

Osteolytic-variant POEMS syndrome: an uncommon presentation of “osteosclerotic” myeloma

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Abstract Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome, a form of osteosclerotic myeloma, is a multisystem disease related to a monoclonal plasma cell proliferative disorder. Osseous lesions are most commonly sclerotic on radiographs and computed tomography (CT), demonstrate low T1 and T2 signal intensity on magnetic resonance imaging (MRI), and have variable degrees of avidity on positron emission tomography (PET) imaging using 18-fluorodeoxyglucose (¹⁸F-FDG). We present three cases of POEMS syndrome manifesting as osteolytic lesions with indolent features, including well-defined thin sclerotic rims, no cortical disruption or periosteal reaction, no associated soft-tissue mass, and a periarticular location, all features that could lead to misinterpretation as benign bone lesions. We also report increased T1 signal and diffuse solid enhancement of these lesions on MRI, features previously unreported. POEMS syndrome should not be discounted as a diagnostic consideration in the setting of osteolytic lesions with non-aggressive imaging characteristics on radiographs or CT, especially in the presence of other supportive clinical features.

Keywords POEMS syndrome · Radiography · CT · PET-CT · Osteosclerotic myeloma

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Introduction

Features of what would later become known as polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome were first described by Crow in 1956 [1] and again by Fukase et al. in 1969 [2]. The POEMS acronym was coined in 1980 by Bardwick et al. [3], but does not reference several additional associations, including sclerotic bones lesions, Castleman disease, edema, papilledema, and thrombocytosis [4].

There is no single test to diagnose POEMS syndrome. Instead, the diagnosis is contingent on a combination of clinical and laboratory features including the presence of polyneuropathy, monoclonal plasma cell proliferative disorder, and at least one additional major or minor criterion [5]. Major criteria include sclerotic bone lesions, Castleman disease, and elevated levels of vascular endothelial growth factor (VEGF). Minor criteria include organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis/polycythemia [4, 6–8]. These diagnostic criteria were affirmed by the International Myeloma Working Group [6].

The pathogenesis of POEMS syndrome is not well understood, but the role of vascular endothelial growth factor in the disease course is becoming increasingly recognized [8]. POEMS syndrome differs clinically from myeloma with paraneoplastic manifestations by its better long-term survival and younger age at onset [7].

Although the presence of osseous lesions is not strictly required for the diagnosis of POEMS syndrome, their presence in the disease is characteristic, with a prevalence reported to be as high as 97% [4]. The existing literature largely describes the radiographic appearance as sclerotic lesions or mixed lytic and sclerotic lesions. Purely osteolytic lesions (or lytic lesions with only a thin sclerotic margin) are the exception rather than the norm [9, 10]. Computed tomography (CT) findings mirror those

of radiography, but CT provides more detail and has been shown to be much more sensitive in the detection of osseous lesions [11].

POEMS syndrome osseous lesions generally demonstrate increased radiotracer uptake on technetium-99m bone scintigraphy, thought to be related to cortical sclerosis and periosteal new bone formation [12, 13]. Positron emission tomography (PET) using 18-fluorodeoxyglucose (^{18}F -FDG) imaging shows increased metabolic activity [11, 14–18]. Bone scintigraphy and PET imaging have been shown to be complementary to radiographic and CT evaluation, as the modalities often detect different lesions [14, 19]. Although increased ^{18}F -FDG PET activity has been demonstrated in both lytic and sclerotic lesions [18], higher levels of FDG activity are typically present in lytic lesions, or the lytic component of mixed lesions, compared with purely sclerotic lesions [15, 16]. The magnetic resonance imaging (MRI) appearance of POEMS-related osseous lesions is what would be expected for the given CT appearance. Osteosclerotic lesions are characterized by low T1 and T2 signal intensity, whereas osteolytic lesions (or the lytic component of sclerotic lesions) are characterized by increased T2 signal intensity. Contrast enhancement has been reported as variably present [11, 16, 20]. The purpose of this report is to describe a series of three cases of POEMS syndrome that did not present with classic osteosclerotic lesions, but rather osteolytic lesions with imaging features suggesting a benign etiology. This case series brings attention to an atypical variant of POEMS syndrome that is nevertheless important to recognize in arriving at an accurate imaging diagnosis.

