1. 背　景

サルコイドーシス(サ症)は，病因，発症機序が完全には解明されていない全身性肉芽腫性疾患である．細菌，抗酸菌，ウイルス，環境物質など何らかの原因抗原に対する免疫応答の異常と考えられている．リンパ節や気管支肺胞洗浄液など，病変局所におけるサイトカインの研究[1)-3)]から，サ症はTh1-diseaseと考えられている．

樹状細胞(dendritic cell:DC)は，骨髄由来の白血球で，強力な抗原提示能を有し，T細胞を介した免疫反応の開始と調節の中心を担う細胞であり，生体内のほぼ全域に分布する．分布する組織によって異なるサブセットが存在し[4)]，末梢血においては，myeloid DC(mDC)とplasmacytoid DC(pDC)の2つのサブセットに分類される．Th1を誘導するDCをDC1，Th2を誘導するDCをDC2と呼び，かつてはmDCがDC1，pDCがDC2であると考えられていた．近年mDCの中にTh1を誘導するmDC1と，Th2を誘導するmDC2の2つのサブセットが存在することが分かってきた．しかし疾患におけるmDC1，mDC2の動態については明らかではなく，これまで，サ症の末梢血においてmDC1，mDC2を含めたサブセットを解析した報告はない．

今回われわれは，Th1-diseaseと考えられているサ症における末梢血DCサブセットを，健常群，Th2-diseaseと考えられるアトピー群と比較して検討した．

2. 対象と方法

各群の患者背景を(表1)に示す．

サ症群(SAR)は，わが国の診断基準を満たし，ステロイドや免疫抑制剤などの使用がない21名とした．健常群(Normal)は，ダニ・ハウスダストに対する特異的IgE抗体が陰性かつ基礎疾患のない9名，アトピー群(Atopy)は，ダニ・ハウスダストに対する特異的IgE抗体陽性(RAST class2以上)で，気管支喘息やアトピー性皮膚炎などを有し，かつ吸入/外用ステロイド等の治療がなされていない11名とした．

表1. 各群の患者背景

	SAR (n=25)	*Atopy* (n=11)	*Normal* (n=9)
mean age (range)	51.0 (24-77)	30.2 (22-45)	42.2 (32-56)
sex (male/female)	10 / 11	9 / 0	5 / 3
smoking status (smoker/non-smoker)	15 / 6	4 / 5	2 / 7
stage I	9 (41%)	-	-
stage II	10 (50%)	-	-
stage III	2 (9%)	-	-

表2. 使用した蛍光標識抗体

	antigen	label	company
Lineage cocktail	CD3	FITC	BD Bioscience
	CD14	FITC	BD Bioscience
	CD16	FITC	BD Bioscience
	CD19	FITC	BD Bioscience
	CD20	FITC	BD Bioscience
	CD56	FITC	BD Bioscience
Other antibodies	CD11c	PE	BD Bioscience
	CD123	PE	BD Bioscience
	CD1a	APC	BD Bioscience
	CD123	APC	BD Bioscience
	BDCA3	APC	Miltenyi Biotec
	HLA-DR	Per-CP	BD Bioscience

新鮮末梢血全血20mLに，直接標識抗体(表2)を添加し，その後溶血させ，赤血球を除去し，白血球全体におけるDCをフローサイトメトリー(FACS-Caliber)で解析した．Lineage-/HLA-DR+の細胞群がDCであり，そのうちCD11c+がmDC，CD123+がpDCである．mDCを2つのサブセットに分類する方法として，CD1a high/lowによるmDC1/mDC2の分類と，BDCA3(blood dendritic cell antigen3) low/highによる分類の2つの方法を用いて検討した．

統計学的解析は，StatView統計プログラムを用い，平均±標準誤差で示した．$p<0.05$を統計学的有意とした．

3. 結　果

1) mDC/pDCサブセット

Normal，SAR，Atopyのいずれも，mDCとpDC

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表3. 各群におけるmDC, pDCサブセット

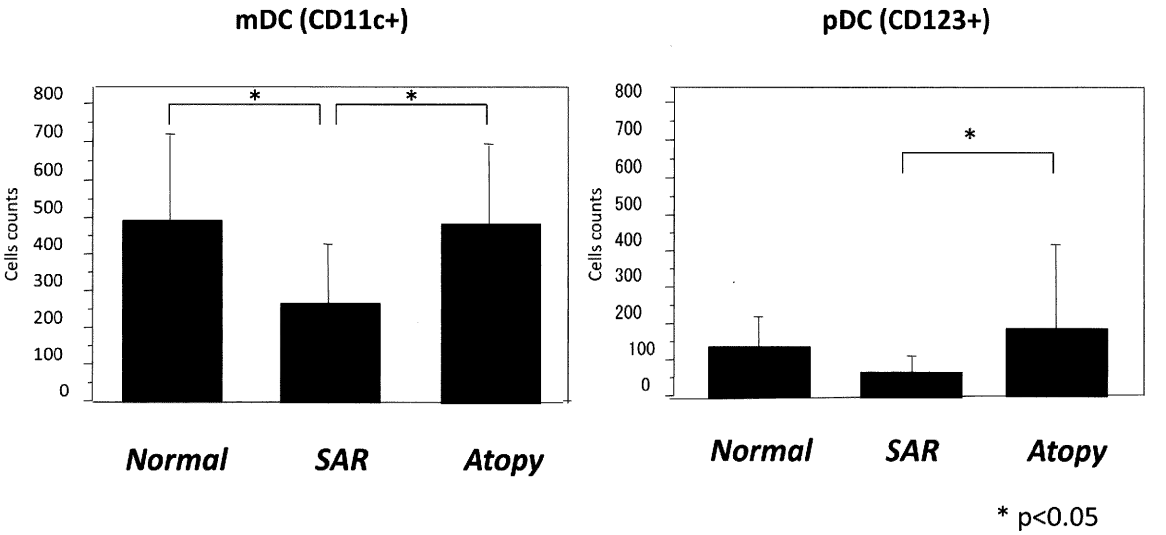
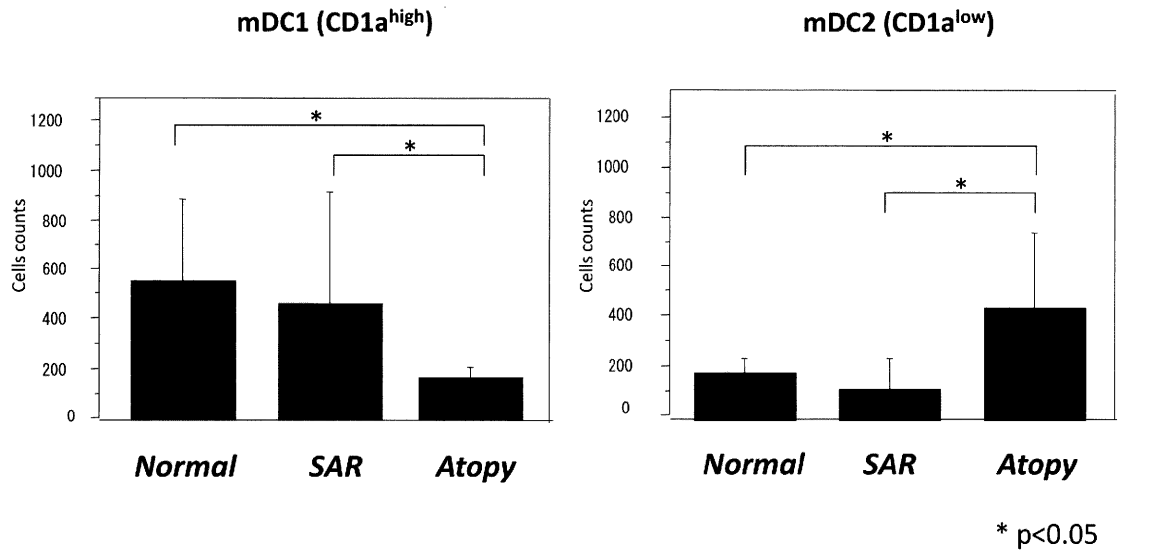


