bodies (Fig. 3) were occasionally found (case 4). Giant cells of foreign body type as well as Langhans type (Fig. 4) were found in five cases (cases 2, 3, 4, 7, 8). Typical histopathologic findings favored sarcoidosis but the ultimate diagnosis needed clinical correlation and other investigations to confirm this disorder.

Among eight patients, seven were female and one was male. They were between the ages of 27 and 48 years except the youngest (case 7) who was only 2 years old at the onset presenting as typical preschool sarcoidosis⁽²⁾. Clinical features of these patients are listed in Table 1, 2. Two patients (cases 1,6) had only mediastinal node enlargement and one case (case 5) had additional abnormal lung change on the chest X-ray. Five patients (cases 2, 3, 4, 7, 8) had skin manifestations while the other three (cases 1, 5, 6) had no skin lesions. One patient (case 8) had multiple skin lesions, mediastinal lymph node and abnormal lung change as diffuse interstitial infiltration. All patients had normal laboratory studies except hypercalcemia which was

noted in one case (case 4). Three cases (cases 1, 5, 6) had stable clinical course after 9, 6 and 2 months of follow up respectively. One case (case 8) improved without any treatment as involution of both skin lesions and lymph nodes but lung lesions did not change by the end of 6 months of follow up. Our youngest patient (case 7) had typical triad of childhood sarcoidosis; skin, eyes and joint were involved (Fig. 5, 6) without lung lesion⁽³⁾. She also had hepatosplenomegaly. Her skin lesions presented as ichthyosiform, erythematous rashes and were successfully treated by topical and systemic corticosteroids. However, her eye symptoms continued to progress and she developed partial blindness due to lens opacity. Two patients (cases 2, 3) were lost to follow up and one case (case 4) returned to a provincial hospital without any additional information.

Among the five patients (cases 2, 3, 4, 7, 8) with skin manifestations showed diverse presentations varying from erythematous, ichthyosiform rash on case 7 (Fig. 5), asymptomatic skin-colored or erythematous papules on two cases (cases 2, 8) and on top of scar on case 2 (Fig. 7, 8). Two patients presented as dermal or subcutaneous nodules (cases 3, 4) and fixed to the

underlying skull (case 4). Biopsy of these skin lesions showed typical findings of sarcoidosis presenting as small dense discrete, uniform granulomas (Fig. 1). Liver

biopsy was done (case 7) and a small focus of naked tubercle described above was found (Fig. 9). Fibrinoid necrosis (Fig. 10) was apparent in one case (case 8).

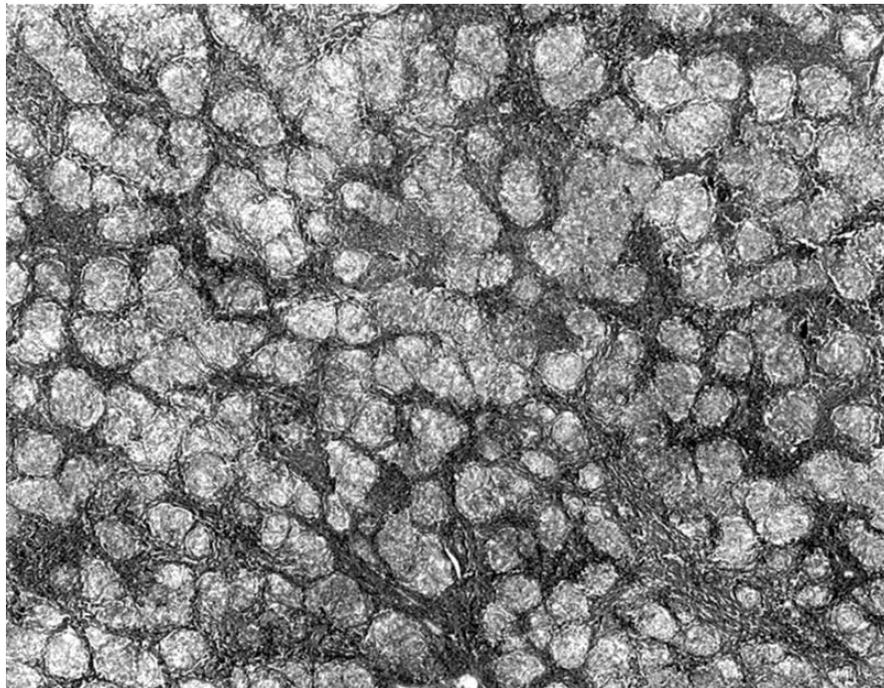


Fig. 1 Typical granulomas as small, uniform, dense, discrete, naked tubercles (Hematoxylin-eosin, original magnification x40)

