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CASE REPORT

Case of non-secretory multiple myeloma eventually diagnosed by ^{18}F-FDG PET/CT

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Abstract

Non-secretory multiple myeloma (NSMM) is a rare type of multiple myeloma characterized by the absence of the M protein, making its diagnosis challenging. Here, we report a 67-year-old female patient eventually diagnosed as NSMM with positron emission tomography-computed tomography (PET/CT) imaging as a clue.

KEYWORDS

M protein, non-secretory multiple myeloma, polymyalgia rheumatica, positron emission tomography–computed tomography, serum free light chain

1 | INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by the neoplastic proliferation of clonal plasma cells that typically produce a monoclonal immunoglobulin (M protein). Its clinical manifestations can be extremely varied, and its classic symptoms are summarized using the acronym "CRAB," referring to calcium elevation, renal insufficiency, anemia, and bone lesions.[1] When MM is suspected, protein electrophoresis of the serum and/or urine is performed to detect the M protein, and the final diagnosis is usually established based on the histological analysis of the bone marrow aspirate or biopsy specimen. However, the patients with MM are sometimes asymptomatic or lack classic symptoms, making the diagnosis challenging.

Although one of the typical methods for diagnosing MM is the detection of the M protein using conventional techniques, some patients lack the M protein; this condition, known as non-secretory MM (NSMM), is a rare subtype of MM, accounting for approximately 3% of all cases.[2] Owing to the lack of a clinical biomarker for MM, the diagnosis of NSMM is more difficult than that of secretory MM.

Here, we report an instructive case of NSMM without CRAB symptoms, in which the patient was initially diagnosed as having and treated for polymyalgia rheumatica (PMR).

2 | CASE REPORT

A 67-year-old female patient with general malaise and slight fever visited a primary care clinic and was found to have elevated C-reactive protein (CRP) levels. Although an antibiotic (levofloxacin) had been administered for several days, her symptoms persisted. As shoulder pain and jaw claudication gradually developed, she was referred to our hospital 3 months after the first onset of symptoms.

She did not look sick and had a blood pressure of 134/74 mmHg, temperature of 37.0°C, pulse of 102 beats per min, respiratory rate of 12 breaths per minute, and oxygen saturation of 98% at room air. Physical examination revealed no particular abnormality, except for tenderness of both the shoulders. Laboratory evaluation revealed that the CRP level and erythrocyte sedimentation rate (ESR) were

TABLE 1 Laboratory findings at the first visit

Hematology			Serology		
WBC	5.48	$\times 10^3/\mu l$	CRP	2.54	mg/dl
Neutrophil	69.5	%	RF	41.8	IU/ml
Lymphocyte	22.3	%	MMP-3	37.4	ng/ml
Monocyte	7.8	%	PR3-ANCA	<1.0	U/ml
Eosinophil	0.2	%	MPO-ANCA	<1.0	U/ml
Basophil	0.2	%	sIL-2R	518	U/ml
RBC	3.90	$\times 10^6/\mu l$	C3	169	mg/dl
Hemoglobin	12.2	g/dl	C4	32	mg/dl
Platelet	219	$\times 10^3/\mu l$	ANA	<×80	
ESR	93.0	mm/h	Anti SS-A	<1.0	U/ml
			Anti SS-B	<1.0	U/ml
Biochemistry					
T-Bil	0.6	mg/dl	Urinalysis		
AST	16	U/L	Specific gravity	1.021	
ALT	19	U/L	pH	5.5	
LDH	158	U/L	Occult blood	Negative	
ChE	304	U/L	Protein	Negative	
ALP	239	U/L	Glucose	Negative	
γ-GTP	22	U/L	Ketone	Negative	
CK	24	U/L	RBC	0	/HPF
Na	141	mEq/L	WBC	1	/HPF
K	3.8	mEq/L	Epithelial cells	0	/HPF
Cl	102	mEq/L	Cast		Negative
Ca	9.4	mg/dl			
Ferritin	340.9	ng/ml			
TP	7.3	g/dl			
Alb	3.8	g/dl			
UN	11.1	mg/dl			
Creatinine	0.49	mg/dl			
UA	4.6	mg/dl			
Blood Sugar	109	mg/dl			
HbA1c	5.5	%			
F-T4	1.5	ng/dl			
TSH	0.711	μIU/ml			