Case studies

Case 1

A 67-year-old man presented with erectile dysfunction, fatigue, exercise intolerance, weakness, and positive sensory symptoms involving the lower limbs followed by the upper limbs, imbalance with recurrent falls, lower extremity pitting edema, skin hyperpigmentation, hypertrichosis, nail changes, and cutaneous angiomas. Laboratory evaluation revealed thrombocytosis; renal dysfunction; low testosterone; elevated thyroid-stimulating hormone, corticotropin, prolactin, and VEGF; and an immunoglobulin-G (IgG) lambda monoclonal gammopathy. There was no record of anemia or hypercalcemia. Electromyography (EMG) revealed severe diffuse sensorimotor polyradiculoneuropathy with features of demyelination and axonal loss. Bone marrow biopsy showed borderline plasma cell involvement at approximately 5%.

Radiographic skeletal survey revealed five lesions within the thoracolumbar spine, left iliac bone, and right supra-acetabular iliac bone (Fig. 1a). These lesions were osteolytic and exhibited well-circumscribed thin sclerotic margins. ^{18}F -FDG PET/CT revealed marked FDG activity, with all but one lesion having a maximum standard uptake value (SUV_{max}) measuring greater than 18.0 (Fig. 1b). MRI showed these lesions to well-circumscribed, T1 hyperintense to skeletal muscle, T2 hyperintense, and solidly enhancing (Fig. 1c). There was no evidence of associated soft-tissue mass, cortical disruption, or periosteal reaction on any of the imaging modalities. Biopsy of a left iliac lesion confirmed a lambda light chain restricted plasma cell neoplasm, confirming the diagnosis of POEMS syndrome.

Case 2

A 36-year-old man presented with progressive symptoms of ascending lower extremity dysesthesias, imbalance with frequent falls, erectile dysfunction, and weakness. Much of the initial workup was performed at an outside institution and was remarkable for an IgG lambda monoclonal gammopathy. EMG revealed severe, length-dependent, motor-predominant peripheral neuropathy. Aside from the history of erectile dysfunction, endocrine workup was unremarkable. Bone marrow biopsy was negative for marrow involvement by plasma cells. There was no record of anemia, hypercalcemia, or renal dysfunction.

Upon referral to our institution, a previously identified osteolytic lesion in the right iliac bone was biopsied under CT guidance. This lesion was positive for a plasmacytic neoplasm. Staging radiographic skeletal survey revealed osteolytic lesions with well-circumscribed thin sclerotic margins in the right iliac bone, left intertrochanteric femur, and left inferior pubic ramus (Fig. 2). The CT portion of an ^{18}F -FDG PET/CT examination (Fig. 2) confirmed these findings and revealed no associated soft-tissue mass or cortical disruption. These lesions were hypermetabolic on FDG PET/CT, with SUV_{max} ranging from 4.1 to 5.4 (Fig. 2).

Case 3

A 50-year-old man presented with bilateral foot swelling, lower extremity dysesthesias, gait difficulties, skin discoloration, gynecomastia, and cherry angiomas. Laboratory evaluation revealed elevated corticotropin. There was no monoclonal gammopathy and VEGF was normal. Bone marrow biopsy was normal. There was no record of anemia, hypercalcemia or renal dysfunction. EMG revealed a predominantly axonal sensorimotor peripheral neuropathy with demyelinating features.

Radiographic skeletal survey revealed a subtle lucent lesion in the left supra-acetabular iliac bone (Fig. 3a), which

