

The utility of FDG-PET/CT imaging in the evaluation of multicentric reticulohistiocytosis

A case report

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Abstract

Introduction: Multicentric reticulohistiocytosis (MRH) is a rare histiocytic disorder that involves the skin, joints, and visceral organs.

Case presentation: We report a 67-year-old woman with MRH who presented with a 2-years history of polyarthralgia and skin nodules. Her symptoms were an inflammatory polyarthropathy with punched-out lesions of the distal interphalangeal (DIP) joints of both hands. Doppler ultrasonography of the hands showed large bone erosions with power Doppler signals in the DIP joints. ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) demonstrated increased FDG uptake in cutaneous papules surrounding the affected joints, suggesting an inflammatory process. There was no evidence of malignancy. Biopsy samples of skin nodules exhibited dermal infiltration with CD68-positive histiocytes and multinucleated giant cells. The patient was diagnosed with MRH and treated with combination therapy comprising a steroid (prednisolone), tacrolimus, methotrexate, and infliximab, which resulted in clinical improvement. Following infliximab treatment, there was a significant decrease in a bone resorption marker (tartrate-resistant acid phosphatase 5b: TRACP-5b), suggesting that tumor necrosis factor- α targeting therapy may inhibit osteoclast formation and resorption activity in patients with MRH.

Conclusion: MRH is a progressive destructive arthritic condition, and early diagnostic and therapeutic strategies are necessary to improve the outcome. FDG-PET/CT and joint ultrasonography might be noninvasive imaging modalities that could help diagnose MRH.

Abbreviations: CT = computed tomography, DIP = distal interphalangeal, FDG-PET/CT = ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography, MMP-3 = matrix metalloproteinase-3, MRH = multicentric reticulohistiocytosis, PIP = proximal interphalangeal, TRACP-5b = tartrate-resistant acid phosphatase 5b.

Keywords: FDG-PET/CT, multicentric reticulohistiocytosis, tumor necrosis factor- α , ultrasonography

1. Introduction

Multicentric reticulohistiocytosis (MRH) is a rare inflammatory disease characterized by skin nodules and associated with destructive arthritis.^[1] Skin lesions are characterized by cutaneous papules and nodules which are located around finger joints and the base of the nails.^[2] Histology of skin lesions reveals histiocytes with

eosinophilic cytoplasm and multinucleated giant cells.^[3] MRH is a destructive joint disease that progresses to arthritis mutilans.^[4] Diagnosis and treatment for MRH should be performed early to avoid its sequelae.^[5] Its definitive diagnosis is based on biopsy of the affected tissues. Previous reports indicated that histiocytes of monocyte/macrophage lineage infiltrate the synovium and skin nodules.^[6] These cells infiltrating the synovium exhibit properties of osteoclasts.^[7] Radiography of the affected joints reveals disproportionate destruction of bone, resembling gouty erosions.^[8] One of the most important associations of MRH is a synchronous malignant neoplasm, which occurs in 20% to 30% of patients.^[9] Hence, the presence of a neoplasm must be ruled out. Among the imaging tests, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) allows evaluation of a neoplasm.^[10] We report a case of MRH with destructive polyarthritis in which FDG-PET/CT could be useful for identifying the characteristic features of MRH in addition to screening for a possibly associated malignancy.

1.1. Consent statement

Informed consent was obtained from the patient for the publication of this study.

2. Case report

A 67-year-old Japanese woman was referred to our hospital with a 2-year history of polyarthralgia that included progressive

