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Asymptomatic tiny subcutaneous eruptions in a patient with sarcoid neuropathy: the effectiveness of fluorine-18 fluorodeoxyglucose positron emission tomography for targeting safe biopsy sites

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Sarcoidosis affects the lungs, heart, eyes, skin, lymph nodes, and central and peripheral nervous system (1). The diagnosis usually requires the histopathological finding of noncaseating granulomas and is relatively straightforward when the symptomatic lesion can be biopsied. However, in neurological sarcoidosis, the diagnosis can be challenging because biopsy of the central and peripheral nervous system often entails invasive procedures and possible neural damage. Therefore, clinicians have to initially search for safer biopsy targets, such as cutaneous sarcoidal lesions (2).

Cutaneous manifestations are estimated to occur in approximately 25-35% of patients with sarcoidosis and classified as specific or nonspecific lesions (1,3-5). Specific lesions contain noncaseating granulomas and may manifest as macules, papules, plaques, nodules, infiltrated scars, and subcutaneous eruptions. Nonspecific lesions are reactive processes and include erythema nodosum, calcifications, erythema multiforme, prurigo, Sweet syndrome, and nail clubbing (4,5). The subcutaneous eruptions consist of flesh-colored, deep-seated, and firm nodules. They are usually between 0.5 and 2 cm in diameter and may be single or multiple (4,5). The lesions are most common in the upper extremities without strong tenderness and may be associated with systemic involvement (5). This type of cutaneous sarcoidosis may tend to be overlooked (4), perhaps because it is visually inconspicuous without strong tenderness.

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) is often employed for detecting sarcoid lesions (6-9). In patients with sarcoidosis, the pathological tracer accumulation indicates increased glucose metabolism in the activated macrophages and $CD4^+$ T lymphocytes, which are components of noncaseating granulomas (8). FDG PET is also used for the evaluation of treatment response and identification of occult biopsy sites (6-9). However, reports about cutaneous sarcoidosis have been scarce, although the lesions are usually considered appropriate sites for biopsy (2). Here, we present the case of a patient with sarcoid neuropathy and asymptomatic tiny subcutaneous eruptions, in whom FGD PET played an important role in identifying an appropriate biopsy site.

A 58-year-old woman presented with a 2-month history of a tingling sensation throughout her body. The patient also complained of month-long facial weakness and was hospitalized for suspected neuropathy. Her medical history included hypothyroidism, which changed from hyperthyroidism after radiation therapy and was treated with levothyroxine sodium 50 μg/day. Other oral medications were methylcobalamin 1500 μg/day and loxoprofen sodium hydrate 180 mg/day. Physical examination revealed bilateral

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peripheral facial palsy, right-dominant distal muscle weakness in the upper extremities, decreased or absent tendon reflexes in the four limbs, and paresthesia over the whole body, without obvious skin change and lymph node swelling.

The physical findings suggested the presence of multiple mononeuropathy and further investigations were performed. Nerve conduction study showed decreased compound muscle action potentials in the bilateral median and right ulnar nerves. Blood tests revealed mildly elevated levels of C-reactive protein (0.26 mg/dL; normal range, <0.15 mg/dL) and soluble interleukin-2 receptor (792 U/ml, 145-519 U/mL). Although serum vitamin B12 was increased (1170 pg/mL, 180-914 pg/mL) probably because of her medication, serum vitamin B1, folic acid, anti-human immunodeficiency virus antibody, angiotensin-converting enzyme, lysozyme, proteinase 3 antineutrophil cytoplasmic antibody, myeloperoxidase antineutrophil cytoplasmic antibody, and anti-Sjögren's syndrome A and B antibodies were normal. With regard to thyroid function, thyroid-stimulating hormone was decreased (0.02 mIU/L, 0.35-4.94 mIU/L) in contrast to increased free thyroxine hormone (1.58 ng/dL, 0.7-1.48 ng/dL). In cerebrospinal fluid analysis, the number of cells was increased (20/μL, 97% monocytes and 3% polycytes) with increased total protein (147 mg/dL; normal range, 15-50 mg/dL) and normal glucose. Polymerase chain reaction for tuberculosis was negative. The patient's chest radiograph, electrocardiogram, and magnetic resonance imaging of the brain and spinal cord with gadolinium revealed no abnormality. On fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), however, pathological accumulations were detected in the lymph nodes of the mediastinum, pulmonary hilum, and hepatic hilum (Figure 1). Moreover, FDG uptake was also abnormal in the lateral side of the right upper arm (Figure 2, arrows).