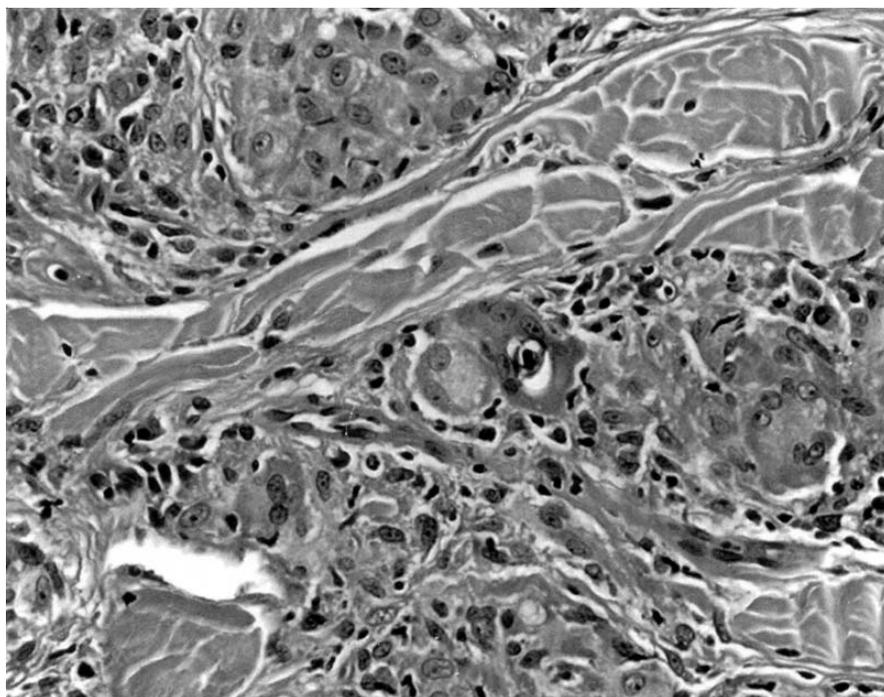


Fig. 2 Histopathology of skin of case 4. Typical Schaumann's body (Hematoxylin-eosin, original magnification x400)

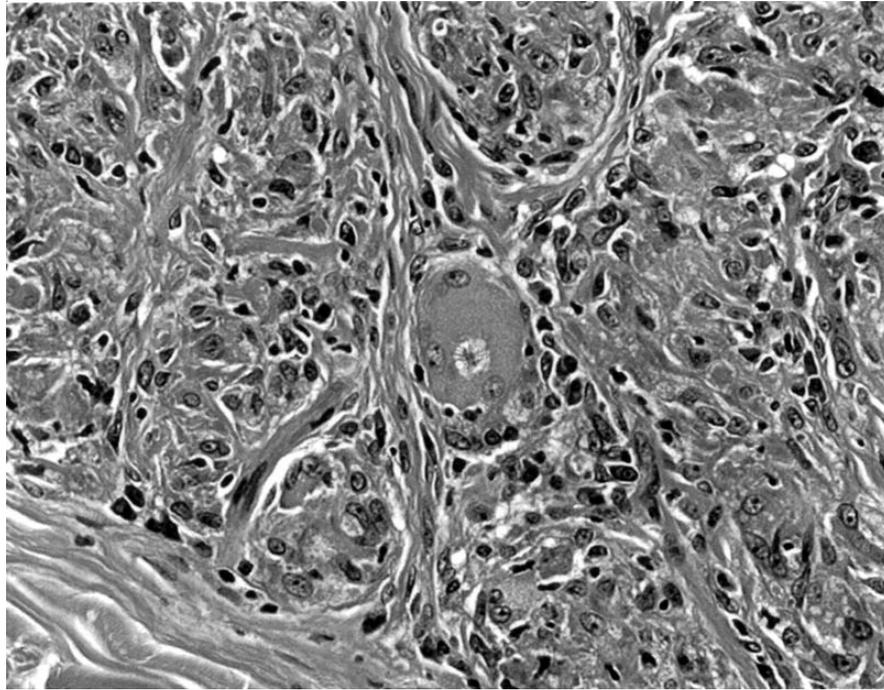


Fig. 3 Histopathology of skin of case 4. Typical Asteroid body (Hematoxylin-eosin, original magnification x400)