表4-1. CD1a $^{high/low}$によるmDC1/mDC2サブセット



の数の比較ではmDCが優位であった(表3). またSARでは，mDC数が他の2群と比較し，有意に少なく，pDC数はAtopyと比較して有意に少なかった(図1-b).

2) CD1a high/lowによるmDC1/mDC2サブセット

mDC1, mDC2数はSARとNormalは同等であった. 一方Atopyでは，Normal，SARと比較してmDC1が有意に少なく，mDC2が有意に多かった(表4-1). 各症例の結果を表3-2に示す. NormalとSARでは全例でCD1a^{high}がCD1a^{low}よりも有意に多かった. 逆にAtopyでは，ほぼ全例でCD1a^{low}がCD1a^{high}よりも有意に多かった.

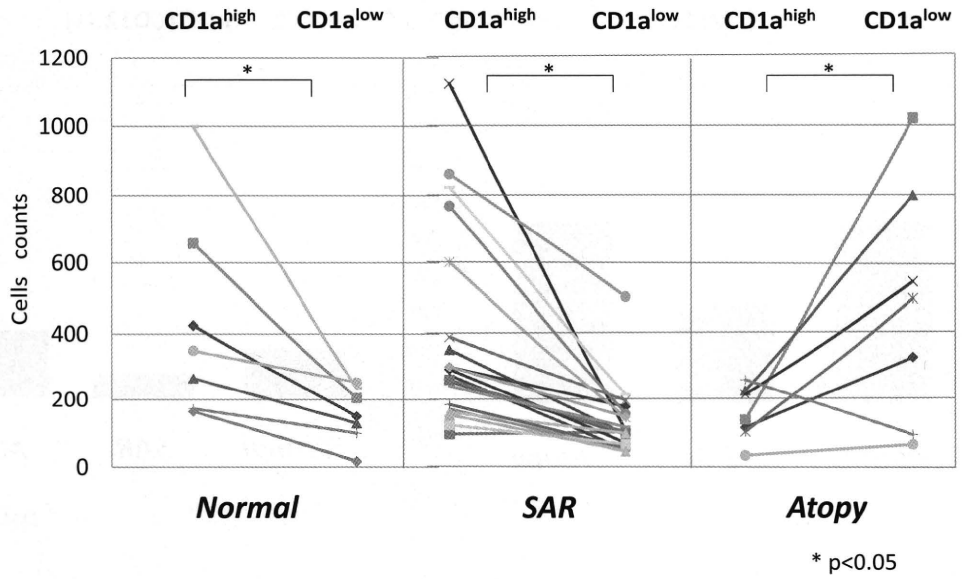
CD1a$^{high/low}$-ratioは，SARが高い傾向はあるものの有意差はなく，一方Atopyは他の2群と比べ有意に低かった(表5).

3) BDCA3 low/highによるmDCサブセット

CD1aと比べて，BDCA3の発現細胞数自体が3群ともに少ない傾向を示した.

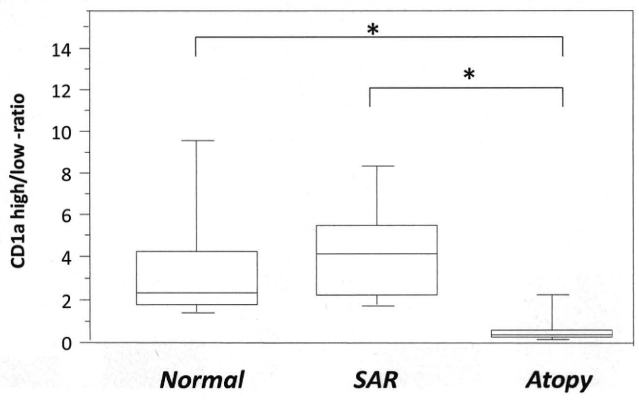
BDCA3 low/highによるmDCのサブセット分類では，BDC3^{low}がAtopyで少ない傾向を示したが，3群間に有意な差は認めなかった(表6-1). 症例ごとの結果では，NormalとSARでBDCA3^{low}が多くBDCA3^{high}が少ない傾向を示したものの，CD1aによる分類と比べると症例ごとのばらつきが多く，有意