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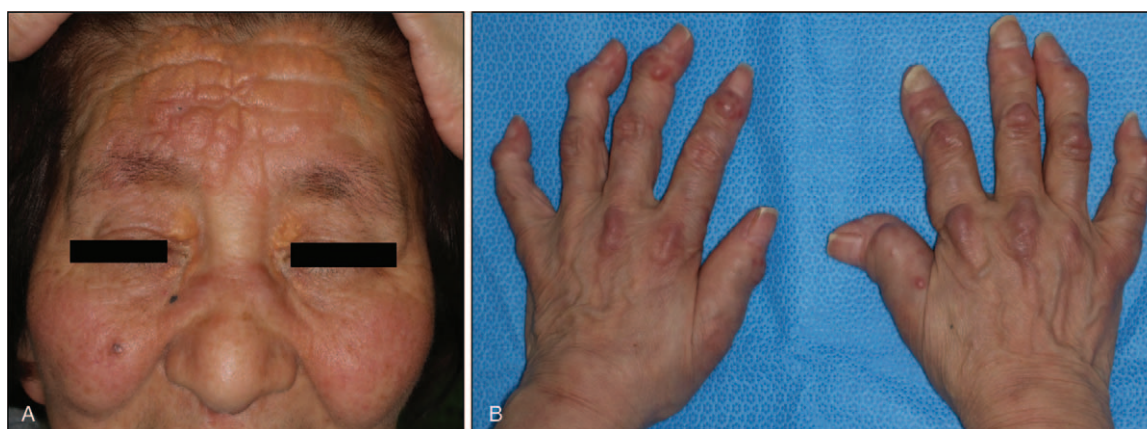


Figure 1. Physical finding of the skin. There were xanthoma-like papules in the upper lid and forehead (left). And papular erythema was seen on the extension side of the finger joints (right).

deformity and pain affecting the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of both hands. Her symptoms were consistent with an inflammatory polyarthropathy, including symmetrical pain and stiffness of both hands. She had been treated with steroid (prednisolone 15 mg/d), tacrolimus (2 mg/d), and methotrexate (6 mg/wk) under a tentative diagnosis of rheumatoid arthritis. Six months prior to this evaluation, her methotrexate dose had been tapered because there was an elevation in her transaminases. She presented now with nodular lesions on the extensor surface of the DIP and PIP joints.

She complained of bilateral joint tenderness in shoulders, hands, and wrists and had suffered morning stiffness that lasted

more than 1 hour. On physical, she presented with mildly erythematous, dome-shaped, skin lesions resembling xanthoma were evident on the frontal area of the face. Skin examination also showed a maculopapular rash, resembling vesicles, on the dorsal surfaces of the DIP and PIP of both hands (Fig. 1). There was no itching or discharge from the rash. Joint examination revealed significant swelling involving the wrists, pain on motion, and decreased range of motion of the PIP and DIP joints. She also exhibited symmetrical polyarthritis involving elbows, shoulders, and knees.

Hematological data revealed no abnormality (Table 1). Although erythrocyte sedimentation rate (8 mm/h) and C-reactive

Table 1

Laboratory findings on admission.

Peripheral blood			Serological tests		
White blood cells	10.7 × 10 ³ /μL	(2.8–8.8)	C-reactive protein	0.13 mg/dL	(0–0.30)
Neutrophil	94.0%	(44–74)	ESR (1 hour)	7 mm	(3–15)
Lymphocyte	3.0%	(20–50)	sIL-2R	366 U/mL	(121–613)
Monocyte	3.0%	(1–14)	MMP-3	241 ng/mL	(17.3–59.7)
Eosinophil	0.0%	(0–6)	IgG	1,206 mg/dL	(870–1,700)
Basophil	0.0%	(0–1)	IgA	249 mg/dL	(110–410)
Red blood cells	4.10 × 10 ⁶ /μL	(3.66–4.78)	IgM	78 mg/dL	(35–220)
Hemoglobin	12.6 g/dL	(11.6–14.0)	TNF-α	0.64 pg/mL	(<1.66)
Hematocrit	38.7%	(34.1–41.7)	IL-6	3.4 pg/mL	(<4.0)
Platelet	27.0 × 10 ⁴ /μL	(14.7–34.1)	VEGF	50 pg/mL	(<38.3)
Blood chemistry			ASO	19 IU/mL	(<240)
Total protein	6.9 g/dL	(6.7–8.3)	ANA	<×80	(<159)
Albumin	3.7 g/dL	(3.9–4.9)	Rheumatoid factor	5.0 IU/mL	(0–15)
Total bilirubin	0.7 mg/dL	(0.2–1.2)	Anti-CCP Ab	<0.5 U/mL	(<4.5)
Aspartate transaminase	23 U/L	(13–33)	Anti-ARS Ab	<5.0 index	(<24.9)
Alanine transaminase	14 U/L	(6–27)	Anti-Jo-1 Ab	<5.0 U/mL	(0–6.9)
Lactate dehydrogenase	326 U/L	(119–229)	Anti-MDA5 Ab	<5.0 index	(<32.0)
Alkaline phosphatase	164 U/L	(115–359)	Infection		
γ-Glutamyltranspeptidase	24 U/L	(10–47)	HBs Ag	(–)	
Creatine kinase	59 U/L	(45–163)	HCV Ab	(–)	
Aldolase	6.5 U/L	(2.7–7.5)	HTLV-I Ab	(–)	
Myoglobin	20.1 ng/mL	(<106.0)	IGRA	(–)	
Blood urea nitrogen	16 mg/dL	(8–22)	Urinalysis		
Creatinine	0.53 mg/dL	(0.4–0.7)	Protein	(–)	
Potassium	9.0 mg/dL	(8.7–10.3)	Blood	(–)	

