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Review

Non-POEMS osteosclerotic multiple myeloma: Clinical characteristics and differential diagnosis

Zi-Yan Li [a], Jiang-Jie Chen [a,b], Fang-Ying Lu [a,b], Mei-Fu Gan [c], Tao-Hsin Tung [d], Dun Hong [a,e,*]

[a] Department of Bone Disease, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai, China
[b] Department of Orthopedics, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai, China
[c] Department of Pathology, Taizhou Hospital affiliated to Wenzhou Medical University, Linhai, China
[d] Evidence-Based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai, China
[e] Bone Metabolism and Development Research Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai, China

HIGHLIGHTS

- Rare non-POEMS osteosclerotic MM case presented and terminology standardized.
- Review since 1990 identifies just 12 non-POEMS osteosclerotic MM cases.
- The disease is divided into osteosclerotic lesion and diffuse osteosclerosis subtypes.
- Polyneuropathy and organomegaly distinguish POEMS from non-POEMS MM.
- Hyperactive osteoblastic process may underlie the etiology.

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ABSTRACT

Osteosclerosis in multiple myeloma (MM) is typically associated with rare POEMS syndrome, characterized by polyneuropathy (P), organomegaly (O), endocrinopathy (E), M-protein (M), and skin changes (S). However, osteosclerosis in multiple myeloma (MM) without POEMS syndrome, defined as non-POEMS Osteosclerotic MM, is exceedingly rare. We report a 70-year-old man with rib pain, remarkably high bone mineral density and diffuse osteosclerosis. The diagnosis of non-POEMS osteosclerotic MM was confirmed by biopsy and aspiration of bone marrow through surgery. A literature review spanning from 1990 identified 12 cases of similar non-POEMS osteosclerotic MM, including 5 males and 7 females with a mean age of 59.7 ± 10.6 years. The non-POEMS osteosclerotic MM can be divided into two subtypes, the osteosclerotic lesion subtype and the diffuse osteosclerosis subtype. Absence of polyneuropathy and organomegaly are the main factors that differentiate non-POEMS osteosclerotic MM from POEMS. A hyperactive osteoblastic process might be the etiology of diffuse osteosclerosis. Further research is needed to understand its etiology and pathophysiology.

1. Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled proliferation of plasma cells and is often associated with lytic bone lesions, hypercalcemia, renal failure, and anemia [1]. Lytic bone lesions are particularly common in MM. However, in rare cases, MM patients present with osteosclerosis rather than osteolysis. This atypical finding is usually associated with POEMS syndrome [2–6], which is characterized by polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal proteinemia (M), and skin changes (S) [4,7]. Over the years, case series have been documented from countries such as France, the United States, China, and India [8–11]. A national survey of POEMS in Japan reported a prevalence of approximately 0.3 per 100,000 [12].

However, cases of osteosclerotic MM that do not align with the diagnostic criteria for POEMS syndrome were exceptionally rare [13–21]. The reported cases have been termed variably, such as osteosclerotic MM without POEMS Syndrome [13], myeloma with diffuse osteosclerotic lesions without features of POEMS [14], MM with diffuse osteosclerosis [15,16], diffuse osteosclerotic myeloma [17], MM with

* Corresponding author at: Department of Bone Disease, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai, China.
E-mail address: hongd@enzemed.com (D. Hong).

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Table1
Main laboratory findings.