表4-2. CD1a $^{high/low}$ によるmDC1/mDC2サブセット



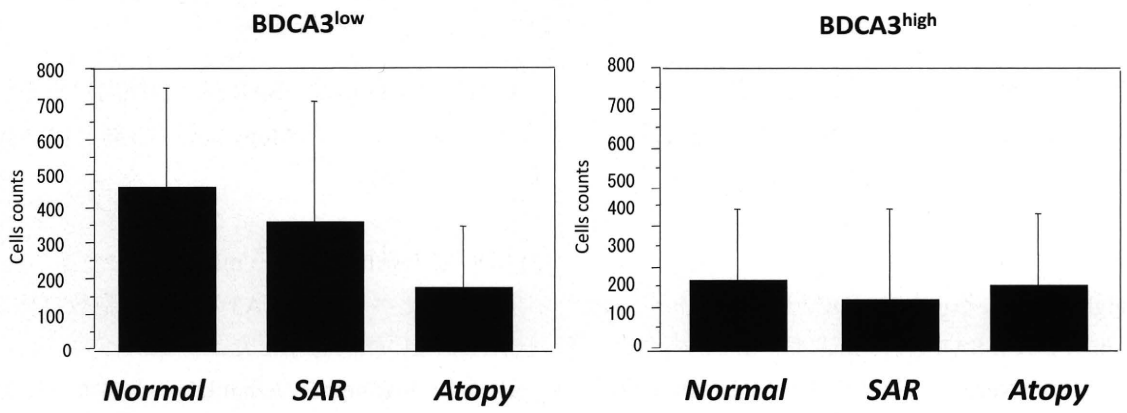
* p<0.05

表5. CD1a high/low -ratio



* p<0.05

表6-1. BDCA3 low/high によるmDCサブセット



差を認めたのはSARでのみであった(表6-2).

BDCA3 low/high-ratioは，SARはNormalと同等で，Atopyは他の2群と比べ有意に比が大きかった(表7).

4. 考　察

サ症において，末梢血中のDCの総数が低下することは報告されている[5]．今回の検討でも，健常群

表6-2. BDCA3 $^{low}/_{high}$ によるmDCサブセット

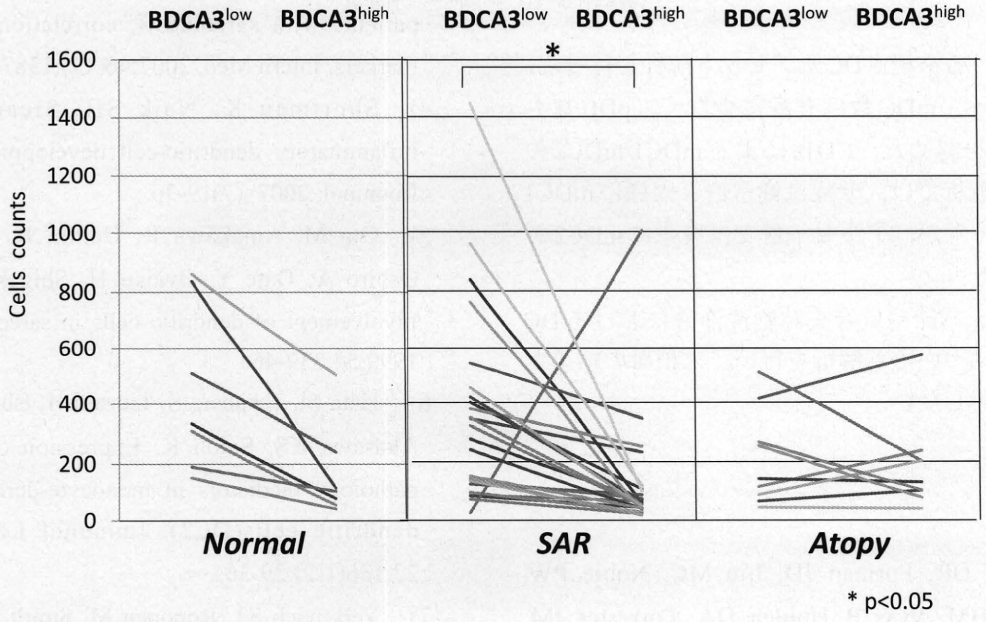
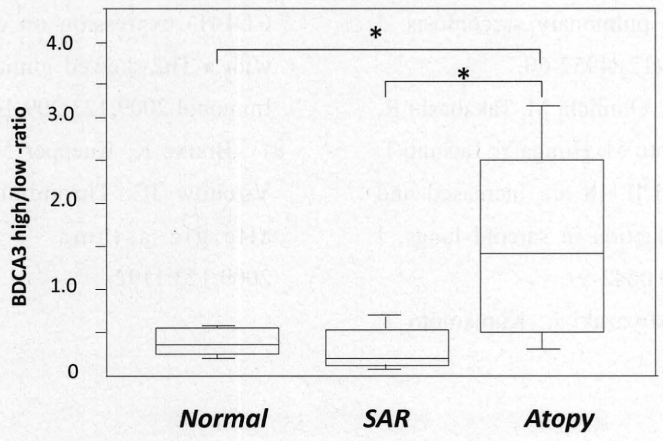


表7. BDCA3 low/high-ratio



と比較して，サ症ではmDC，pDCいずれの数も少なく，その傾向はとくにmDCで顕著であった．サ症で末梢血中のDC数が低下する理由としては，肺や皮膚などのサ症の病変局所へ，末梢血中からDCが動員されることなどが考えられる．

Hataらは，末梢血から精製した単核球を，GM-CSF+IL-4，IL-3+IL-4で分化，成熟させることでmDC1，mDC2を作成し，さらに両者におけるCD1aの発現強度の違いから，CD1aがmDC1のマーカーとなることを報告した[6]．CD1aを用いたmDC1/mDC2サブセット分類では，SARとNormalは同等で差がなかった一方で，Atopyでは有意にmDC2にシフトしていた．末梢血のmDC1/mDC2バランスと病態としてのTh1/Th2バランスの関連が示唆されるが，症例数を増やしてさらに検討を行いたい．