ANA = antinuclear antibody, Anti-ARS Ab = anti-aminoacyl-tRNA synthetase antibody, Anti-CCP Ab = anticyclic citrullinated peptide antibody, Anti-ds-DNA Ab = antidouble stranded-deoxyribonucleic acid antibody, Anti-MDA5 Ab = antimelanoma differentiation-associated gene 5 antibody, ASO = antistreptolysin O, ESR = erythrocyte sedimentation rate, HBs Ag = hepatitis B virus surface antigen, HCV ab = antihpatitis C virus antibody, HTLV-I Ab = human T-cell leukemia virus type 1, Ig = immunoglobulin, IGRA = interferon γ release assay for *Mycobacterium tuberculosis*, IL-6 = interleukin-6, MMP-3 = matrix metalloproteinase-3, sIL-2R = soluble interleukin-2 receptor, TNF-α = tumor necrosis factor-α, VEGF = vascular endothelial growth factor.



Figure 2. (A) X-ray of the hand. Marked erosion with punched-out resorptive lesion and dilatation of joint cleft, on the distal interphalangeal joint, were seen. In addition, bone erosion and narrowing of the joint cleft were seen on carpometacarpal joint. (B) Bone scintigraphy.

protein (0.13 mg/dL) were within normal levels, serum levels of matrix metalloproteinase-3 (MMP-3, 241 ng/mL) were elevated. The blood chemistry results were within the normal range. The autoantibody results were negative for antinuclear antibody and tests for specific autoantibodies including anti-CCP antibody, were all negative.

Plain radiographs of the hands showed periarticular osteopenia, osteolytic lesions (punched-out erosions), and deformities of mainly the DIP and PIP joints (Fig. 2). Ultrasonography of PIP

joints showed large, well defined, bone erosions accompanied by linear power Doppler signals that flows into the deep layer inside the joint space (Fig. 3A). On the other hand, strong power Doppler signals consistent with remarkable thickened synovium, similar to the synovitis findings of rheumatoid arthritis, were found of her elbow and knee (Fig. 3B and C). ^{18}F -FDG PET/CT image showed the abnormal uptake of FDG in wrist, elbow and shoulder joints (Fig. 4). The corresponding slice of computed tomography (CT) showing an enhancing lesion in shoulders was inside of the inner edge of scapula. These FDG uptakes were recognized as being secondary synovitis of these joints. Also, FDG-PET/CT revealed the foci with increased FDG uptake around the DIP joints. The corresponding slice of CT showed that the enhancing lesions were outside of DIP joints. This demonstrates that increased FDG uptake was observed in the cutaneous papules surrounding DIP joints. There were no findings that suggested internal malignancy. A skin biopsy specimen from a cutaneous nodule on a dorsal finger showed that the nodular infiltrate was composed predominantly of multinucleated histiocytes with “glassy” cytoplasm. Stained with CD68, these cells were positive for macrophage markers and HLA-DR, and they were positive for TNF- α (Fig. 5).