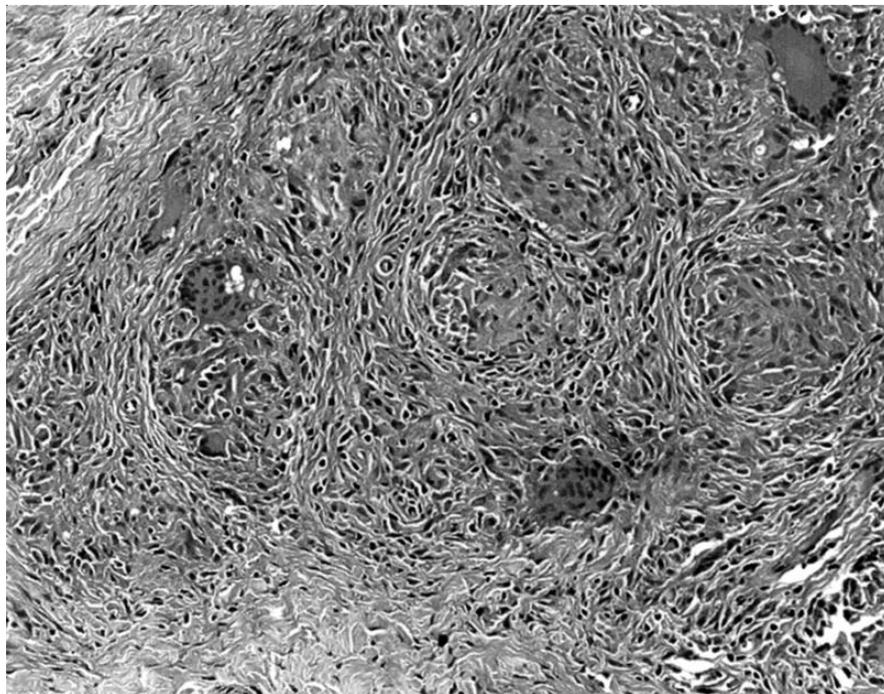


Fig. 4 Histopathology of cases 2-4, 7, 8. Both Langhans and foreign body type giant cells (Hematoxylin-eosin, original magnification x100)

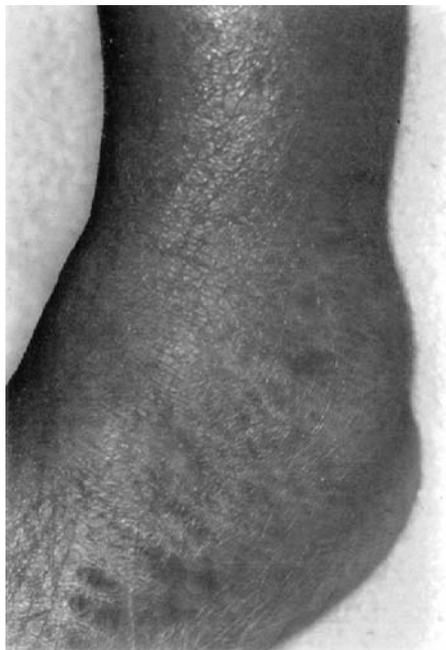


Fig. 5 Ichthyosiform dermatitis on case 7

Lymph node biopsy were performed (cases 1,5,6), interestingly, all of them showed similar histopathologic features composed of granulomas described above (Fig.11). Special staining and polarised light technique were done on each case to rule out infectious causes such as tuberculosis, fungal infections or foreign substances. The Kveim-Siltzbach test was not done due to the lack of available antigenic suspension. Because of the typical histopathologic findings the primary diagnosis of sarcoidosis was given. Subsequently, careful search for other causes of granuloma by clinical data, laboratory tests showed no positive results. The pathologic changes and clinical findings were believed to represent this disease.