BDCA3は，mDC2に高く発現し，mDC2のマーカーとなりうるという報告がある[7][8]が，その発現意義や機能については，まだ十分に解明されているとはいえない．CD1aと比べ，BDCA3の発現細胞自体が少なく，また症例ごとのCD1a low/highとBDCA3 high/lowの結果(表4-2，6-2)で，BDCA3ではCD1aと似たような傾向を示すもののCD1aと比べ疾患群内でのばらつきを認めた．BDCA3発現の意義とその解釈については更なる検討が必要である．

5. 結　論

サ症における末梢血DCサブセット解析を行った．健常人と比べ，mDC数は有意に少なく，pDC数も少ない傾向を認めた．CD1aによるmDC1/mDC2のサブセット解析では，サ症は健常群と同様にmDC1が優位であったが，アトピー群では有意にmDC2が優位であった．

今後，リンパ節や気管支肺胞洗浄液におけるDCサブセットについても解析を行い，末梢血の結果とあわせて検討したい．

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manuscript before submission

Diagnostic guidelines for sarcoidosis in Japan

Japan Society of Sarcoidosis and Other Granulomatous Disorders(JSSOG); The Japanese Respiratory Society; Japanese College of Cardiology; Japanese Ophthalmological Society; Japanese Dermatological Association; Japanese Society of Neurology; Diffuse Lung Diseases Research Group from the Ministry of Health, Labour and Welfare, Japan

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Introduction

The first diagnostic criteria for sarcoidosis used in Japan were those proposed at the International Conference on Sarcoidosis held in 1960. The criteria drafted by the Research Committee of Sarcoidosis of the Ministry of Health and Welfare were first reported in 1989, and revised in 1992. The revised criteria have since served as diagnostic criteria for sarcoidosis (Guidelines for Diagnosis and Treatment of Intractable Diseases 1997, edited by Planning Committee of Japan Intractable Diseases Research Foundation and supervised by Diseases Control Division, Public Health Bureau, the Ministry of Health and Welfare). In recent years, significant advances in understanding sarcoidosis and diagnostic technologies have been made. Diagnostic accuracy has been improved by the introduction of diagnostic imaging methods, such as high resolution computed tomography (HRCT), gallium-67 citrate scintigraphy and other radioisotope examinations, as well as serum angiotensin converting enzyme (ACE) measurement and use of bronchoalveolar lavage. More patients were diagnosed as having sarcoidosis (estimated number of patients: 3,329 in 1972; 15,100 in 1991), which highlighted the involvement of individual organs, suggesting the necessity of diagnosing sarcoidosis developed in each organ. The 2006 revision aimed to update criteria for comprehensive diagnosis, and more importantly, to improve diagnostic guidelines for sarcoidosis with each organ involvement, such as "Diagnostic Guidelines for Cardiac Lesions" and "Diagnostic Guidelines for Ocular Lesions" . The conventional diagnostic guidelines used in Japan were partly modified to adapt to current circumstances with renewal of diagnostic guidelines for each organ involvement and the literature presenting evidence for them as much as possible.

Diagnostic criteria

Diagnosis of sarcoidosis should be performed according to the following criteria, and classified into a histologic diagnostic group and a clinical diagnostic group (Figure 1).

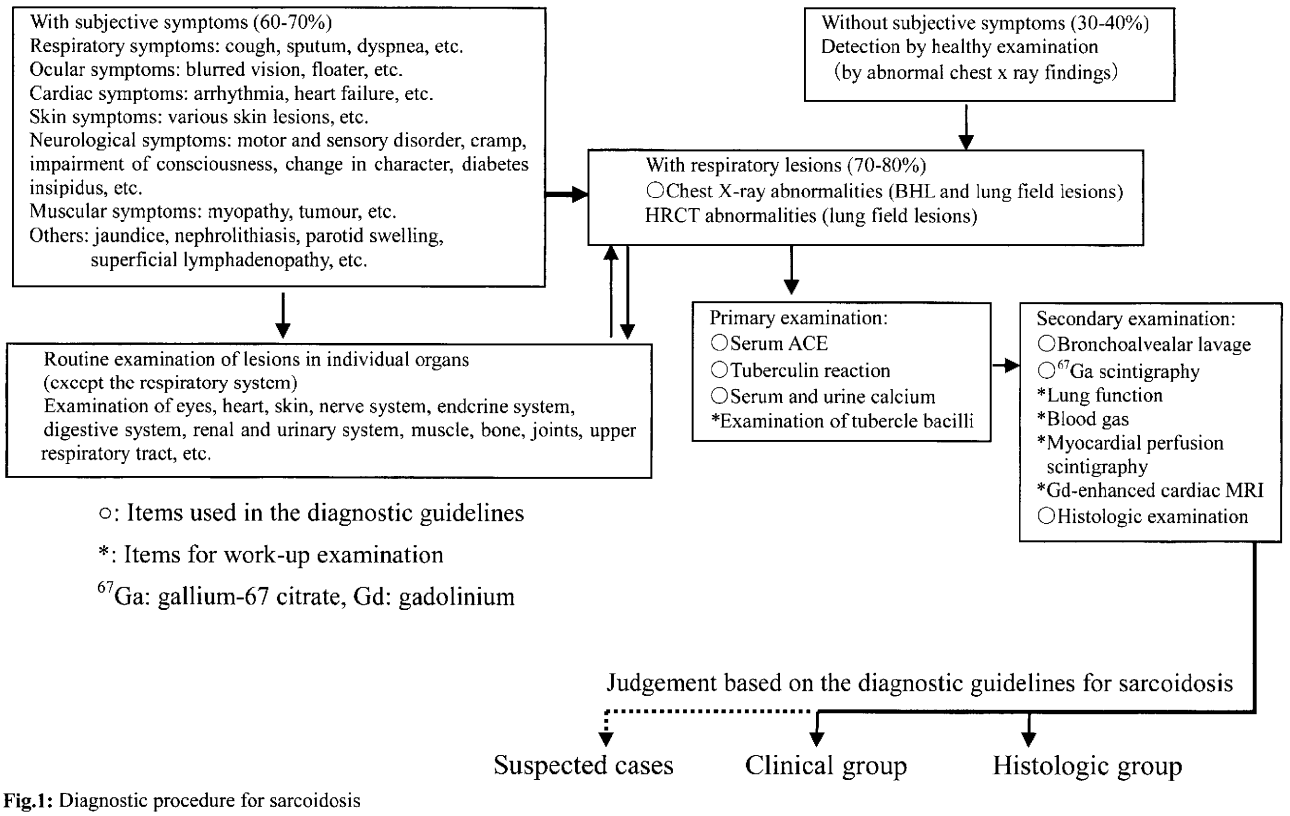

Fig.1: Diagnostic procedure for sarcoidosis

1. Histologic diagnostic group

A group presenting histologic evidence of noncaseous epithelioid cell granuloma in an organ, which is supported by any one of the following three findings:

1) Evidence of noncaseous epithelioid cell granuloma in other organ(s).
2) Clinical findings in other organ(s) that strongly suggest lesions of sarcoidosis.
3) Two or more out of the six clinical and laboratory findings indicative of systemic reactions listed in Table 1.

2. Clinical diagnostic group

A group without histologic evidence of noncaseous epithelioid cell granuloma, but demonstrating clinical findings strongly suggesting lesions of sarcoidosis in two or more organs, together with two or more out of the six clinical and laboratory findings indicative of systemic reactions listed in Table 1.

Table 1. Clinical and laboratory findings indicative of systemic reactions

1) Bilateral hilar lymphadenopathy
2) Elevated serum ACE
3) Negative tuberculin test
4) Abnormal uptake on gallium-67 citrate scintigraphy
5) An increase in lymphocyte count or an elevated CD4/CD8 ratio in bronchoalveolar lavage fluid
6) Elevated serum or urine calcium

3. Exclusions

It is necessary to exclude the other disorders according to the diagnostic guidelines of individual organs.

Diagnostic guidelines

As for diagnostic guidelines, the characteristics of lesions of sarcoidosis in the respiratory system, eyes, heart, skin, neuromuscular system, and other organs are described below in that order, together with a list of diseases to be excluded.

1. Diagnostic guidelines for respiratory lesions

The respiratory lesions of sarcoidosis include lesions of alveolus (alveolitis), the bronchovascular sheath, hilar lymph node, trachea, bronchus, and pleura.

Clinical findings 1) or 2) are strongly suggestive of respiratory lesions of sarcoidosis.

1) Bilateral hilar lymphadenopathy (BHL).
2) Without BHL, any one of the following findings listed in Table 2.

In the cases with BHL, it is also useful.

Table 2. Chest imaging features and bronchoscopic findings

1. Chest radiological findings
   1) The distribution is diffuse but upper predominant. Fine nodular, linear and patchy shadows are common.
   2) Irregular thickening of bronchovascular markings are commonly seen.
   3) Fibrotic lesions with shrinkage are seen predominantly in the upper lung zone, when the disease has progressed.
2. CT / HRCT findings
   1) Small nodules and thickening of bronchovascular bundles are common. Local shrinkage is sometimes seen. Small nodules locate on both centrilobular structures and perilobular ones such as pleura, intralobular septa, bronchi, bronchioles, and pulmonary arteries, which reflects their perilymphatic distribution .
   2) Large nodules, conglomerate masses, and airspace consolidation are sometimes seen. Pleural effusion is rare.
   3) Typical honeycombing is rare even if the lesions have progressed to fibrosis. In the fibrotic phase or end-stage shrunken air space consolidation with traction bronchiectasis is commonly seen.
3. Bronchoscopic findings
   1) Network formed of mucosal venous dilatation (network formation)
   2) Small bronchial nodules
   3) Bronchial stenosis

Exclusions

The following disorders should be excluded: chronic beryllium disease, pneumoconiocis, tuberculosis and infectious granulomatosis, malignant lymphoma and other lymphoproliferative disorders, hypersensitivity pneumonitis, Wegener's granulomatosis, pulmonary metastasis, and amyloidosis.

Notes

1. The following bronchoalveolar lavage findings are useful for the diagnosis.
   1) Increase in cell recovery
   2) Increase in percent lymphocytes
   3) Increase in CD4/CD8 ratio

   Percent lymphocytes >16% and CD4/CD8 >3.5 are useful in the diagnosis of sarcoidosis. But smoking habit should be taken into account because it influences strongly the bronchoalveolar lavage fluid findings. Percent lymphocytes 1-20% and CD4/CD8 ratio 1.0-3.8 in nonsmokers, and percent lymphocytes 0-9% and CD4/CD8 ratio 0-2.6 in smokers in Japanese healthy subjects are also useful findings.

2. The following findings in gallium-67 citrate scintigraphy are useful for the diagnosis:
   1) Hilar lymph node accumulation is marked.
   2) Lung accumulation is marked.

3. At the histologic diagnosis of the respiratory lesions, the following procedures and histologic features are useful.

   Biopsy sites:
   1) Transbronchial lung biopsy / bronchial biopsy
   2) Thoracoscopic lung biopsy, pleural biopsy, open lung biopsy
   3) Lymph node biopsy with mediastinoscope

   Histologic features:

   In biopsy tissues obtained by the above procedures, noncaseous epithelioid cell granulomas of sufficient quantity can be detected. Pulmonary epithelioid cell granulomas are commonly formed around bronchovascular sheaths, but they are also formed in the bronchial mucosa, intralobular septa, and alveolar wall. They are often accompanied by alveolitis characterized by invasion predominantly by lymphocytes of the alveolar wall.

2. Diagnostic guidelines for ocular lesions

1. Ocular findings

   Two or more out of 6 intraocular signs are strongly suggestive of the ocular lesions of sarcoidosis.
   1) Granulomatous anterior uveitis
      (Mutton fat keratic precipitates and / or iris nodules)
   2) Trabecular meshwork nodules and / or tent-like shaped peripheral anterior synechiae
   3) A mass of vitreous opacities
      (Snow-balls / string of pearls vitreous opacities)
   4) Retinal perivasculitis (mainly periphlebitis) with perivascular nodules
   5) Multiple candle wax type retinochoroidal exudates and /or laser photocoagulation spot-like retinochoroidal atrophy
   6) Optic disc nodule(s) / granuloma(s) and/or solitary choroidal nodule

2. Other ocular manifestations

   Keratoconjunctivitis sicca
   Episcleritis/scleritis
   Lacrimal gland(s) enlargement
   Eye lid(s) swelling
   Signs and symptoms associated with facial nerve palsy

3. Exclusions

   The following disorders should be excluded: tuberculous uveitis, herpetic uveitis, human T cell lymphotrophic virus type 1 (HTLV-1) associated uveitis, Posner-Schlossman syndrome (glaucomatocyclitic crisis), Behçet disease, and intraocular malignant lymphoma.