Based on these results, the patient was diagnosed with MRH and was started on treatment with methotrexate (8 mg/wk) was combined with the base maintenance treatments consisting steroids and bisphosphonate. After discharge, she was followed-up at an outpatient clinic. Although her skin lesions were diminishing, she was started on a TNF- α inhibitor (infliximab 5 mg/kg every 8 weeks) because her arthralgia was not completely resolved. Her symptoms were markedly alleviated after the infliximab treatment. Three months later, the skin condition had resolved, and the joint pain was relieved in parallel with the decline in bone resorption markers after the infliximab treatment (Table 2).

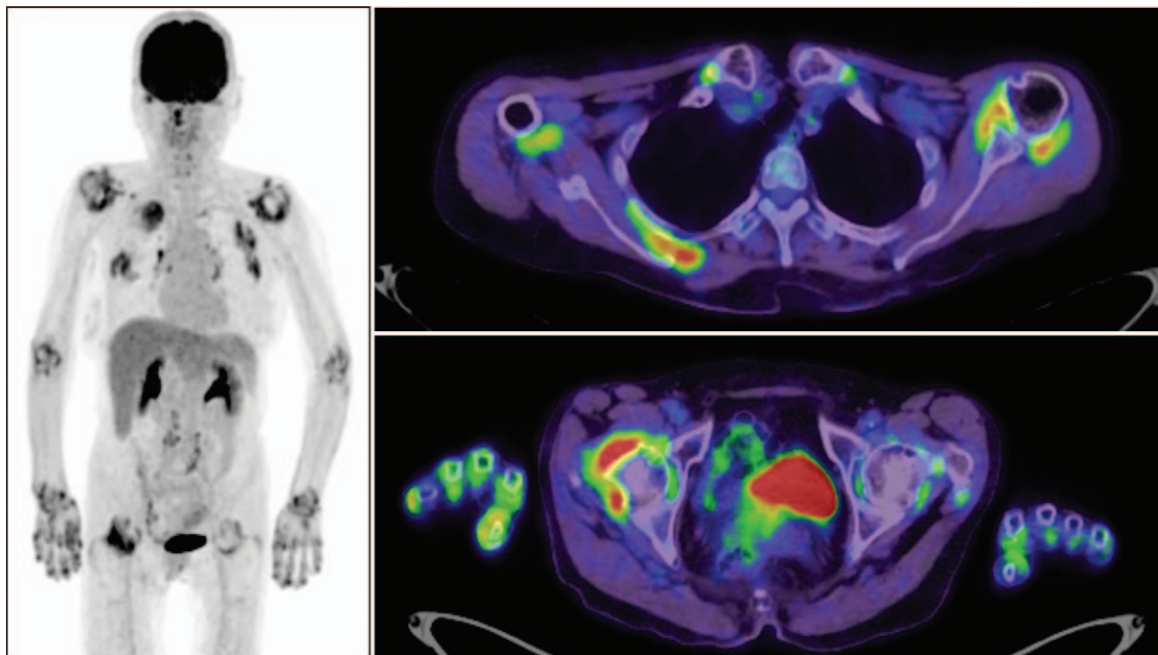


Figure 3. Positron emission tomography-computed tomography findings. Increasing of soft tissue in ventral side of scapula. Fluorodeoxyglucose (FDG) accumulations were seen in same area, shoulders, elbows, hands, fingers, knee and hip joints. FDG=fluorodeoxyglucose.