Discussion

Sarcoidosis is a systemic disease of unknown etiology and shows distinctive, diverse clinical manifestations involving the lungs, lymph nodes, liver, spleen, bone marrow as well as various skin lesions as mentioned earlier. Papulonecrotic tuberculid like lesion was also reported⁽⁴⁾. The cause remains obscure for a number of reasons including the heterogenicity of the manifestations of the disease, clinical overlap with other disorders^(1,2,5). This disease was found to develop in the patients with various hematologic malignancies. Among these were chronic lymphocytic leukemia⁽³⁾, polycythemia vera⁽⁶⁾ and CD8⁺/CD4⁻ primary cutaneous

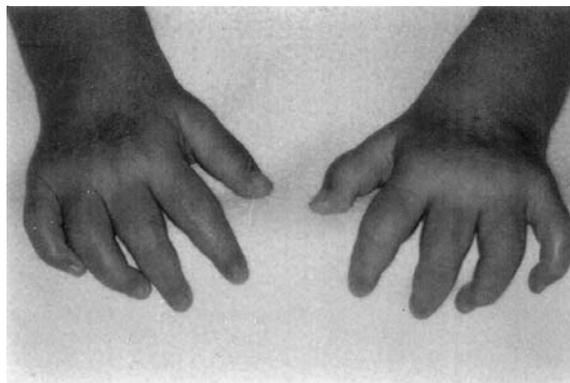


Fig. 6 Joints involvement on case 7



Fig. 7 Erythematous plaque and scar on case 2



Fig. 8 Erythematous, scaly plaques on case 8

CD30⁺ lymphoproliferative disorder⁽⁷⁾. Granulomatous dermatitis related to soy has also been reported⁽⁸⁾. Papageorgiou, et al⁽⁹⁾ reported an association of systemic sarcoidosis with tattoo granulomas. Generally, the presence of foreign bodies was thought to exclude

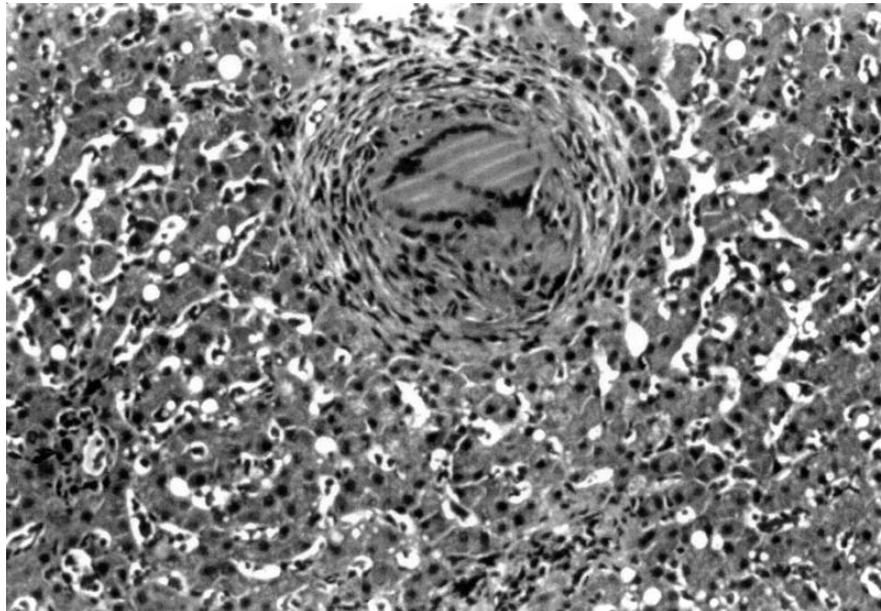


Fig. 9 Histopathology of liver biopsy on case 7 shows small granuloma and Langhans' giant cell (Hematoxylin-eosin, original magnification x400)