3. Diagnostic guidelines for cardiac lesions

Characteristic laboratory features are divided into 'Major Criteria' and 'Minor Criteria' and when fulfilling either 1 or 2 below described, they are strongly

suggestive of cardiac lesions of sarcoidosis.

1. Two or more out of 4 items of Major Criteria are satisfied.
2. One out of 4 items of Major Criteria together with 2 or more out of 5 items of Minor Criteria are satisfied.

Major Criteria

1) Advanced atrioventricular block
2) Basal thinning of the interventricular septum
3) Abnormal myocardial uptake on gallium-67 citrate scintigram
4) Left ventricular systolic dysfunction (ejection fraction < 50%)

Minor Criteria

1) Electrocardiography (ECG): Ventricular arrhythmias (ventricular tachycardia, multifocal or frequent ventricular premature beats), right bundle branch block, axis deviation or abnormal Q-wave
2) Echocardiography: Regional wall motion abnormalities or structural abnormalities such as aneurysm formation or thickening of the ventricular wall
3) Radionuclide studies: Perfusion abnormalities detected by thallium-201 chloride, technetium -99m methoxyisobutylisonitrile or technetium-99m tetrofosmin myocardial scintigraphy
4) Gadolinium-enhanced cardiac magnetic resonance imaging (MRI): Delayed enhancement of myocardium
5) Endomyocardial biopsy: Significant interstitial fibrosis or mononuclear cell infiltration

Exclusions

Giant cell myocarditis should be excluded.

Notes:

1) Coronary angiography should be performed in cases which we need to exclude the presence of coronary artery disease.
2) Since cardiac lesion is confirmed several years after the diagnosis of extra-cardiac sarcoidosis in some cases, repeat evaluation including ECG and echocardiography should be required at follow-up visit.
3) Abnormal accumulation of fluorine-18 fluorodeoxyglucose in the heart is a useful diagnostic finding.
4) Some cases of cardiac sarcoidosis are manifested only by advanced atrioventricular block without any other items of Minor Criteria.
5) Acute pericarditis as the first manifestation is rarely experienced.
6) Endomyocardial biopsy specimens do not often demonstrate noncaseous epithelioid cell granulomas.

4. Diagnostic guidelines for cutaneous lesions

Because of the various manifestations of the cutaneous lesions of sarcoidosis, the diagnosis of cutaneous lesions in sarcoidosis requires histologic findings confirming the presence of noncaseous epithelioid cell granulomas, and clinical and laboratory findings of systemic granulomatous changes based on the diagnostic criteria of sarcoidosis. Also, other granulomatous skin disorders and sarcoid reactions should be excluded.

1. Clinical findings

The skin lesions are divided into three categories: 1) non-specific lesions such as erythema nodosum, 2) specific lesions such as nodular, plaque, lupus pernio, subcutaneous, and other rare types of cutaneous sarcoids, 3) scar infiltration containing granulomas and foreign body confirmed by histologic examination. The presence of the skin lesions is determined based on the following clinical findings supported by histologic confirmation.

1) Cutaneous sarcoids

(1) Nodular type: Elevated lesions characterized by red or violaceous papules and nodules with infiltration.
(2) Plaque type: Non-elevated annular lesions or ill-defined erythematous patches. Annular eruptions are lesions that spread outward. The center of the

lesion is slightly atrophic, while the red rim shows slight bank-like elevation. Ill-defined patches are circular or irregularly shaped erythematous lesions.

(3) Lupus pernio: Bluish-red papulonodules resembling pernio, mainly seen in the fingers, toes, cheeks and earlobes.

(4) Subcutaneous type: Elastic hard, often disseminated subcutaneous nodules in various sizes. The surface skin is usually normal.

(5) Others:

i) Lichenoid eruptions: Clusters of flat miliary papules, which sometimes systemically disseminate.

ii) Erythema nodosum-like eruptions: Lesions clinically similar to erythema nodosum, but with the presence of epithelioid cell granulomas confirmed by histological examination.

iii) Ichthyosiform type: Fish scale-like skin eruptions found most commonly on the legs.

iv) Other rare types: Psoriatic lesions, wart-like lesions, and vitiligo.

2) Scar infiltration: Lesions occurring at the sites exposed to external stimuli such as trauma. The clinical features show various types of manifestations depending on scarring. These lesions are most commonly noted on the knees, elbows, and face.

3) Erythema nodosum: Subcutaneous nodules with erythema and tenderness, mainly occurring in both extensor aspects of the legs.

2. Histologic findings

Epithelioid cell granulomas without caseous necrosis can be found in cutaneous lesions of sarcoidosis. Foreign body is also present in scar infiltrations. Similar to erythema nodosum induced by other causes, erythema nodosum in sarcoidosis is septal panniculitis without granulomatous changes.

3. Exclusions

1) Other skin granulomas should be excluded, including granuloma annulare, annular elastolytic giant cell granuloma, necrobiosis lipoidica, Melkerson-Rosenthal syndrome, lupus miliaris disseminates faciei, rosacea, and cutaneous tuberculosis.

2) Sarcoid reaction to foreign body and cancer should be excluded.

5. Diagnostic guidelines for nervous system and muscle lesions

Neurosarcoidosis or muscular sarcoidosis is diagnosed by the following criteria for the diagnosis of 'definite', 'probable' and 'possible' disease.