On the basis of the FGD PET/CT finding in the right upper arm, a thorough physical examination was performed. There was no tenderness, bulging, or discoloration in the corresponding site (Figure 3A), but a few tiny lumps were found on palpation. Their diameters were about 2 mm. Cutaneous biopsy around these lumps was performed, and microscopic examination revealed numerous nodules consisting of noncaseating epithelioid cell granulomas and multinucleated giant cells in the subcutaneous tissue (Figure 3B).

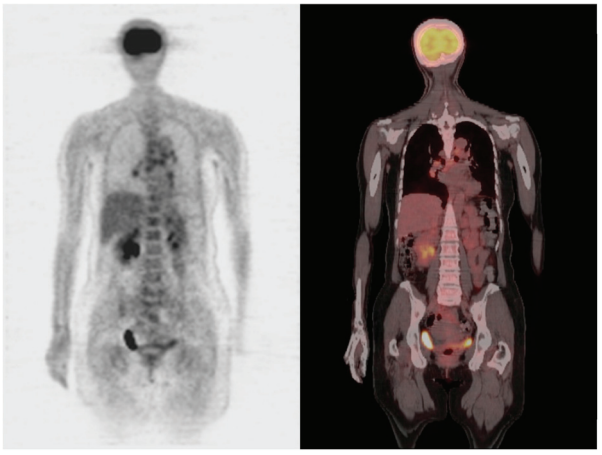

Fig. 1. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography revealed abnormal tracer accumulations in the mediastinum and pulmonary hilum lymph nodes (left panel). The lesion locations were more clearly displayed in the fused image (right panel).

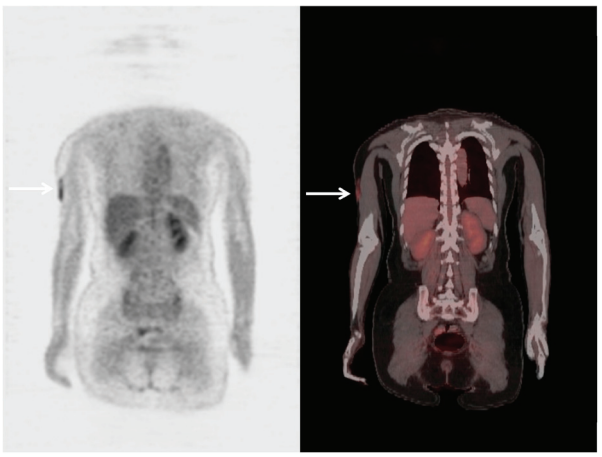

Fig. 2. On fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography, fluorodeoxyglucose uptake was increased in the lateral side of the right upper arm (arrow, left panel). The lesion was located mainly in the subcutaneous tissue (arrow, right panel)

According to the physical and electrophysiological findings, cerebrospinal fluid abnormalities, and subcutaneous eruptions that histologically consisted of noncaseating granulomas, she was diagnosed as having multiple mononeuropathy due to sarcoidosis (10). Treatment was initiated with intravenous steroid therapy (methylprednisolone 1000 mg/day for 5 days), followed by oral prednisolone 40 mg/day. The

