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CASE REPORT

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A case of nodular-type muscular sarcoidosis: findings of imaging, histopathology, and polymerase chain reaction

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Abstract We report a case of nodular-type muscular sarcoidosis with no systemic symptoms. Thallium-201 scintigraphy showed intense uptake in the muscular lesion mimicking malignant soft tissue tumor. Magnetic resonance imaging (MRI) demonstrated characteristic signal patterns of peripheral high intensity with central low intensity ("three stripes" pattern). Microscopy revealed sarcoid granuloma with typical histopathological characteristics. *Propionibacterium acnes* was detected on polymerase chain reaction analysis of the excised tissue.

Key words Magnetic resonance imaging (MRI) · Muscular sarcoidosis · Polymerase chain reaction (PCR) · *Propionibacterium acnes* · Thallium-201 scintigraphy

Introduction

Sarcoidosis is a multisystemic disease of unknown etiology with various clinical manifestations, including formation of noncaseating epithelioid granulomas. However, sarcoidosis presents with muscular lesions relatively rarely.[1–15] In particular, the occurrence of a muscular lesion as a primary symptom without bilateral hilar lymphadenopathy (BHL) or elevated serum angiotensin-converting enzyme (ACE) is very rare.[5,10,15,16] We report a case of nodular-type muscular sarcoidosis in the medial side of the leg as the presenting and only symptom.

The etiology of sarcoidosis remains unknown. In the present case, the bacterial genome of *Propionibacterium acnes* was detected on polymerase chain reaction (PCR) but that of *Mycobacterium tuberculosis* and *Propionibacterium granulosum* were not.[17,18]

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Case report

A 54-year-old woman consulted our department with a 3-month history of a mass on the medial side of the right leg. She reported a 2-year history of Meniere's disease and a 1-year history of hypertension. No superficial lymph nodes were palpable. Range of motion in the right knee and ankle joint was full, muscle strength was not decreased, and there were no neurological abnormalities. The diameter of the affected lower leg was increased by 3 cm. An ill-defined elastic-hard mass measuring 6 × 8 cm was noted in the gastrocnemius muscle on the medial side of right leg, which was swollen but not tender. The lesion was nonpulsatile. Laboratory investigations demonstrated slightly elevated C-reactive protein (CRP) (0.68 mg/dl [normal range: 0–0.25 mg/dl]), raised erythrocyte sedimentation rate (ESR) (22 mm/1 h, 62 mm/2 h), and slightly elevated serum lysozyme (10.7 μg/ml [normal range: 3.0–10.6 μg/ml]) and γ-globulin levels (20.5% [normal range: 8.6%–20.0%]). Serum ACE and calcium were within normal limits. Tuberculin reaction was negative. Electrocardiography (ECG) and respiratory function tests did not demonstrate any abnormalities.

Radiographs revealed a soft tissue mass on the medial side of the right leg and computed tomography (CT) demonstrated an ill-defined mass lesion in the gastrocnemius muscle with a density equivalent to that of muscle (Fig. 1). On magnetic resonance imaging (MRI), axial views showed the mass to be slightly heterogeneous and faint, exhibiting

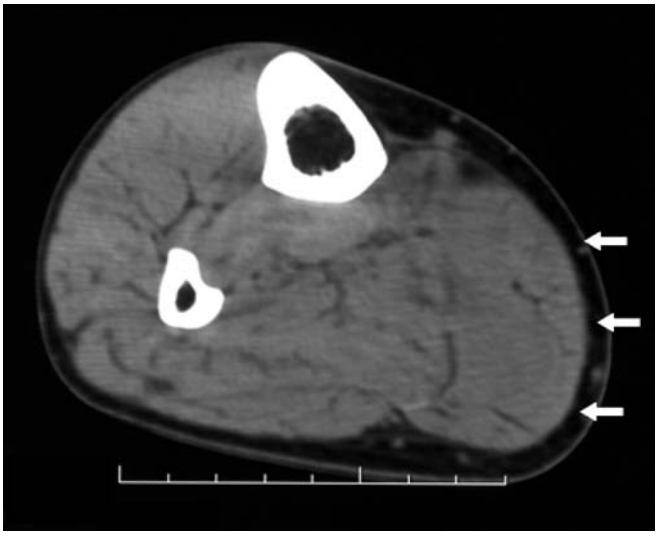

Fig. 1. Computed tomography demonstrated an ill-defined mass (*arrows*) in the gastrocnemius muscle with density equivalent to that of the muscle