Items	Values	Reference range	Status
Blood routine			
Erythrocytes × 10^{12}/L	2.45	3.8–5.1	↓
Hemoglobin g/L	75	115–150	↓
Leukocytes × 10^{9}/L	3.3	3.5–9.5	↓
Bone turnover markers			
β-CTX pg/mL	482.2	< 704.0	–
PTH pg/mL	173.7	15–65	↑
P1NP μmg/mL	340.5	9.1–76.2	↑
N-MID OCN ng/mL	201.1	14–46	↑
Serum Phosphorus mmol/L	2.70	0.85–1.51	↑
Serum Calcium mmol/L	1.83	2.11–2.52	↓
ALP (blood) U/L	129	45–125	↑
Light Chain			
Blood K light chain mg/dL	72.2	170–370	↓
Blood L light chain mg/dL	775.0	90—210	↑
λ Free light chain mg/L	61.7	8.3–27.0	↑
κ Free light chain mg/L	12.0	6.7–22.4	–
K/L ratio	0.09	0.26–1.65	↓
Urinary light chain κ mg/dL	2.0	0–0.7	↑
Blood IFE			
IgG M-protein	Positive	Negative	Positive
λfree Light Chain	Positive	Negative	Positive
Urine IFE			
IgG, IgM, IgA M-protein	Negative	Negative	Negative
free Light Chain	Negative	Negative	Negative
Quantity of blood Ig			
IgG mg/dL	3079.0	860.0—1740.0	↑
IgA mg/dL	6.0	100.0–220.0	↓
SPE			
SPE β %	7.5	8.5–14.5	↓
SPE γ %	31.3	11.0–21.0	↑
Beta2 microglobulin mg/L	3.00	1.09–2.53	↑
Inflammation makers			
Hypersensitivity CRP mg/dl	3.56	0.00–8.00	
ESR mm/H	43	0–15	↑
IL-6 ng/mL	4.86	0.1–2.90	↑
Others			
Ferritin ng/mL	828	7.0–323	↑
A/G ratio	0.8	1.2–2.4	↓

P1NP: Procollagen Type 1 N-Terminal Propeptide.
N-MID OCN: Osteocalcin N-terminal mid-molecular fragment.
Ig: Immunoglobulin
M-protein: Monoclonal immunoglobulin
SPE: Serum protein electrophoresis.
A/G ratio: Albumin to globulin ratio.
K/L ratio: Serum K/L light chain ratio.
PTH: Parathyroid hormone.
CRP: C-reactive protein
IFE: Immunofixation electrophoresis.
ALP: Alkaline phosphatase.
ESR: Erythrocyte Sedimentation Rate.

diffuse osteosclerotic bone lesions [18], MM with widespread osteosclerotic lesions [19], osteosclerotic myeloma [20], or sclerosing MM [21]. This diversity in terminology reflects the extreme rarity of the disease and requires a clear nomenclature, classification, and differentiation from POEMS.

This report presents a rare case of diffuse osteosclerotic MM that does not meet the criteria for POEMS diagnosis [22]. We identified a further 11 cases after a thorough review of analogous cases in the literature from 1990 onwards. After analyzing the clinical features of the total of 12 cases, we proposed the term "non-POEMS osteosclerotic MM" for these cases and compared the differences between POEMS and non-POEMS osteosclerotic MM.

2. Case presentation

2.1. Patient history

A 70-year-old man, weighing 63.5 kg with a height of 165 cm, was admitted for bilateral rib pain lasting for two months. The bone biopsy at the posterosuperior iliac spine prior to admission failed twice because of bone hardness. The patient had no symptoms such as nausea, vomiting, fever, or numbness in both lower limbs and still sustained routine daily activities and work. On physical examination, cardiovascular, respiratory, and abdominal examinations revealed no abnormalities. The sensation of extremities was normal. There was tenderness over both ribs.

2.2. Main laboratory findings

The laboratory findings indicated anemia, evidenced by reduced erythrocyte count and hemoglobin levels. The detection of IgG M-protein and an elevated IgG level at 3079.0 mg/dL (reference 860.0–1740.0 mg/dL) in serum were indicative of MM. The abnormal free kappa (K) and lambda (L) light chains, along with a decreased K/L ratio of 0.09 (reference 0.26–1.65), pointed to monoclonal plasma cell activity. Serum protein electrophoresis showed a reduced β fraction at 7.5 % (reference 8.5–14.5 %) and an increased γ fraction at 31.3 % (reference 11.0–21.0), suggesting a monoclonal gammopathy. These results collectively supported a MM diagnosis (Table 1).

Additional tests revealed elevated bone turnover markers, including Procollagen Type 1N-Terminal Propeptide (P1NP), Osteocalcin N-terminal mid-molecular fragment (N-MID OCN), and Parathyroid Hormone (PTH). The patient also presented with hyperphosphatemia and hypocalcemia, alongside elevated inflammatory markers such as Erythrocyte Sedimentation Rate (ESR) and Interleukin-6 (IL-6) (Table 1).