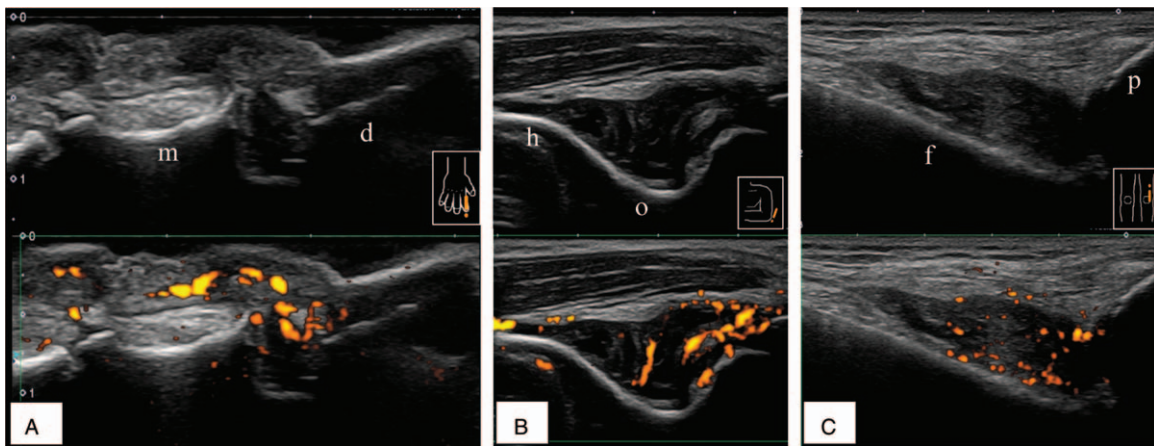


Figure 4. Ultrasound findings of finger (A), elbow (B), and knee (C). d: distal phalanx; m: middle phalanx; h: humerus; o: olecranon fossa; f: femur; p: patella. Cleft of distal interphalangeal joint was expanded widely and abnormal blood flow signal flow into the deep part of the joint. (B) The synovium in olecranon fossa was markedly thickened, and much linear blood flow signals were observed which did not decay to the deep layer. (C) Also well-thickened synovium on suprapatellar pouch and spotted blood flow signals were seen.

3. Discussion

MRH is a rare disorder that is frequently described as destructive polyarthritis accompanied by the development of cutaneous nodules and a significant association with malignancies.^[11] Although MRH is uncommon, it can result in irreversible destructive arthritis.^[4] Hence, early recognition and management of this disease is crucial.^[5] We presented a patient with MRH in whom FDG-PET/CT and ultrasonography prior to the histological examination allowed identification and a later update of the presence of papulonodular skin lesions in addition to active synovitis, which was compatible with a diagnosis of inflammatory arthritis secondary to MRH. This case suggests that combined FDG-PET and ultrasonography could help diagnose MRH.

A diagnosis of MRH should be suspected in a patient with skin lesions typically associated with erosive arthritis. Although MRH is generally diagnosed based on clinical manifestations, histological

results, and radiographic findings,^[12] FDG-CT/PET (which demonstrates FDG uptake in papulonodular skin lesions) in combination with ultrasonography provides further useful information with which to establish the diagnosis of MRH.

FDG-PET/CT provides valuable information about inflammatory and granulomatous diseases because FDG is easily taken up by granulomas and inflammatory cells.^[13] Unsurprisingly, FDG-PET/CT has detected malignant tumors successfully, although some benign lesions, such as sarcoidosis, also have shown intensive focal uptake.^[10] Although the skin lesions of MRH are benign, FDG uptake was confirmed in the skin nodules in addition to synovitis of the patient with MRH reported here. Thus, combined with ultrasonography, which reveals bone erosions with vascularity, FDG-PET could be a useful imaging modality for diagnosing MRH.

Histologically, MRH consists of multinucleated giant cells and histiocytes containing eosinophilic cytoplasm with a ground-glass