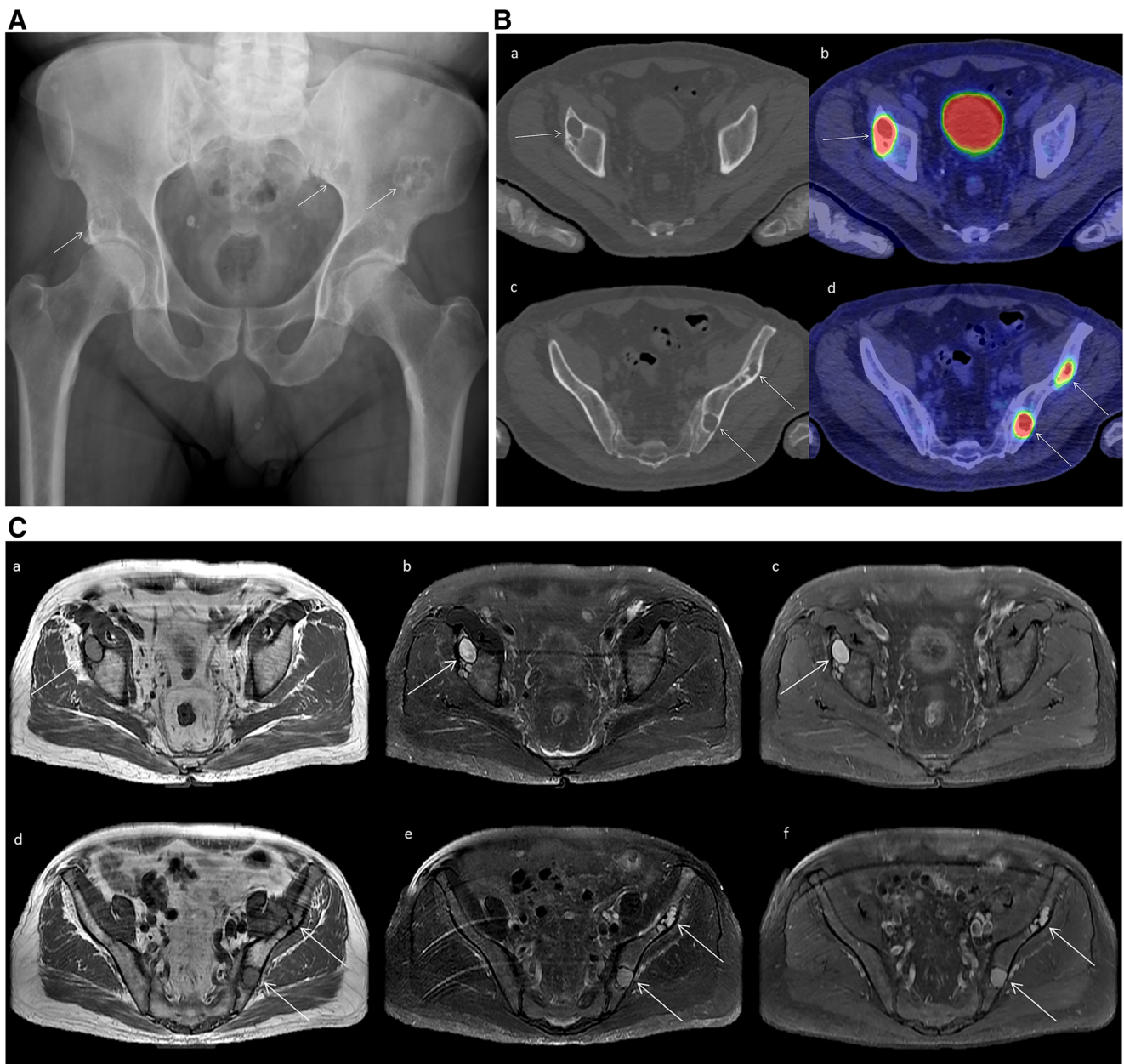


Fig. 1 Fig. 1. A 67-year-old man with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. **a** Frontal radiograph of the pelvis demonstrates osteolytic lesions with thin sclerotic margins in the right supra-acetabular iliac bone, left iliac wing, and posterior left iliac bone adjacent to the sacroiliac joint (*arrows*). **b** Axial CT (*a, c*) and fused PET/CT (*b, d*) images show FDG-avid

osteolytic lesions with thin sclerotic rims (*arrows*). **c** Axial T1-weighted (*a, d*), fat-saturated T2-weighted (*b, e*), and fat-saturated T1-weighted post-gadolinium (*c, f*) images show well-circumscribed T1 hyperintense, T2 hyperintense, enhancing lesions in both iliac bones (*arrows*)

was better characterized by FDG PET/CT (Fig. 3b) as a well-defined osteolytic lesion with thin sclerotic margin. No other lesions were identified. The supra-acetabular iliac lesion was FDG-avid with SUV_{max} of 9.5 (Fig. 3b). On MRI, the lesion was T1-hyperintense, T2-hyperintense, and showed solid enhancement after the administration of gadolinium (Fig. 3c). MRI also showed enlargement and increased T2 signal of the lumbosacral plexus and proximal sciatic nerves

(Fig. 3c). Biopsy of the lesion confirmed lambda immunoglobulin-restricted plasmacytoma.