2.3. Imaging studies

Radiographs showed widespread sclerosis of the pelvis and femur (Fig. 1A) compared with the pelvis and femur of a normal 70-year-old man with a T-score of +0.5 (Fig. 1B). The sclerotic lumbar spine (Fig. 1C) was contrasted with the lumbar spine of the same normal man (Fig. 1D). In addition, widespread sclerosis was also seen on the radiographs of the thoracic spine and skull (data not shown). CT scans confirmed diffuse osteosclerosis in the skull, ribs, and sternum (Fig. 1E-F). Whole-body Emission Computed Tomography (ECT) revealed abnormal bone metabolic patterns suggestive of malignant lesions in the left 9th posterior rib and the right 9th and 10th posterior ribs. The faint renal image was suggestive of superscan associated with the diffuse osteosclerosis (Fig. 2). Dual-Energy X-ray Absorptiometry (DEXA) for bone mineral density (BMD) yielded extremely high T-scores: Lumbar 1–4 at +11.9 and Femoral neck at +10.8. Ultrasonography showed that the liver and spleen was of normal size.

2.4. Surgical biopsy

The biopsy of iliac bone was performed by orthopedic surgeons under general anesthesia. The iliac crest had a thick cortical layer (~10 mm) and increased hardness, making it difficult to penetrate. Using a sharp bone chisel, a cortical bone of more than 10 mm thick was removed and a small sample of bone marrow was extracted.