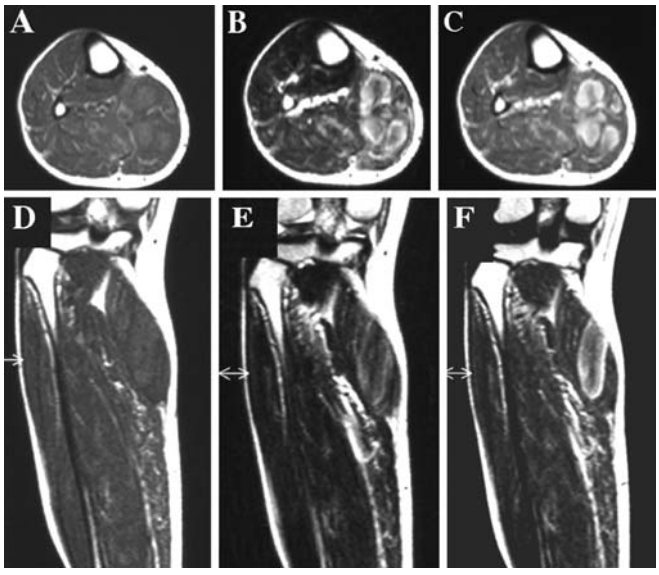

Fig. 2. **A** T1-weighted (TR, 350 ms; TE, 14 ms) axial magnetic resonance (MR) image. The mass exhibited heterogeneous and slightly elevated signal intensity. **B** T2-weighted (TR, 3000 ms; TE, 105 ms) axial image. The periphery of the lesion exhibited very high signal intensity, while the center demonstrated heterogeneous low- to isointensity. **C** Gadolinium–diethylenetriamine penta-acetic acid (DTPA)-enhanced T1-weighted image. The periphery of the mass was markedly enhanced. **D** T1-weighted (TR, 350 ms; TE, 14 ms) coronal image. The coronal MR image demonstrated findings similar to those of axial images, but allowed better visualization of tumor localization along the gastrocnemius muscle fibers. **E** T2-weighted (TR, 3000 ms; TE, 105 ms) coronal image. **F** Gadolinium–DTPA-enhanced T1-weighted coronal image

high signal intensity on T1-weighted images (T1WI). On T2-weighted images (T2WI), the periphery showed very high signal intensity, while the center exhibited heterogeneous low-to-iso signal intensity. The periphery of the lesion was markedly enhanced with gadolinium (Gd) (Fig. 2A–C). The coronal view demonstrated similar findings, but allowed better visualization of tumor localization along the fibers of the gastrocnemius muscle (Fig. 2D–F). Thallium-201 (Tl-201) scintigraphy demonstrated increased accumulation in the region corresponding to the tumor. The lesion was relatively well defined, but minimal washout was observed and the intense uptake persisted on delayed images taken after 2 h (Fig. 3A,B). Whole-body ^{99m}Tc hydroxymethylene diphosphonate bone scintigraphy demonstrated increased accumulation in the left shoulder, right wrist, right ankle, and right foot, suggesting osteoarthritic changes. However, no extraosseous accumulation was evident in the area corresponding to the tumor. Radiographs and CT of the chest demonstrated no abnormalities in the hilar regions and lung fields.