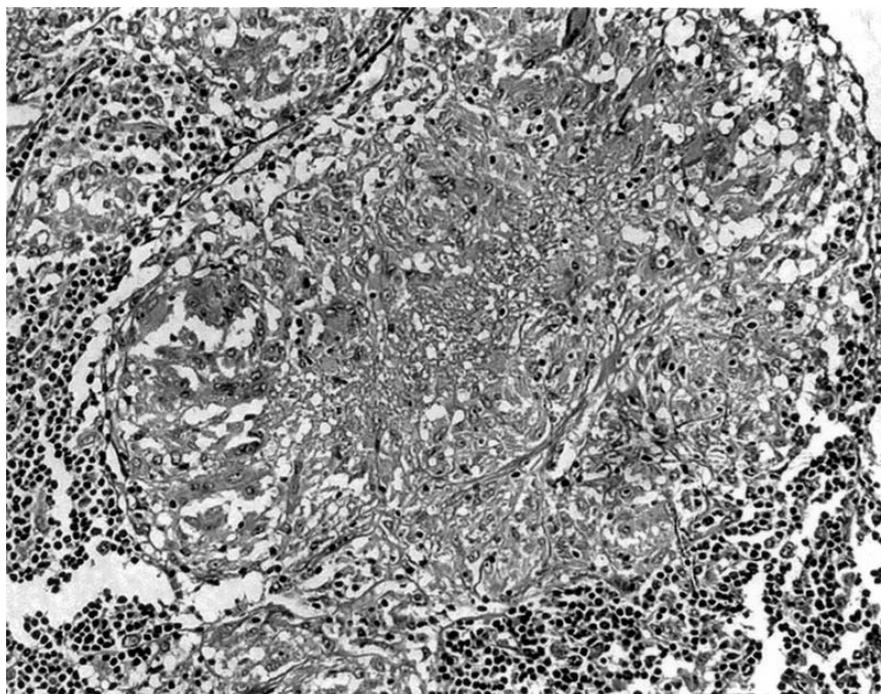


Fig. 10 Histopathology of case 8. Fibrinoid necrosis (Hematoxylin-eosin, original magnification x400)

this disease, however, a report argued this concept⁽¹⁰⁾. Most cases were around the fourth decade. Our youngest patient (case 7) was only 2 years at the onset

and had the typical triad of preschool sarcoidosis as skin, eyes and joint involvement without lung manifestations⁽¹¹⁻¹⁴⁾. In the patients presenting only medi-

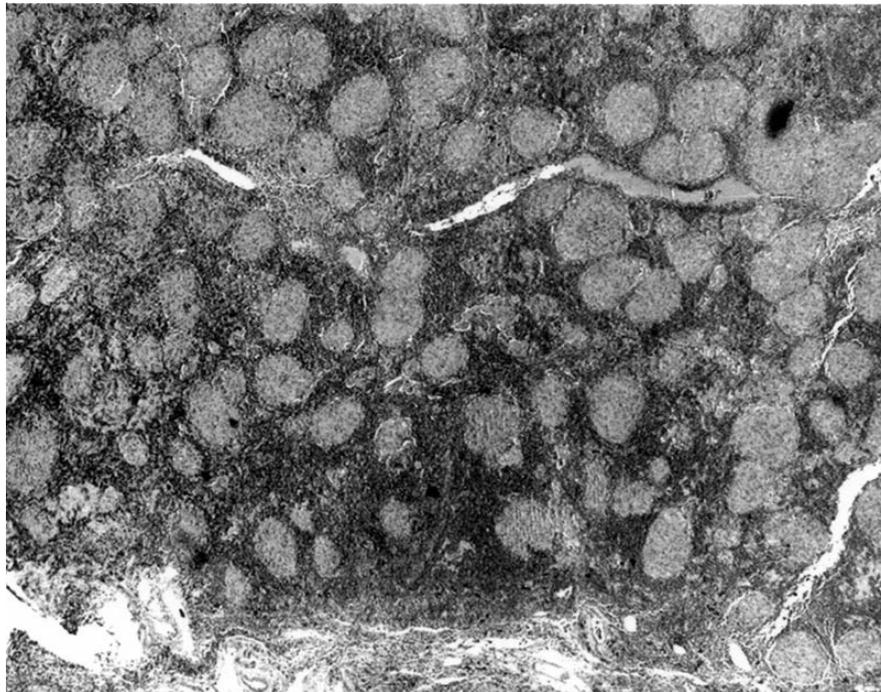


Fig. 11 Histopathology of lymph node biopsy on cases 1, 5, 6. Similar findings as typical granulomas described above (Hematoxylin-eosin, original magnification x100)