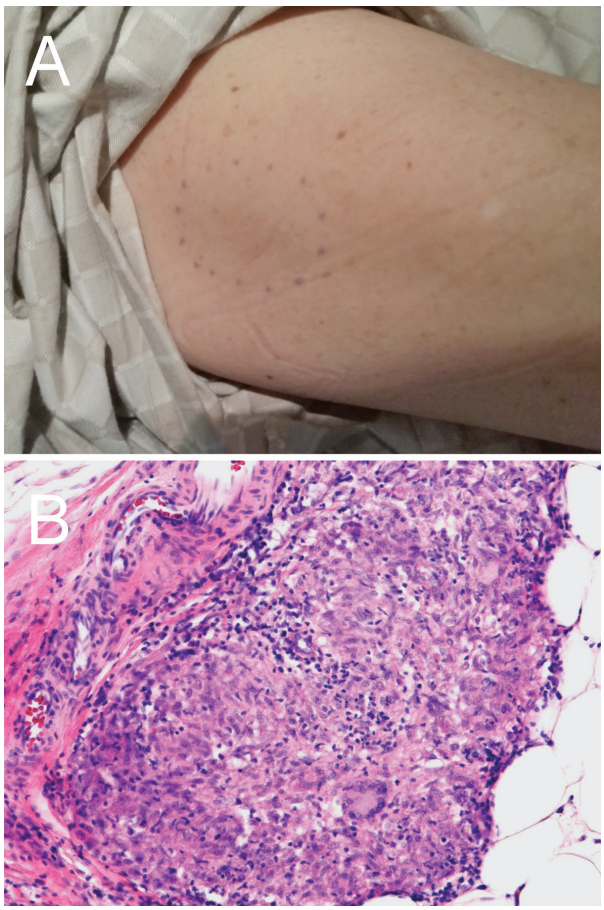

Fig. 3. On visual inspection, there was no bulging and discoloration in the lateral side of the right upper arm (A). However, we found a few 2-mm-diameter lumps by palpation in the dotted circle of panel A. Cutaneous biopsy around these lumps was performed and microscopic investigation revealed numerous nodules consisting of noncaseating epithelioid granulomas and multinucleated giant cells in the subcutaneous tissue (B, hematoxylin and eosin staining)

upper limb weakness and tingling sensation almost completely disappeared, but the facial palsy improved only partially. After the oral prednisolone was tapered to 35 mg/day with an adjustment of levothyroxine sodium to 25 μg/day, she was discharged. At the patient's follow-up visits, the prednisolone was gradually reduced to 15 mg/day, and the multiple mononeuropathy did not recur.

In this presented case, the subcutaneous sarcoid eruptions were not apparent on the initial physical assessment, but we were able to find the eruptions with the aid of FDG PET. Abnormal FDG uptake was distinctly demonstrated in the lateral side of the right upper arm, whereas only a few slightly palpable lumps were observed in the corresponding site. Because FDG PET sensitively detects inflammation throughout the body, it can suggest the diagnosis of sarcoidosis, indicate appropriate biopsy sites, and help assess the prognosis and treatment response during immunosuppressive therapy (6-9). However, reports regarding its effectiveness in cutaneous sarcoidosis are scarce.

In some case reports, authors described patients in whom FDG PET clearly detected scar sarcoidosis (11,12). For example, a 60-year-old man with a medical history of colon adenocarcinoma and clear cell renal cell carcinoma presented with cough and dyspnea. Tumor recurrence was suspected and FDG PET was performed; FDG uptake was increased in the previous surgical scars. Microscopic examination of the scar revealed noncaseating epithelioid granulomas (11). According to another report, in a 37-year-old woman, FDG PET showed increased tracer accumulations in the lower back tattoo. Histopathological findings of the skin around the tattoo suggested cutaneous sarcoidosis (12). Other several reports concerned patients who had clearly delineated subcutaneous sarcoid nodules over wide ranges of their bodies (13-15). These patients included a 28-year-old woman complaining of painful knots in her neck and groin (13), a 50-year-old man with diffuse skin pain and pruritus (14), and a 37-year-old woman whose FDG PET findings looked like those of cutaneous lymphoma (15). However, a localized subcutaneous FDG PET abnormality, as in our patient, is rare and can be missed without sufficient attention.

This patient had a distinct FDG PET lesion in the lateral side of the right upper arm, while physical examination revealed a few tiny eruptions. The lesion size on FDG PET was disproportionately large in comparison with the eruptions. In contrast to the small number of eruptions found on physical examination, microscopic examination showed numerous sarcoidal nodules in the subcutaneous tissue, most of which were too small to be detected on palpation. This contrast probably suggested that FDG PET showed inflammation not only in the palpable tiny nodules but also in the nodules that were nonpalpable but microscopically apparent.

Neurological manifestations of sarcoidosis include intracranial and spinal cord masses, leptomeningeal abnormalities, hydrocephalus, and polyneuropathy (16,17). Before biopsy of the affected neural

lesions is performed, clinicians have to initially search for safer targets, such as cutaneous sarcoidal lesions (2). Cutaneous involvement is relatively common in sarcoidosis (1,18), but the lesions can be asymptomatic and virtually unrecognizable on physical examination. In such cases, FDG PET may help detect occult skin lesions and indicate safe biopsy targets.

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