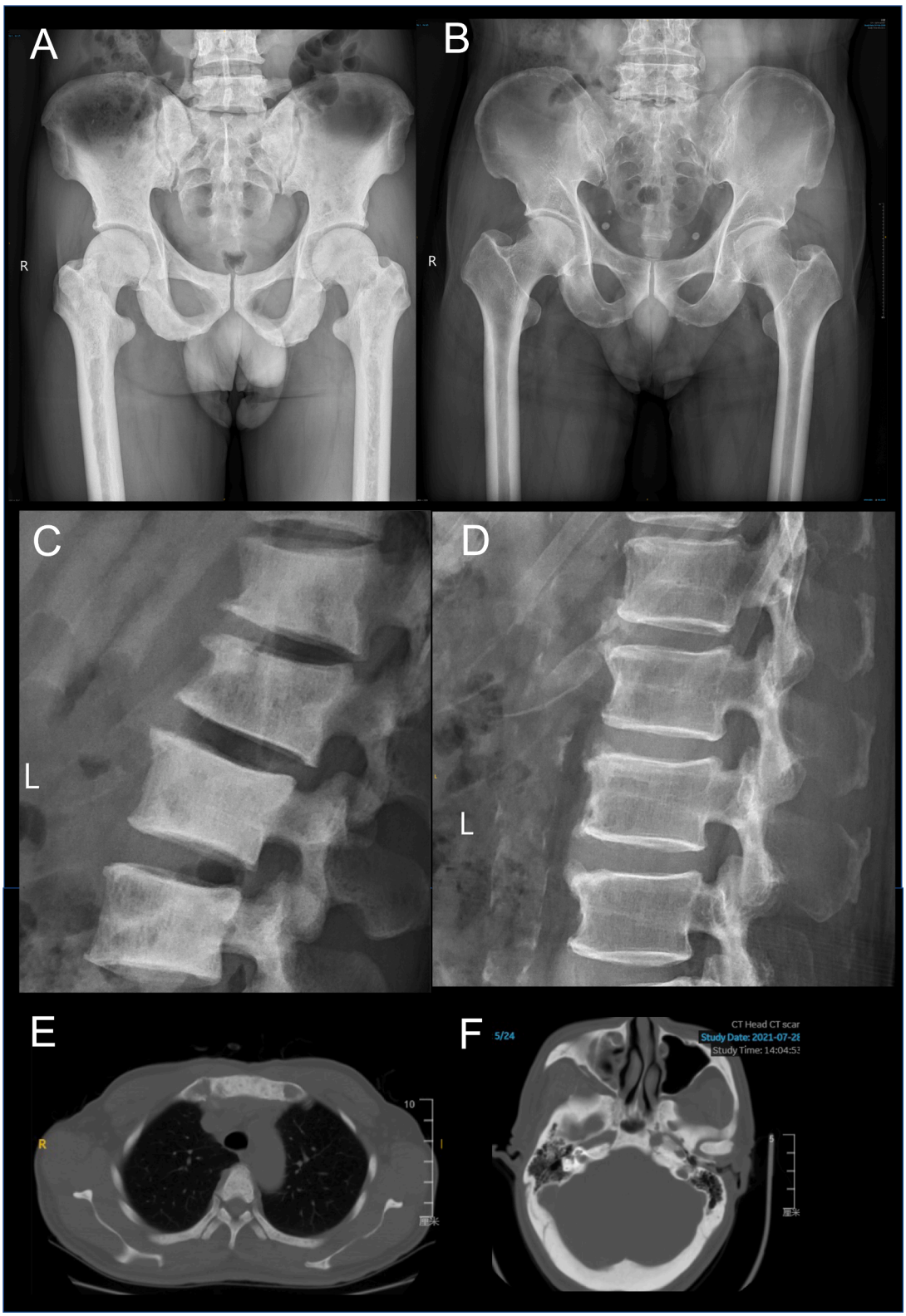

Fig.1. The radiographs show diffuse osteosclerosis in the patient's pelvis and femur (A) compared to those of a healthy man of the same age, with a T-score of +0.5 (B). Diffuse osteosclerosis in the patient's spine (C), in contrast to the lumbar spine of that healthy man (D). CT imaging reveals diffuse osteosclerosis in the ribs, sternum (E) and the skull (F).

2.5. Hematological findings

The bone histopathology of the iliac bone reported a thickened cortical bone of the iliac crest (Fig. 3A). Bone marrow smear cytology indicated that it was infiltrated by 35 % immature plasma cells (Fig. 3B and 3C). Immunohistochemistry revealed that the immature plasma cells were positive for CD79a, CD138 (partial), Lambda, Mum-1 (partial) and negative for CD56, CyclinD1, CD3, EMA, Kappa, CD20, ki-67, and CK.