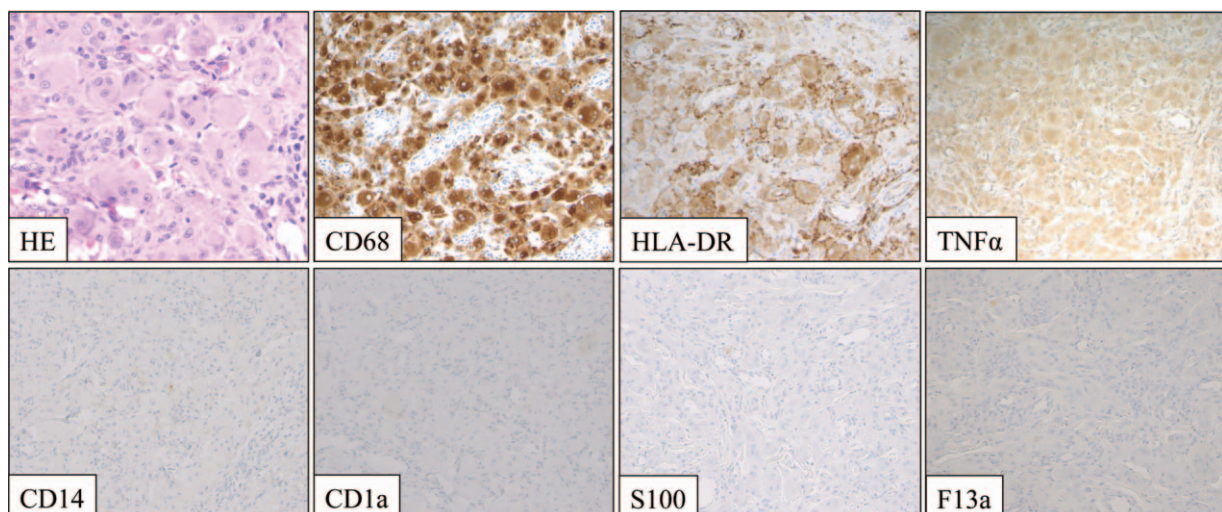


Figure 5. Histopathological findings of skin biopsy (finger). CD=cluster of differentiation, F13a=factor 13a, HE=hematoxylin eosin, HLA-DR=human leukocyte antigen-DR, TNF=tumor necrotizing factor.

Table 2**Serum bone metabolism marker's profile and longitudinal changes.**

	Normal range	Time point	Day 62	Day 104	Day 131
			Before anti-TNF therapy	After anti-TNF therapy	
BAP	9.6–35.4 (μg/L)		12.1	10.2	8.9
TRACP-5b	120–420 (mU/dL)		329	290	157
NTx	10.7–24.0 (nmol/L)		17.5	14.2	12.9

BAP = bone alkaline phosphatase, NTx = type I collagen cross-linked N-telopeptide, TNF = tumor necrosis factor, TRACP-5b = tartrate-resistant acid phosphatase 5b.

appearance.^[1] Although the natural course of MRH is variable, progressive symmetrical erosive polyarthritis occurs.^[4] Marginal erosions commonly occur, developing into progressive joint destruction.^[5] Because of the rarity of the disease and the unfeasibility of a controlled trial, a consensus treatment for MRH has not been established. A previous review, however, showed that the most effective initial disease-modifying antirheumatic drug to use is methotrexate.^[14] In our case, methotrexate resolved skin lesions but achieved only partial control in joints. Recent reports have suggested a promising therapeutic effect of anti-TNF-α antibodies.^[15] It is demonstrated that synovial tissue staining in macrophages is positive for several cytokines including TNF-α. These findings suggest that targeting TNF-α could be the therapeutic strategy for treating refractory MRH. Indeed, remarkable responses to a TNF-α antagonist in MRH patients unresponsive to multiple interventions has been reported.^[16]

It has been shown that histiocytes in synovial membranes can differentiate into osteoclasts specialized to carry out bone resorption.^[17] It was demonstrated that macrophages from MRH synovial fluid contribute to bone erosion by differentiating into mature osteoclasts by a RANKL-dependent mechanism.^[18] MRH synovial fluid contains an increased amount of TNF-α,^[19] which is known to promote osteoclast formation.^[20] The maintenance of bisphosphonate treatment may decrease macrophage–osteoclast differentiation and resorption, whereas a decline in the bone resorption marker, TRACP-5b, was demonstrated after the introduction of infliximab treatment in this patient. These findings suggest that treatment targeting TNF-α directed at inhibiting osteoclast differentiation and resorption—may be useful in controlling the destruction associated with MRH. Given the low number of MRH cases; however, it is difficult to assess its superiority over traditional disease-modifying antirheumatic drugs. Further prospective investigations are required to standardize its application in the treatment of patients with MRH.

4. Conclusions

In conclusion, MRH is a rare disease with unique clinical and radiographic features that set it apart from other inflammatory arthritis. The present case report suggests that FDG-PET/CT is a potentially useful means to detect and evaluate the grade of inflammatory involvement of MRH and to assess the possible association of malignant neoplasms. We propose that the combination of methotrexate and anti-TNFα therapy could be useful in the treatment of this potentially devastating disease.

5. Method

Ethical approval for this study (No. 2835) was provided by the Ethics Committee of Fukushima Medical University and written informed consent was obtained from the patient.

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