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; anti SS-A, anti-Sjögren's-syndrome-related antigen A antibody; anti SS-B, anti-Sjögren's-syndrome-related antigen A antibody; AST, aspartate aminotransferase; C3, complement component 3; C4, complement component 4; ChE, cholinesterase; CK, creatine kinase; Cl, chlorine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F-T4, free thyroxine; HbA1c, hemoglobin A1c; K, potassium; LDH, lactate dehydrogenase; MMP-3, matrix metalloproteinase 3; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; Na, sodium; PR3-ANCA, proteinase-3-antineutrophil cytoplasmic antibody; RBC, red blood cell; RF, rheumatoid factor; sIL-2R, soluble interleukin-2 receptor; T-Bil, total bilirubin; TP, total protein; TSH, thyroid-stimulating hormone; UA, uric acid; UN, urea nitrogen; WBC, white blood cell; γ-GTP, γ-glutamyltransferase.

2.54 mg/dl and 93.0 mm/h, respectively. Table 1 lists other laboratory findings. Two sets of blood cultures were negative. Contrast-enhanced computed tomography (CT) did not demonstrate any significant findings. Consequently, she was diagnosed with PMR, possibly complicated with giant cell arteritis, and treated with glucocorticoids. A dosage of 15 mg/day of prednisolone was initially administered orally and significantly relieved her symptoms; thereafter, its dosage was planned to be gradually reduced.

The CRP level and ESR also initially improved with symptom improvement. However, they rose again after reducing the prednisolone dose to 12.5 mg/day, although symptoms did not recur. To exclude malignancy or vasculitis, whole-body positron emission tomography–CT

(PET/CT) was performed, which demonstrated osteolytic lesions with Fluorine-18 deoxyglucose (^{18}F-FDG) accumulation in the frontal bone, bilateral clavicle, and sacrum, suggesting punched-out lesions indicative of MM (Figure 1). However, the serum immunoglobulin (Ig) levels were within the normal ranges (NR): IgG of 909 mg/dl (NR: 870–1,700 mg/dl), IgA of 162 mg/dl (NR: 110–410 mg/dl), and IgM of 52 mg/dl (NR: 46–260 mg/dl). In addition, M protein was not detected in the serum or urine on conventional immunofixation. Hence, she was referred to the department of hematology to undergo bone marrow biopsy, which exhibited hyperplasia of CD138 and epithelial membrane antigen (EMA)-positive atypical plasma cells, occupying approximately 80% of the nucleated cells (Figure 2). Serum free light chain (FLC) assay revealed that κ/λ ratio of FLC increased up to 179.70 (NR: 0.25–1.80): κ chain of 2,390 mg/L (NR: 2.42–18.92) and λ chain of 13.30 mg/L (NR: 4.44–26.18). Serum β2 microglobulin was 2.62 mg/dl. She was eventually diagnosed as having NSMM (International Staging System stage Ⅱ) and treated with bortezomib and dexamethasone.

3 | DISCUSSION

The diagnosis of MM, especially among patients without CRAB symptoms, is challenging. In this case, it took nine months since the first visit of the patient to our hospital to reach a final diagnosis. As MM causes various symptoms apart from CRAB, nearly 20% of patients with symptomatic MM have only non-CRAB symptoms.[1] In patients with symptomatic MM, the most common symptom was bone pain, followed by a general feeling of illness, such as general malaise or slight fever.[3] To reduce the risk of delayed diagnosis, MM should be considered as a differential diagnosis when a patient presents with symptoms shown in this case.

This case was initially diagnosed as PMR based on Bird's criteria.[4] PMR is an inflammatory disorder characterized by pain and stiffness of the shoulders, neck, and pelvic girdle. In most cases, glucocorticoids (prednisolone doses ranging between 12.5 and 25 mg per day) dramatically improve these symptoms.[5] In this case, her incomplete response to glucocorticoid lead us to reconsider other possible disorders.

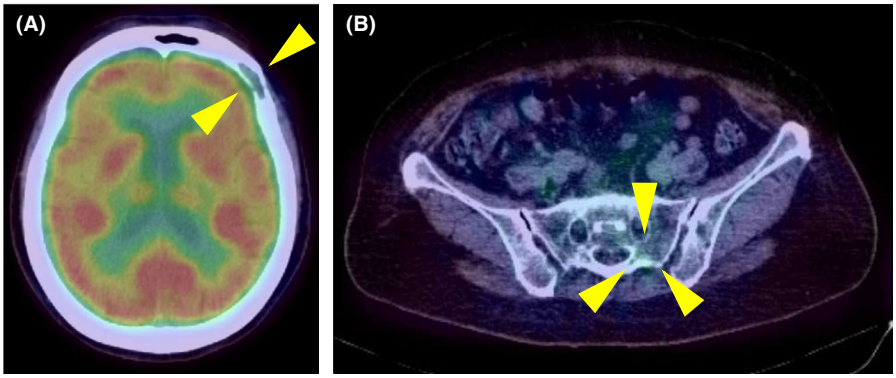

FIGURE 1 Positron emission tomography–Computed tomography showing osteolytic lesions with Fluorine-18 deoxyglucose accumulation in the frontal bone ((A) SUV max 2.57) and sacrum ((B) SUV max 2.82)