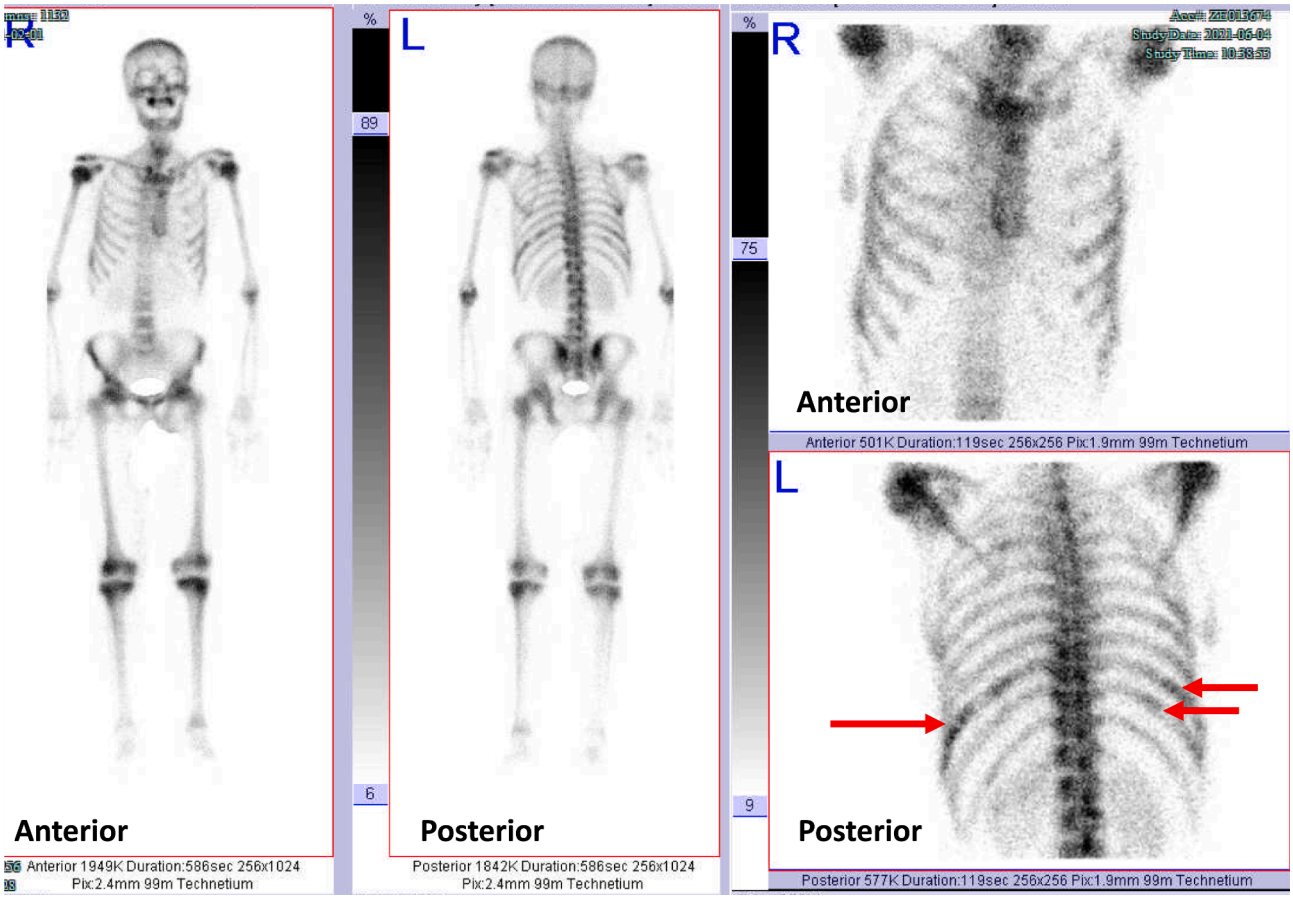

Fig.2. Whole body bone scan shows abnormal bone metabolism in the left posterior 9th rib and the right posterior 9th and 10th ribs, evidence of malignant lesions (red arrows). The faint renal image suggests a superscan, a phenomenon characterized by intense tracer uptake in the bones and diminished visibility of the kidneys on the scan.

2.6. Treatment and outcomes

The patient started treatment with an oral pomalidomide-cyclophosphamide-dexamethasone (PCD) regimen. However, the treatment was suspended due to subsequent bone marrow suppression that required transfusions and leukocyte-boosting drugs. One month later, treatment was switched to a daratumumab-dexamethasone-lenalidomide protocol. This change resulted in a marked clinical improvement, allowing for the completion of 8 chemotherapy cycles. Two years following this adjustment, the patient maintained clinical stability and was pain-free. The levels of P1NP decreased from 340.5 to 159 μg/mL, N-MID OCN from 201.1 to 64.5 ng/mL, while β-CTX levels rose from 482.2 to 1530 pg/mL.

3. Discussion

In this case, the diagnosis of MM was confirmed by bone tissue immunohistochemistry and bone marrow cytology. The X ray and CT imaging showed diffuse sclerosis in the skull, spine, ribs, pelvis, and sternum. In addition, the patient had an extremely high BMD, especially in the lumbar spine. The new criteria for POEMS in 2021 include two mandatory major criteria (polyneuropathy and monoclonal plasma cell-proliferative disorder), other major criteria (Castleman disease, sclerotic bone lesions, and elevation of vascular endothelial growth factor-VEGF), and minor criteria (organomegaly, extravascular volume overload, endocrinopathy, and skin changes) [22]. The diagnosis of POEMS is established when both mandatory major criteria, one of the other three major criteria, and one of the six minor criteria are met [22]. However, this patient did not have polyneuropathy, organomegaly, or skin changes and met only one mandatory criterion (monoclonal plasma cell-proliferative disorder) and one minor criterion (endocrinopathy-elevated PTH), therefore was excluded from POEMS.

We conducted a literature search in English-language sources from 1990 onwards and listed a total 12 non-POEMS osteosclerotic MM in Table 2. None of them had polyneuropathy and therefore did not fulfill the diagnostic criteria of POEMS. The 12 patients included 5 males and 7 females with a mean age of 59.7 ± 10.6 years. The chief complaints among these patients varied, including general symptoms of MM such as weakness, lethargy, and fatigue, and weight loss. Additionally, the patients presented back pain, chest pain, shortness of breath, and rib pain. Measurement of PTH was reported in 4 cases and was elevated in 3 cases. Bone formation markers, P1NP and OCN, were measured only in our case and were found to be significantly elevated compared to the reference range. The bone resorption marker β-CTX was measured in three cases and found to be elevated in two (Table 2).