astinal lymphadenopathy, fine needle aspiration method provided a safe, effective way to obtain evidence of the disease⁽¹⁵⁻¹⁷⁾. It was necessary to correlate both the clinical and histopathologic changes for the definite diagnosis. There was no single laboratory test or group of tests for diagnosis of this disease. The Kveim-Siltzbach test had long been the traditional diagnostic test⁽¹⁸⁾. However, the author has no available standard antigen. An elevated (Angiotensin-converting enzyme) level had been used to confirm the diagnosis though it was not specific too⁽¹⁹⁾. On average, cutaneous involvement in sarcoidosis was about 25 percent⁽²⁾ and 32.9 percent⁽¹⁾ and the most common skin lesion was erythema nodosum⁽¹⁾. Other skin manifestations as maculopapular, erythematous rash, plaques, subcutaneous nodules, lupus pernio⁽²⁰⁾, and scar lesions had been observed⁽¹⁾. Biopsy of either lymph node or skin lesion was the recommended diagnostic tool^(2,15-17). In the present study, the authors retrospectively studied both clinical and histopathologic findings and the authors strongly agreed in that none of our cases could be diagnosed unless or until the biopsy of either lymph node or skin lesion was done. The typical findings as dense, discrete, small, uniform, noncaseating granulomas were the hallmark.

As in the presented cases, necrosis was usually absent^(2,9) except in one case (case 8). Necrosis composed of fibrinoid material and demonstrated by Masson's trichrome staining was found centrally. Caseous necrosis, as a rule was not the picture⁽²¹⁾. In conclusion, the authors strongly emphasized that the diagnosis of this disease was established via biopsy findings. The presence of small, isolated naked epithelioid granulomas was the hallmark for this disease. All suspected cases should have infections or malignant conditions excluded⁽³⁾.

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การอาศัยลักษณะจุลพยาธิวิทยาในการวินิจฉัยโรค Sarcoidosis: รายงานผู้ป่วย 8 ราย

เจน มโนกุล, รังสิมา วณิชภักดีเดชา, วาณี วิสุทธิ์เสรีวงศ์, พนิดตา ธิรโพธ

Sarcoidosis เป็นโรคที่ไม่ทราบสาเหตุ และสามารถเกิดโรคได้ในหลายระบบ ทำให้เกิดลักษณะทางคลินิกได้หลากหลาย ปอดและต่อมน้ำเหลืองจะเกิดโรคนี้ได้บ่อย นอกจากนั้นยังพบโรคได้ในอวัยวะต่าง ๆ เช่น ตับ, ม้าม, ตา, ข้อต่อกระดูก รวมทั้งผิวหนัง อาการแสดงที่ผิวหนังพบทั้ง *maculopapular*, *erythematous plaques*, *nodules*, *scars* รวมทั้ง *Lupus pernio* ไม่มีวิธีที่แน่นอนในการวินิจฉัยโรคนี้ นอกจากอาศัยการเปลี่ยนแปลงทางจุลพยาธิวิทยา รวมทั้งเปรียบเทียบกับลักษณะทางคลินิก ผลการตรวจทางห้องปฏิบัติการ และการตรวจ X-ray ของปอด ผู้รายงานได้ศึกษาย้อนหลัง ผู้ป่วย 8 ราย ในโรงพยาบาลศิริราช ตั้งแต่เดือน มกราคม พ.ศ. 2540 ถึง เดือนธันวาคม พ.ศ. 2547 ที่ให้การวินิจฉัยเบื้องต้น โดยอาศัยการเปลี่ยนแปลงทางจุลพยาธิวิทยา ลักษณะที่พบเป็น *small, uniform, dense, discreted, naked granuloma* ในอวัยวะต่าง ๆ ที่เกิดโรค ซึ่งยืนยันว่าการเปลี่ยนแปลงทางจุลพยาธิวิทยา มีประโยชน์ในการวินิจฉัยโรคนี้