Discussion

The POEMS syndrome is a rare multisystem disease characterized by polyneuropathy, endocrinopathy, organomegaly, M

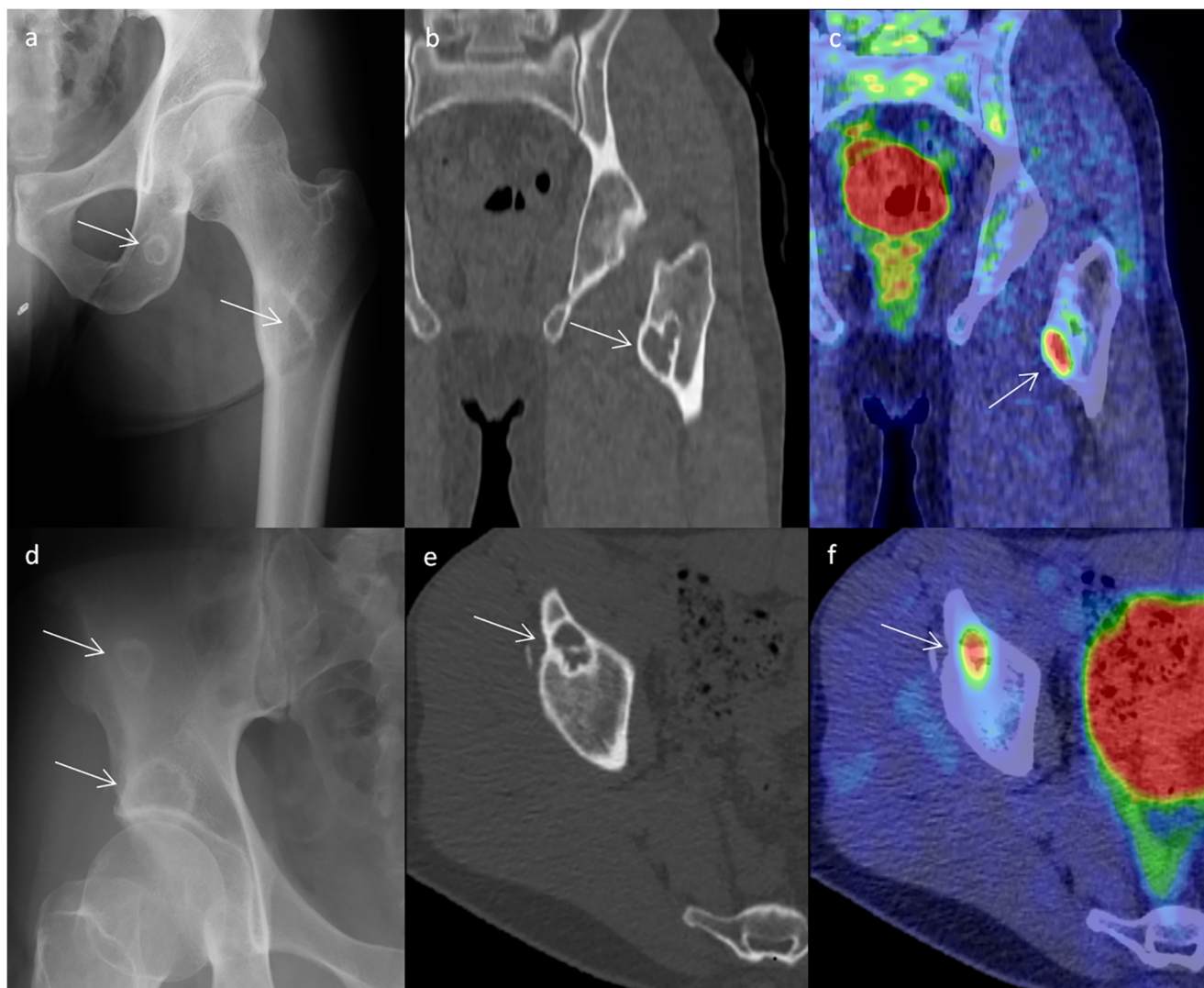


Fig. 2 A 36-year-old man with POEMS syndrome. **a, d** Frontal radiographs of both hips demonstrate osteolytic lesions with sclerotic margins in the right iliac bone, left intertrochanteric femur, and left