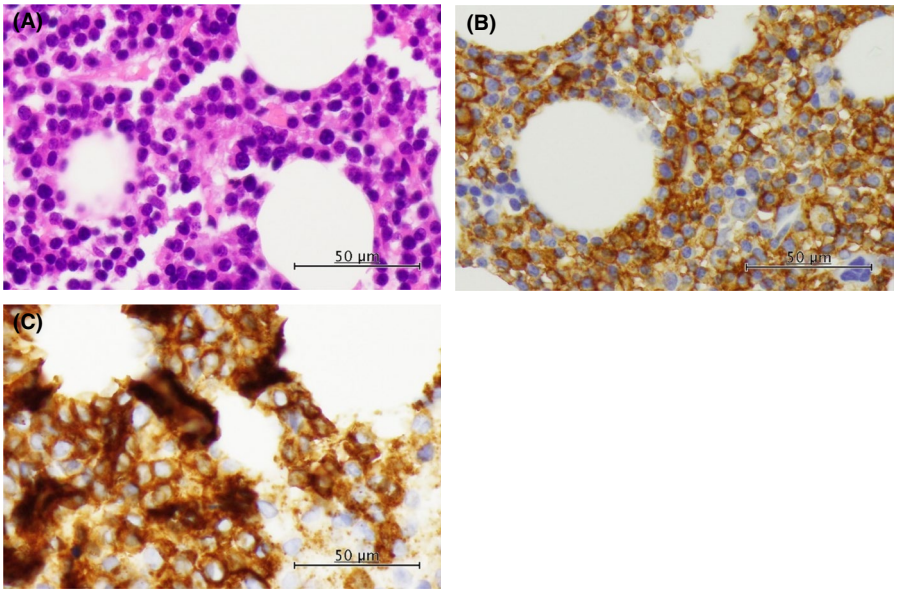

FIGURE 2 (A) A bone marrow biopsy specimen showing hyperplasia of atypical plasma cells on hematoxylin and eosin staining. (B and C) Immunohistochemical analysis showing the plasma cells as being positive for CD138 (B) and EMA (C)

^{18}F-FDG PET/CT should be considered as a valuable tool for the work-up of patients with MM as it can detect bone lesions.[6] In addition, PET/CT substantially contributes to the diagnosis and differential diagnosis of fever of unknown origin (FUO) and inflammation of unknown origin (IUO) with a sensitivity and positive predictive value of 91.8% and 65.4%, respectively.[7] In this case, PET/CT played a pivotal role for the diagnosis of NSMM by detecting multiple bone lesions. PET/CT may be a promising examination tool for patients with FUO/IUO like the one in this case, although its high cost and limited availability remain a limitation.

This case was eventually diagnosed as NSMM as no M protein was detected in the serum or urine on conventional immunofixation. In recent years, even a small amount of M protein can be detected using a novel diagnostic tool, the serum FLC assay; therefore, NSMM is classified into two distinct subtypes: "true non-secretory myeloma" and "serum free light chain-only myeloma".[8] With the detection of abnormal κ/λ ratio on serum FLC, high M protein sensitivity is achieved (lower detection limit for FLC is 0.2 mg/L).[9] This case was found to be "serum free light chain-only myeloma" with an abnormal κ/λ ratio. Several studies have reported that the diagnostic sensitivity of serum FLC assay for NSMM is within the range of 68%–86%, suggesting that serum FLC assay is highly recommended for the diagnosis of "serum free light chain-only myeloma".[10,11]

In conclusion, this case suggests that we should consider NSMM as one of the differential diagnoses for inflammatory disorders, including those presenting without CRAB symptoms. ^{18}F-FDG PET/CT can detect bone lesions with high sensitivity and specificity so that it can be a valuable tool for the diagnosis of NSMM.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Daisuke Haratake collected the data and drafted the article. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

CONSENT

Written informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

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