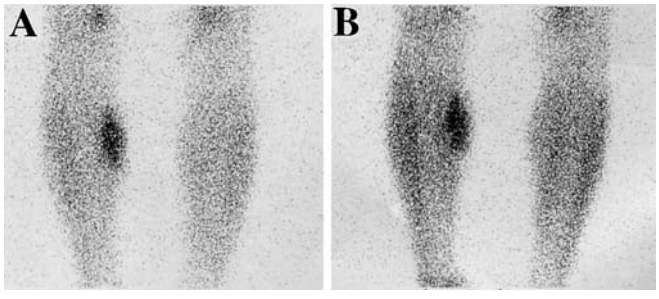

Fig. 3. **A** Thallium-201 (Tl-201) scintigraphy, early phase (10 min); **B** Tl-201 scintigraphy, delayed phase (2 h). Thallium-201 scintigraphy revealed increased accumulation in the area corresponding to the tumor. The lesion was relatively well defined, but minimal washout was observed and intense uptake persisted on the delayed image

At open biopsy, an elastic-hard, ill-defined mass without a capsule was revealed in the muscular coat of the gastrocnemius muscle. The color of the biopsied tumor was white to grayish white. Histopathological examination demonstrated multiple epithelioid cell granulomas of various sizes. Granulomas were composed primarily of epithelioid cells with round nuclei and exhibited areas of fibrinoid necrosis (Fig. 4A,B). No bacteria were detected after several months of tissue culture.

After open biopsy, the patient was referred for cardiac and ophthalmological investigations. No abnormalities were observed initially; however, follow-up at one and a half months revealed mild retinal periphlebitis, which was asymptomatic.

The patient was eventually diagnosed as having nodular-type muscular sarcoidosis on the basis of the histopathological findings and the retinal periphlebitis. Tuberculosis was excluded based on the fact that tubercle bacillus was not cultured and tuberculin testing was negative. The retinal periphlebitis resolved completely in around 2 months. The patient was subsequently followed without active treatment and the mass in the medial side of the right leg disappeared spontaneously. No local recurrences or new masses at other sites have occurred during 5 years of follow-up.

Although the etiology of sarcoidosis is unknown, many researchers have considered infection to be a causative factor.[17,18] *Mycobacterium tuberculosis*, *Propionibacterium*

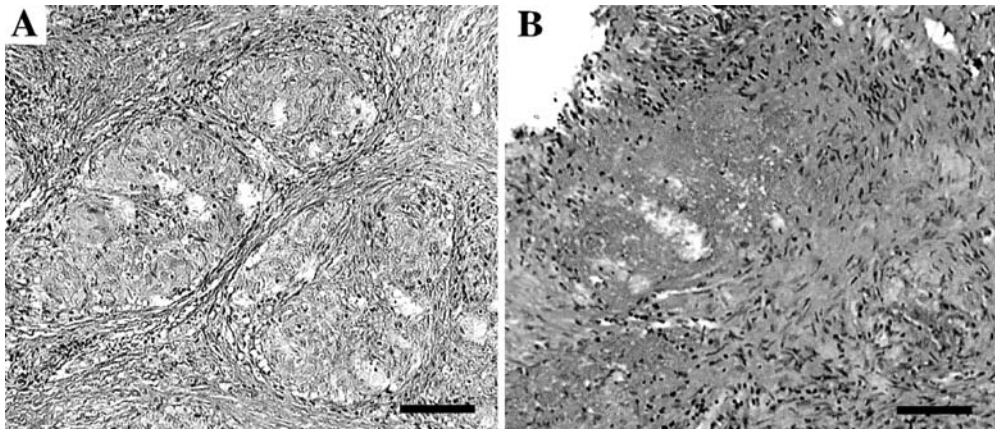

Fig. 4. **A** Histopathological findings of the biopsied specimen. Low-power view. *Bar* 100 μm with H&E staining. **B** High-power view. *Bar* 50 μm with H&E staining. Histopathological examination demonstrated multiple epithelioid cell granulomas of various sizes. Granulomas were composed primarily of epithelioid cells with round nuclei. An area of fibrinoid necrosis was observed