We categorize the non-POEMS osteosclerotic MM into two subtypes, the osteosclerotic lesion subtype of 3 cases (3/12, 25 %) [13,14,16] and the diffuse osteosclerosis subtype of 9 cases (9/12, 75 %) [15,17–21]

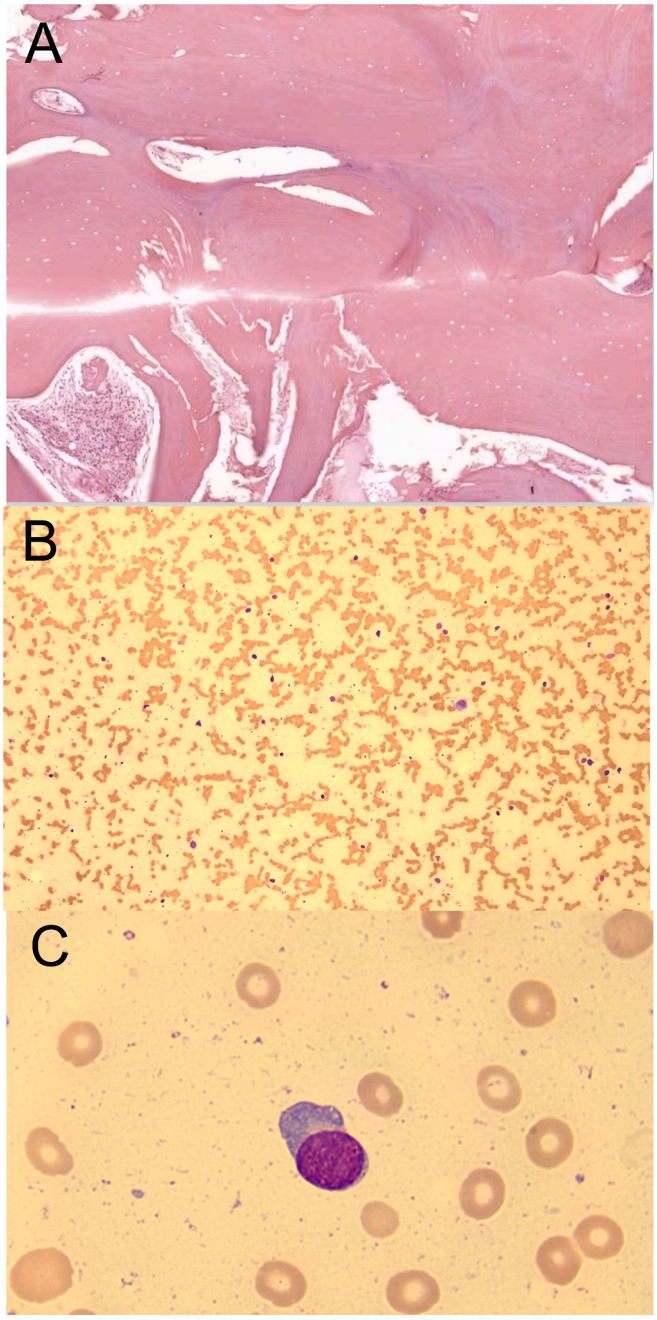

Fig.3. Histopathological examination (H.E. staining) of the iliac bone biopsy showed a thickened cortical bone of the iliac crest (A). The proportion of immature plasma cells in the bone marrow smear was 35% (B). Morphology of the stained immature plasma cell (C).

(Table 2). An osteosclerotic lesion or sclerotic bone lesion typically refers to a localized area where bone density is abnormally high. Diffuse osteosclerosis describes a condition where there is a generalized increase in bone density throughout the skeletal system, leading to a widespread appearance of denser bone. Osteolytic lesions [20,21] or multiple bone infarcts [15] may also occur in the region of osteosclerosis.