inferior pubic ramus, seen to better advantage on **b, e** CT. **c** Coronal and **f** axial fused PET/CT images show the lesions to be FDG-avid

protein, and skin changes. Several additional associated features not described by the POEMS acronym include sclerotic bones lesions, Castleman disease, edema, papilledema, and thrombocytosis [3, 4].

Osseous lesions are characteristic of the disease, with prevalence on radiography reported to be as high as 97% [4, 21–24]. The radiographic appearance has been variable in the literature, reflecting the variable expression of the disease. Purely sclerotic lesions are the most common manifestation, occurring in 41–56% of cases, and for this reason, the disease has historically been referred to as osteosclerotic myeloma. Osteolytic lesions are reported to occur in 0–13% of cases, and mixed lytic and sclerotic lesions in 31–59% of cases [4, 21, 22].

Computed tomography findings reflect the radiographic findings, although Glazebrook and colleagues found radiographic skeletal survey to be insensitive relative to CT, with

a 36% false-negative rate, likely because of the frequently small size of lesions. In that study, every patient ($n = 24$) with recently diagnosed POEMS syndrome had at least one sclerotic lesion on CT [11]. Seventy-five percent of patients had at least 5 small lesions measuring less than 1 cm each. These findings are similar to those reported by Shibuya et al., who found that 68% of lesions measured less than 1 cm in their cohort [19]. Some larger sclerotic lesions in the Glazebrook series demonstrated a lytic center, but only one patient had true osteolytic lesions. Similarly, Shi and colleagues reported osteolytic lesions in 4.2% of patients in their 2016 study [25]. Other studies examining the CT appearance of POEMS lesions cite higher frequencies of osteolytic lesions, even as high as 15.8% [26] to 17.9% of patients [15].

We present three cases of POEMS syndrome consisting of osteolytic lesions that feature well-defined sclerotic margins,