granulosum, and *Propionibacterium acnes* have been implicated, but have not been unequivocally demonstrated to have a causative role.[17,18] In the present case, we used the polymerase chain reaction (PCR) to search for the bacterial genomes of *M. tuberculosis*, *P. granulosum*, and *P. acnes* in the biopsied tissue, using a case of synovial sarcoma as a control. A 10-μm section cut from a formalin-fixed and paraffin-embedded block was deparaffinized with xylene and ethanol, and digested with 0.1 mg/ml proteinase K, 1.0% sodium dodecyl sulfate in SEDTA (50 mm ethylenediaminetetra-acetic acid, 150 mM NaCl) for 2 days at 55°C. DNA was extracted from the tissue pellets with phenol–chloroform and ethanol, and DNA concentration was measured by spectrophotometry. About 200 ng of DNA from each extract was used for PCR. Primers were designed as described previously[17,18]: MT-F (5′-TCCTATGACAATGCACTAGCCG-3′) and MT-R (5′-GCCAACTCGACATCCTCGAT-3′) were designed to amplify a 101-bp portion of insertion sequence 6110 of *M. tuberculosis*; PG-F (5′-ACATGGATCCGGGAGCTTC-3′) and PG-R (5′-ACCCAACATCTCACGACACG-3′) were designed to amplify a 102-bp portion of *P. granulosum* 16S rRNA; PA-F (5′-GCGTGAGTGACGGTAATGG GTA-3′) and PA-R (5′-TTCCGACGCGATCAACCA-3′) were designed to amplify a 131-bp portion of *P. acnes* 16S rRNA. Primers β-actin-F (5′-TGTTTGAGACCTTCAAC ACCCC-3′) and β-actin-R (5′-TCCATCACGATGCCA GTGGTAC-3′) were designed to amplify a 94-bp portion of the β-actin gene as a control. The PCR was performed in 10 μl of solution containing 1.0 μl of DNA samples, 0.5 μM each of forward and reverse primers, 2.5 U of Taq DNA polymerase (Ex Taq, Takara Shuzo, Tokyo, Japan), 0.2 mM dNTPs, and 10× Ex buffer (containing 20 mM Mg^{2+}). Polymerase chain reaction cycles for *P. acnes*, *P. granulosum*, and *M. tuberculosis* were 95°C for 5 min and 50 cycles of 95°C for 15 s and 60°C for 1 min, and PCR cycles for β-actin were 94°C for 5 min, and 35 cycles of 94°C for 15 s, 55°C for 15 s, 72°C for 30 s, and 72°C for 5 min. Polymerase chain reaction products were electrophoresed on 3.0% agarose gel and bands were visualized by ethidium bromide staining. The results are shown in Fig. 5. In the present case, the genome of *P. acnes* was detected, but those of *M. tuberculosis* and *P. granulosum* were not. No genetic material from these three bacteria was detected in the synovial sarcoma negative control.

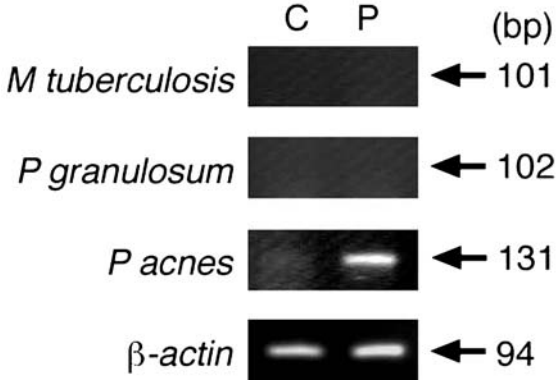

Fig. 5. Polymerase chain reaction band patterns for *Mycobacterium tuberculosis*, *Propionibacterium granulosum*, and *Propionibacterium acnes*. In the present case, the genome of *P. acnes* was detected, while those of *M. tuberculosis* and *P. granulosum* were not. *C*, control (a case of synovial sarcoma); *P*, present case