We compared the clinical features of POEMS and non-POEMS osteosclerotic MM in Table 3. None of the non-POEMS cases had polyneuropathy, which is a mandatory major criterion for POEMS [22]. In addition, non-POEMS cases did not have organomegaly, which is common in POEMS with a prevalence of 45–85 % [22]. Endocrinopathy is a minor criterion with a prevalence of 67–84 % in POEMS, typically presenting as hypogonadism [5,22,23]. However, the non-POEMS cases reported elevated PTH but not hypogonadism. Monoclonal Proteinemia was present in all cases of both POEMS [22] and non-POEMS. The skin changes occurred in about 50 % or 68–89 % of POEMS cases [22,24] and were rare in non-POEMS cases. Sclerotic bone lesions were found in 95 % of POEMS cases [5,24] but only 25 % (3/12) of non-POEMS cases. Elevated VEGF levels are a major criterion for POEMS, with a sensitivity of 68 % and specificity of 16.6 % for POEMS diagnosis [22]. However, elevated VEGF was reported in only two non-POEMS cases. Extravascular volume overload, papilledema, and thrombocytosis/polycythemia are minor criteria in POEMS [4,5], with thrombocytosis occurring in 54–88 % of cases and polycythemia in 12–19 % of cases [24]. However, these symptoms were not reported at the onset in our non-POEMS cases. (Table 3) In brief, polyneuropathy and organomegaly are the main factors that differentiate POEMS cases from non-POEMS cases.

In our case, the bone turnover markers indicated enhanced osteoblastic activity, with bone formation markers P1NP and osteocalcin levels increased to 4.5 and 4.4 times above the upper reference limits, respectively, while bone resorption marker β-CTX remained within normal ranges. After chemotherapy, the P1NP level decreased to twice the normal upper reference, osteocalcin to 1.4-times, and β-CTX increased to approximately twice the normal upper reference. The etiology of osteosclerosis in MM remains unclear, with hypotheses ranging from increased osteoblastic activity to osteoclast dysfunction [25,26]. Bone lesions in POEMS syndrome often present with both osteosclerotic and osteolytic features [27]. The diffuse osteosclerosis in other malignancies should be differentiated from the non-POEMS, such as myelofibrosis [28,29], acute megakaryocytic leukemia [30], hairy cell leukemia [31], systemic mastocytosis [32], bone lymphoma [33], and prostate cancer [34]. In brief, diffuse osteosclerosis and elevated bone formation markers in our MM case suggest a hyperactive osteoblastic process. After chemotherapy, the previously hyperactive osteoblastic activity in our case shifted towards a high-turnover yet balanced bone remodeling state.

In conclusion, non-POEMS osteosclerotic MM is different from POEMS syndrome. The non-POEMS osteosclerotic MM can be divided into two subtypes, the osteosclerotic lesion subtype and the diffuse osteosclerosis subtype. Polyneuropathy and organomegaly are the main factors that differentiate POEMS from non-POEMS osteosclerotic MM. A hyperactive osteoblastic process might be the basis of the diffuse osteosclerosis. Further research is needed to understand its etiology and pathophysiology.

4. Declarations

Ethical Approval - All procedures performed with the involved human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent - Written informed consent was obtained from the patient for the publication of this case report and any accompanying data and images.

Author contributions - Hong D designed the study. Li ZY collected the data. Li ZY, Chen JJ, Lu FY, Gan MF analyzed the data. Li ZY. wrote the first draft. Hong D and Tung TH reviewed and edited the manuscript.

Table 2
Summary of the clinic cases of non-POEMS osteosclerotic MM from 1990.