A. Definite

1. Clinical presentation suggestive of nervous system or muscular sarcoidosis (Note 1)
2. The presence of noncaseous epithelioid cell granuloma on nervous system or muscle histology (Note 2)
3. Presenting with evidence from two or more out of the six clinical and laboratory findings listed in Table 1
4. Exclusion of other possible diagnoses where the findings (items A1 to A3) are met (Note 3)

Take notice of the presence of isolated neurosarcoidosis without other organ or tissue involvement and systemic reactions in sarcoidosis.

B. Probable

1. Clinical presentation suggestive of nervous system or muscular sarcoidosis (Note 1)
2. The presence of histologic evidence of noncaseous epithelioid cell granulomas in other organ(s), and evidence from two or more out of the six clinical and laboratory findings listed in Table 1
3. Exclusion of other possible diagnoses where the findings (items B1 and B2) are met (Note 3)

C. Possible

1. Clinical presentation suggestive of nervous system or muscular sarcoidosis (Note 1) without histologic evidence of noncaseous epithelioid cell granulomas in other organ(s)
2. Presenting with evidence from two or more out of the six clinical and laboratory findings listed in

Table 1

3. Exclusion of other possible diagnoses where the findings (items C1 and C2) are met (Note 3)

Note 1. Clinical presentation suggestive of nervous system or muscular sarcoidosis

1 Asymptomatic

Nervous system or muscle lesions may be observed even on laboratory examinations including radiological imaging, despite the absence of any clinical signs and symptoms.

2 Symptomatic

2-1 Central nervous system lesions

a. Intraparenchymal granulomatous lesions

a-1 Solitary mass lesion (some sarcoid nodules fuse with each other and then form intraparenchymal granulomatous lesions)

Hypothalamic and pituitary lesions can be involved in diabetes insipidus and hypopituitarism.

Optic chiasm lesions often cause bitemporal homonymous hemianopsia.

Patients may have headache, memory loss, aphasia, hemiplegia, sensory disturbance, visual field defect, and others.

a-2 Diffuse granulomatous infiltrated lesions (sarcoid granulomatous lesions disperse into cerebral intraparenchymal areas)

Patients often show seizures, mental disturbance, memory loss, aphasia, apraxia, agnosia, and extrapyramidal signs and symptoms.

a-3 Spinal cord lesions

Patients often show paraplegia, bladder and bowel disturbance, sensory disturbance, Brown-Séquard syndrome, and conus syndrome.

b. Meningeal lesions

b-1 Sarcoid meningitis and meningoencephalitis

Most patients are asymptomatic.

Patients sometimes show an acute or chronic course.

Headache, choked disk, seizure, and fever are rare.

b-2 Sarcoid hypertrophic pachymeningitis

c. Hydrocephalus (caused by obstruction within the ventricular system or impaired absorption of cerebrospinal fluid due to chronic meningitis)

Patients often show headache, memory loss, and gait disturbance.

d. Vascular lesions

d-1 Angiitis (with mental disturbance, pyramidal signs, memory loss, dementia, etc)

d-2 Periventricular white matter lesions (with mental disturbance, dementia, etc)

d-3 Sinus thrombosis (inducing pseudotumor cerebri, etc.)

e. Encephalopathy

2-2 Peripheral nerve lesions

a. Cranial nerve lesions

a-1 Facial nerve palsy (quite possible if palsies are bilateral)

a-2 Glossopharyngeal and vagal nerve palsies (with hoarseness, dysphagia, etc.)

a-3 Acoustic nerve palsy (with hearing impairment, tinnitus, vertigo, etc.)

a-4 Optic nerve palsy (with visual impairment, etc.)

a-5 Trigeminal nerve palsy (with sensory disturbance in the face, trigeminal neuralgia, etc.)

a-6 Olfactory nerve palsy (with disturbances of the sense of smell, etc.)

a-7 Other cranial nerve palsies (with ophthalmoplegia, diplopia, etc.)

b. Peripheral nerve lesions

b-1 Mononeuropathy multiplex

b-2 Polyneuropathy (including small-fiber neuropathy)

b-3 Mononeuropathy (with respiratory disturbance due to phrenic nerve palsy, etc.)

b-4 Other involvements: radiculopathy, cauda equina syndrome (bladder and bowel disturbance, muscle weakness of the legs, low back pain, etc.)

2-3 Muscle lesions

a. Acute and subacute myositis (with proximally

dominant muscular weakness, myalgia, grasping pain, fever, and sometimes painful muscle cramps, etc.)

b. Chronic myopathy (with slowly progressive, proximally dominant or diffuse muscular weakness and wasting, sometimes pseudohypertrophy in mainly menopausal woman, and severe distal muscle involvement if accompanied by peripheral nerve involvement)

c. Nodular myopathy (Intramuscular nodules are palpable. Myalgia, muscle weakness, and wasting are rare)

Note 2. Histologic diagnosis

Positive nervous system or muscle histology is defined by the presence of non-caseous epithelioid cell granulomas in nervous system or muscle specimens obtained on biopsy, surgery, or autopsy. Nervous system or muscle biopsy under the guidance of magnetic resonance imaging or gallium-67 citrate scan is more useful for the diagnostic work-up.

Note 3. Exclusions

The following disorders should be excluded:

Central nervous system lesions

a. Cerebral vascular diseases: multiple cerebral infarct, Binswanger disease, etc.

b. Tumors: gliomas, lymphomas, leptomeningeal metastasis, metastatic brain tumor, lymphomatoid granulomatosis, multicentric Castleman's disease, etc.

c. Infectious diseases: tuberculosis, fungous infection, bacterial infection, AIDS, etc.

d. Demyelinating diseases: multiple sclerosis, etc.

e. Vasculopathies: granulomatous angiitis, Wegener's granulomatosis, neuro-Behçet's syndrome, neuro-Sweet's disease, connective tissue diseases such as Sjögren's syndrome, etc.

f. Drugs: drug-induced encephalopathy, etc.