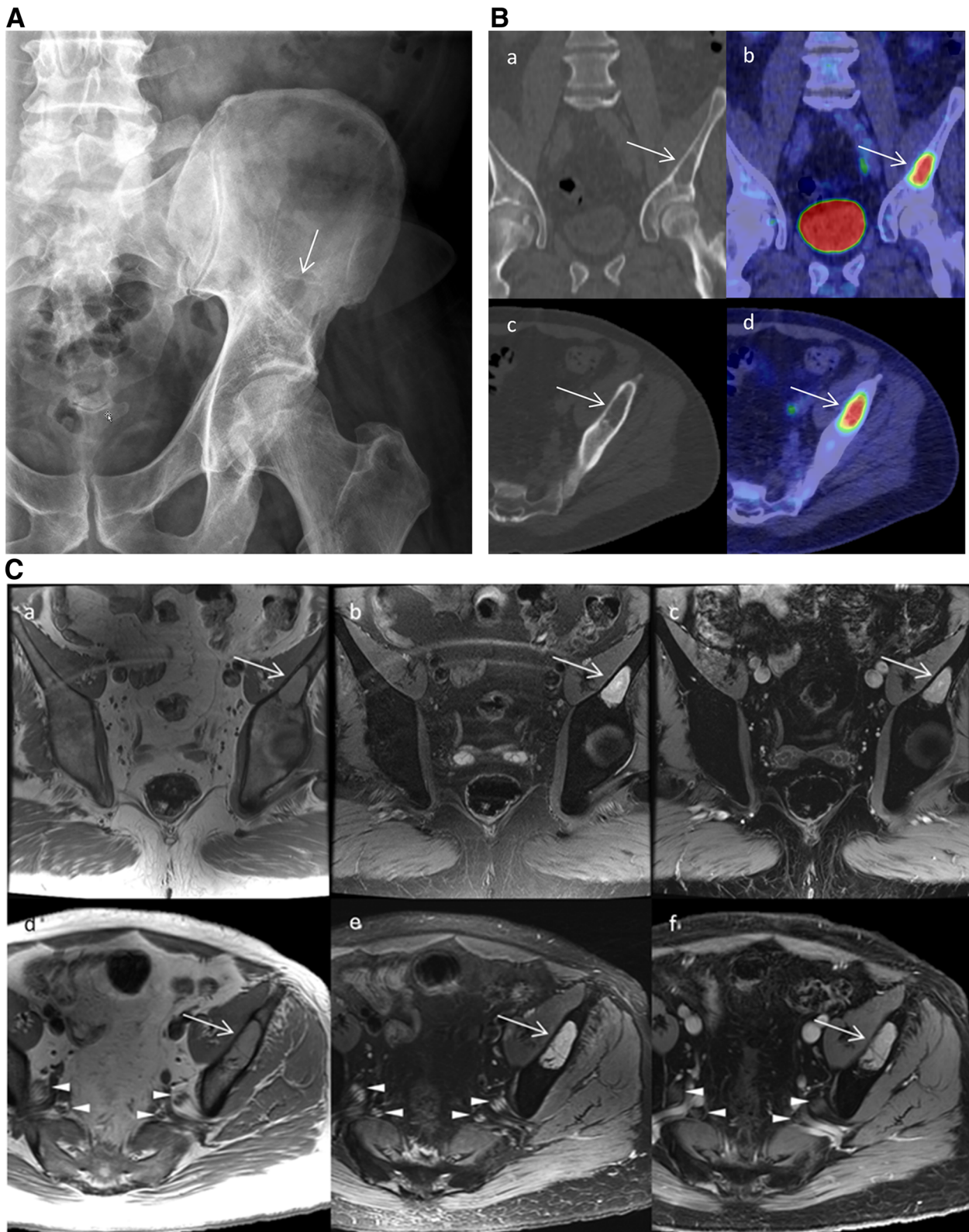


Fig. 3 A 50-year-old man with POEMS syndrome. **a** Frontal radiograph of the left hip shows a subtle lucency in the left supra-acetabular iliac bone (*arrow*). **b** Coronal (*a*) and axial (*c*) CT images better characterize the radiographic finding as an osteolytic lesion with a thin sclerotic margin (*arrow*). Fused PET/CT images (coronal [*b*] and axial [*d*]) demonstrate elevated FDG uptake within this lesion (*arrow*). **c** Coronal

oblique and axial T1-weighted (*a, d*), fat-saturated T2-weighted (*b, e*), and fat-saturated post-gadolinium spoiled gradient (SPGR; *c, f*) images demonstrate the lesion to be T1 hyperintense, T2 hyperintense, and enhancing (*arrows*). MRI also showed the lumbosacral plexus and sciatic nerves to be diffusely enlarged, with increased T2 signal and no significant enhancement (*arrowheads*)

periarticular location, and no cortical disruption or periostitis. These imaging features may mimic several benign osseous lesions, including unicameral bone cyst, fibrous dysplasia, and degenerative subchondral cysts (geodes). These cases highlight that in the appropriate clinical setting, it is important not to discount the possibility of POEMS syndrome simply based on a non-aggressive radiographic and/or CT appearance of osseous lesions. Although osseous lesions are not required to make a diagnosis of POEMS syndrome, the presence of osteosclerotic lesions is one of several possible major criteria. Given the frequency of osteolytic lesions in POEMS syndrome, and rare cases where POEMS patients may present with only lytic lesions, there may be a need to update the diagnostic criteria for POEMS syndrome to include both osteolytic and osteosclerotic lesions.

^{18}F -FDG PET/CT has been found to be useful in the evaluation of patients with POEMS syndrome. In a prospective review of 90 patients, Pan et al. demonstrated a correlation between the degree of metabolic activity and the CT appearance of osseous lesions. Osteolytic lesions (25 out of 140 patients) demonstrated a higher SUV_{max} (average SUV_{max} 10.36) than sclerotic lesions (50 of 140 patients; average SUV_{max} 4.51). Mixed lesions (65 out of 140 patients) demonstrated an average SUV_{max} of 7.52 [15]. Similar findings were observed by Shi et al., who reported on a single patient with multiple different types of osseous lesions. Although there was only mildly increased ^{18}F -FDG activity in sclerotic or mixed lytic and sclerotic lesions (SUV_{max} 3.5), there was markedly elevated ^{18}F -FDG activity in a single large lytic lesion (SUV_{max} 22.0) [16]. In the Glazebrook series, increased FDG uptake was often seen within the lucent center of larger sclerotic lesions, and less commonly within the sclerotic rim [11]. Lack of significant FDG activity can be seen in smaller lesions owing to a partial volume averaging effect, or in previously treated lesions. It has been suggested that lesions < 1 cm in size may be poorly FDG-avid, whereas untreated lesions larger than 2 cm should always be FDG-avid [11, 15].