N.	Age/ Sex	Mandatory major criteria	Other major criteria	Minor criteria	Bone metabolism markers	Anemia	Chief Complaint	Treatment	Result	References
1	78/ Female	IgG-κ,	Sclerotic bone lesions	PTH^	ALP^, Ca^{2+} ↑	Yes	Lethargy and fatigue	MP/Thalidomide	Resolved	Mohamed 2014 [16]
2	55/ Male	IgA-λ	Sclerotic bone lesions	None	Ca^{2+}^, ALP↑	No	Chest pain	Bortezomib/CP/ DEX	Resolved	Zheng 2021 [14]
3	60/ Female	λ, M-band negative	Sclerotic bone lesions	PTH↑	Ca^{2+}^ALP↑	No	Low back pain	Chemotherapy, but regimen not mentioned	Resolved	Divakar 2022 [13]
4	71/ Male	IgG-λ	Diffuse osteosclerosis	None	ALP ↑	Yes	Progressive exertional dyspnea and weight loss	CP/Vincristine/ Prednisolone	Resolved	Kuo 1995 [17]
5	51/ Female	IgA-λ	Diffuse osteosclerosis	None	Ca^{2+}^	Yes	Lethargy and low back pain	MP/Allopurinol	Several readmissions, humerus fracture	McCluggage 1995 [21]
6	60/ Female	IgG-κ	Diffuse osteosclerosis	None	/	No	Flu-like illness	Vincristine/ doxorubicin/and DEX	Improved	Lacy 1997 [3]
7	53/ Male	Urine λ light chain, serum M-protein not detected	Diffuse osteosclerosis	None	Ca^{2+}^	Yes	Back pain	First MP, later CP; Pamidronate	Improved by Pamidronate	Lacy 1997 [3]
8	50/ Female	IgA-λ	Diffuse osteosclerosis	None	ALP ↑, Ca^{2+}^	Yes	Dyspnea on exertion	MP	Resolved	Lacy 1997 [3]
9	74/ Female	IgA-λ, -	Diffuse osteosclerosis	PTH↑	ALP↑, β-CTX↑	No	Back pain, weakness, and weight loss	MP	Improved	Mulleman 2004 [19]
10	44/ Female	IgG-κ	Diffuse osteosclerosis, VEGF↑	None	β-CTX^, OCN ↑, ALP ↑	Yes	Right shoulder pain	Melphalan/Stem cell transplant	Improved	Vignon 2018 [15]
11	50/ Male	IgG-κ	Diffuse osteosclerosis, VEGF↑	None	β-CTX^, ALP^	Yes	Shortness of breath and frequent nosebleeds	Bortezomib/ Lenalidomide/DEX	Good	Terao 2019 [20]
12	70/ Male	Ig G-λ	Diffuse osteosclerosis	PTH ↑	P1NP ↑, OCN ↑, β-CTX^	Yes	Bilateral rib pain	Daratumumab/ DEX/Lenalidomide	Improved	Our case

"/": The test was not performed, or the results were not reported.; "^": data within the normal reference range. None: Meet none of the above criteria.
MP: Melphalan and Prednisone; CP: Cyclophosphamide; DEX: Dexamethasone.
Mandatory major criteria 1. Polyneuropathy; 2. Monoclonal plasma cell-proliferative disorder.
Other major criteria: 1. Castleman disease; 2. Sclerotic bone lesions; 3. Vascular endothelial growth factor (VEGF) elevation
Minor criteria: 1. Organomegaly; 2. Extravascular volume overload; 3. Endocrinopathy; 4. Skin changes; 5. Papilledema.

Table 3
Comparison of Prevalence of symptoms between non-POMES osteosclerotic MM and POMES.

Prevalence	non-POMEs osteosclerotic MM	POEMS	POEMS criteria
Polyneuropathy	~0	100 %	Mandatory major
Organomegaly	~0	45–85 %	Minor criteria
Endocrinopathy	Elevation of PTH in some cases	67–84 %, usual hypogonadism	Minor criteria
Monoclonal proteinemia	100 %	100 %	Mandatory major
Skin changes	~0	~50 %, 68–89 %	Minor criteria
Castleman disease	~0	11–25 %	Other major criteria
Sclerotic bone lesions	25 % Sclerotic bone lesions; 75 % diffused osteosclerosis	95 % Sclerotic bone lesions	Other major criteria
Elevation of VEGF	Usually not measured, elevated in ~ 16.6 %	VEGF > 200 pg/mL: 68 % Sensitivity, 95 % Specificity for POEMS Diagnosis	Other major criteria
Extravascular volume overload	~0	29–87 %	Minor criteria
Papilledema	~0	29–64 %	Minor criteria
Thrombocytosis/ polycythemia	~0	Thrombocytosis 54–88 %; polycythemia 12–19 %	Minor criteria

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CRediT authorship contribution statement

Zi-Yan Li: Writing – original draft, Investigation. **Jiang-Jie Chen:** Formal analysis. **Fang-Ying Lu:** Formal analysis. **Mei-Fu Gan:** Formal analysis, Data curation. **Tao-Hsin Tung:** Writing – review & editing, Methodology. **Dun Hong:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

- The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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