g. Others

Peripheral nerve lesions

a. Peripheral neuropathy

a-1 Inflammatory neuropathy: i) Guillain-Barré syndrome, ii) chronic inflammatory demyelinating polyneuropathy (CIDP), iii) others

a-2 Metabolic neuropathy: i) diabetic, ii) alcoholic, iii) renal, iv) others

a-3 Hereditary neuropathy

a-4 Neuropathies associated with systemic disease; i) vasculitis (periarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome, etc.), ii) connective tissue diseases (Sjögren's syndrome, rheumatic arthritis, etc.), iii) infectious diseases (leprosy, tuberculosis, fungous disease, AIDS, etc.), iv) compression (carpal tunnel syndrome, etc.), v) drug, intoxication, vi) immunological and hematological diseases (cancer-associated syndrome, etc.), vi) other systemic diseases

b. Cervical and lumbar spondylosis, other spinal diseases

c. Motor neuron disease

d. Tumor of peripheral nerves

Muscle lesions

a. Myopathy

a-1 Muscular dystrophies

a-2 Inflammatory myopathy: i) polymyositis, ii) dermatomyositis, iii) others

a-3 Metabolic myopathy: i) thyroid myopathy, ii) steroid myopathy, iii) others

a-4 Granulomatous myopathy: i) vasculitis (Wegener's granulomatosis, Churg-Strauss syndrome, etc.), ii) connective tissue disease (rheumatoid arthritis, progressive systemic sclerosis, etc.), iii) inflammatory bowel disease (Crohn's disease, primary biliary cirrhosis, etc.), iv) infectious myopathy (tuberculosis, syphilis, leprosy, fungous infection, AIDS, etc.), v) autoimmune overlap syndrome (myasthenia gravis, myocarditis, thyroiditis, and thymoma), vi) inorganic material (beryllium, titanium, aluminum, zirconium, etc.)

a-5 Other myopathies

b. Motor neuron disease: i) amyotrophic lateral sclerosis, ii) spinal muscular atrophy, iii) others
c. Peripheral nerve lesions

6. Diagnostic guidelines for other lesions

Other lesions of sarcoidosis include those other than eye, heart, skin, nerve and muscle lesions. They include lesions of liver, spleen, bone marrow, kidney, esophagus, stomach, colon, pancreas, gallbladder, bile duct, peritoneum, abdominal and superficial lymph nodes, thyroid gland, parotid gland, nasal cavity, tonsils, pharynx, larynx, bone, joint and reproductive organs.

1) Hepatic lesion: hepatic dysfunction, occasionally portal hypertension, chronic cholestasis syndrome, hepatomegaly, yellowish and whitish nodules on liver surface detected by peritoneoscopy, multiple hypoechoic areas in the liver by abdominal echography, multiple space occupying lesions in the liver on abdominal CT, abnormal findings of liver on abdominal magnetic resonance imaging (MRI).
2) Splenic lesion: splenomegaly, abdominal pain, hypersplenism, yellowish and whitish nodules on spleen surface detected by peritoneoscopy, multiple hypoechoic areas in the spleen by abdominal echography, multiple space occupying lesions in the spleen by abdominal CT, abnormal findings of spleen by abdominal MRI, marked splenic uptake on gallium scintigraphy and fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET).
3) Bone marrow lesion: leucopenia, anemia, thrombocytopenia, pancytopenia, abnormal FDG- PET imaging of bone marrow.
4) Renal lesion: hypercalcemia, hypercalciurea, renal and urinary stone, renal dysfunction, renal failure, renal tumor on abdominal echography and CT, marked renal uptake on gallium scintigraphy.
5) Gastrointestinal tract lesion: dysphagia, epigastralgia, abdominal pain, hematemesis, melena; gastric ulcer, nodular change, thickening of mucous membrane, linitis plastic, pyloric deformity and ulcer, obstruction of intestine, mass in intestine, detected by barium study and endoscopy.
6) Pancreatic lesion: abdominal pain, jaundice, elevated serum amylase level, abnormal findings on abdominal echography, CT, MRI and endoscopic retrograde cholangiopancreatography (ERCP), marked pancreas uptake on gallium scintigraphy.
7) Bile duct lesion: abdominal ERCP findings.
8) Peritoneal lesion: ascites; whitish and yellowish nodules on peritoneum detected by peritoneoscopy or at laparotomy
9) Abdominal lymph node lesion: abdominal lymph node enlargement on abdominal echography and CT, marked abdominal lymph node uptake on gallium scintigraphy and FDG-PET, abdominal ERCP findings due to marked abdominal lymph node enlargement.
10) Superficial lymph node lesion: superficial lymph node enlargement, occasional asymptomatic marked lymph node uptake on gallium scintigraphy and FDG-PET.
11) Thyroid gland lesion: thyroid gland enlargement, hyperthyroidism or hypothyroidism.
12) Parotid gland lesion: bilateral or unilateral parotid gland enlargement, marked parotid gland uptake on gallium scintigraphy.
13) Upper respiratory tract lesion: nasal obstruction, abnormalities of nasal mucosal membrane and nasal cavity, swelling of tonsils, pharyngeal tumor, hoarseness, abnormal findings at laryngoscopy,
14) Bone lesion: bones of hands and feet, nasal bones, skull, vertebra, pelvic, ribs, sternum, long bones, painful swelling, deformity of fingers, uniform lace-like appearance, lytic lesions, round punched out cysts, destructive lesions and pathological fracture on bone radiology, marked bone uptake on bone and gallium scintigraphy, low density areas on T1 weighted MRI.
15) Joint lesion: symptoms of acute polyarthritis and chronic arthritis, occasional deformity or destruction of joint on radiology, marked joint uptake on gallium scintigraphy.
16) Reproductive organ lesion: tumor formation in the mammary gland, uterus, testis, epididymis, and spermatic cord.

Exclusions

1) The following disorders should be excluded;

tuberculosis, malignant lymphoma, other lymphoproliferative diseases, primary or metastatic malignant tumor.

2) Sarcoid reaction to foreign body, malignancy and others should be excluded.

Addendum

This version of "Diagnostic guidelines for sarcoidosis in Japan" was revised in 2006, and its suitably was subsequently reviewed. It continues to be used today. These guidelines included general remarks regarding sarcoidosis that were omitted from the English version. Furthermore, the most recent literature from 2006 was added. Titles of Japanese articles included in the references were translated into English. The Committee of Diagnostic Criteria for Sarcoidosis, Japan Society of Sarcoidosis and Other Granulomatous Disorders takes full responsibility for the translations of the titles.

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