Discussion

Sarcoidosis is characterized by multisystemic chronic inflammation of unknown etiology associated with formation of epithelioid cell granulomas. Hilar lymphadenopathy is frequently observed (90%), as are pulmonary, ophthalmologic, and cutaneous changes; in 41%, 30% and 10% of cases, respectively. Musculoskeletal lesions due to sarcoidosis were first reported in 1908, when Licharew et al. documented a case of multiple palpable intramuscular masses that had an indolent course.[4,19,20] Subsequently, Silverstein and Siltzbach[10] classified sarcoidosis into asymptomatic and symptomatic types, with the latter being subdivided into three categories according to clinical features: (1) palpable muscle nodule (tumor) type, (2) acute myositis type, and (3) chronic myopathy type. The incidence of the palpable muscle nodule type is reported to be as low as 1 in 800 cases.[10] Moreover, nodular-type muscular sarcoidosis with a

chief presenting complaint of a muscular lesion is even more rare.[9,10,12,16] Reports describing nodular-type muscular sarcoidosis have been summarized by Gaulke and Suppelna[5] and Zisman et al.[15] Gaulke and Suppelna[5] reported the existence of a solitary muscle mass in 9 of 61 patients, with 3 of these exhibiting no other systemic lesions. Zisman et al.[15] examined 59 patients and reported that lesions were confined to the muscles in only 1 of 30 cases in which the relevant information was provided. Based on the above, it appears that less than 60 reports of nodular-type muscular sarcoidosis have been published. The condition can thus be considered exceedingly rare. To the best of our knowledge, the present case is 4th reported of nodular-type muscular sarcoidosis in which the sole chief complaint was intramuscular mass.[5,15]

In the present case, findings of initial imaging studies led to a differential diagnosis that included sarcoma and malignant lymphoma. Sarcoidosis was subsequently diagnosed on the basis of open biopsy findings. Characteristically, the central regions of muscular sarcoid lesions exhibit low signal intensity on T2WI MR images and are rich in fibrous tissue with sparse cellular components, while the margins exhibit high signal intensity on T2WI MR images and contain dense granulomatous tissue and sparse fibrous components.[7,8] Retrospectively, in the present case a "three stripes" pattern could be determined on coronal MRI, and a "dark star" pattern could be observed on axial views; patterns that are relatively characteristic in sarcoidosis.[7,8,11,21] Furthermore, Tl-201 scintigraphy on admission demonstrated intense uptake and little washout as well as an appearance similar to sarcoma or malignant lymphoma.[3,20]

On the basis of a presumptive preoperative diagnosis of malignancy, we performed Tl-201 scintigraphy, which has specific accumulation (Fig. 3), in place of gallium-67 (Ga-67) scintigraphy, considering it to be adequate in detecting local secondaries in the extremities. In retrospect, Ga-67 scintigraphy should have been performed early in the course of the disease. The value of Tl-201 scintigraphy in nodular-type muscular sarcoidosis has not previously been discussed in the literature. Although some authors recommend diagnostic needle biopsy,[5] it is difficult to differentiate the condition from sarcoma and, in particular, malignant lymphoma from needle biopsy specimens.[7,19,22] We would therefore advocate open biopsy, from which it is easier to form a definitive diagnosis.

Many infectious agents have been suggested to play an etiological role in sarcoidosis, particularly *M. tuberculosis* in Europe and *P. acnes* in Japan. Eishi et al.[17] and Ishige et al.[18] used quantitative PCR and detected a considerable amount of genetic material from *P. acnes* and *P. granulosum* in the lymph nodes of patients with sarcoidosis. In the present case, we used PCR to search for bacterial genomes of *M. tuberculosis*, *P. granulosum*, and *P. acnes*, and detected genetic material from *P. acnes*. Although we did not quantify the bacterial genetic material, this finding suggests that *P. acnes* infection might have been the triggering factor for this patient.

Nodular-type muscular sarcoidosis tends to have a favorable course, resolving spontaneously in many cases.[12–14] The present patient was followed without any surgical or medical treatment and has not developed recurrence for 5 years.

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