Our cases corroborate the presence of elevated FDG activity (SUV_{max} range 4.1–18.7) within osteolytic POEMS lesions. Further, these cases highlight how increased FDG activity on PET/CT can lead to a diagnosis of malignancy, despite a relatively indolent appearance on radiographs and CT. It is important to note, however, that several benign osseous lesions may also be FDG-avid, including fibrous dysplasia and Langerhans cell histiocytosis. These may also be multifocal [27]. As previously detailed, FDG PET/CT can also help to facilitate histopathological diagnosis by demonstrating lesions with the high rates of metabolic activity to target for biopsy [14].

One of the first reports describing the MRI appearance of osseous POEMS lesions detailed a patient with numerous osteosclerotic lesions on radiographs with corresponding low T1 and T2 signal intensity on MRI. There was a thin rim of increased T2 signal intensity around a larger lesion [20]. Neither the lesions nor the rim demonstrated contrast

enhancement, although enhancement of such a rim has been described separately [11]. Shi and colleagues published a review of 22 patients with POEMS syndrome evaluated by MRI in which they detailed increased T2 signal within lytic POEMS lesions, or within the lytic component of mixed lesions [16].

Both cases evaluated by MRI in our series showed T2 hyperintensity, concordant with previous reports of osteolytic POEMS lesions. Interestingly, these lesions showed T1 signal intensity above that of adjacent skeletal muscle, a finding that has not been previously reported. Greater numbers of lesions evaluated by MRI will be needed to validate if relative T1 hyperintensity is a useful discriminating feature. The presence of solid diffuse enhancement seen in our two patients on MRI has also not been previously reported, but is not surprising given the nature of these lesions. One of our patients exhibited neural enlargement and T2 hyperintensity of the lumbosacral plexus and proximal sciatic nerves, findings that can be seen with chronic inflammatory demyelinating polyneuropathy (CIDP) [20]. Because the neuropathy in POEMS syndrome is similar to that of CIDP [8, 28], if these nerve abnormalities are present on MRI, they can be supportive of the diagnosis of POEMS syndrome, although the findings do not distinguish between the two.

Conclusions

Osteolytic POEMS syndrome lesions are infrequent and may have a relatively non-aggressive appearance on radiographs and CT. ^{18}F -FDG PET/CT can be helpful in these lesions by demonstrating elevated FDG activity. T1 hyperintensity, T2 hyperintensity, and solid diffuse enhancement can be seen on MRI. Often, a multimodality imaging approach is needed in these patients. Importantly, POEMS syndrome should not be discounted as a diagnostic consideration in the setting of osteolytic lesions with non-aggressive imaging characteristics on radiographs or CT, especially in the presence of other supportive clinical features.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research.

Disclosure None of the authors have any relevant financial or non-financial relationships to report.

References

- Crow RS. Peripheral neuritis in myelomatosis. *Br Med J*. 1956;2(4996):802–4.
- Fukase M, Kakimatsu T, Nishitani H. Report of a case of solitary plasmacytoma in the abdomen presenting with polyneuropathy and endocrine disorders [abstract]. *Clin Neurol*. 1969;9:657.
- Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. *Medicine (Baltimore)*. 1980;59(4):311–22.
- Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therau TM, Larson DR, et al. POEMS syndrome: definitions and long-term outcome. *Blood*. 2003;101(7):2496–506.
- Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2015;90(10):951–62.
- Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538–48.
- Dispenzieri A. POEMS syndrome. *Blood Rev*. 2007;21(6):285–99.
- Dispenzieri A. POEMS syndrome: 2011 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2011;86(7):591–601.
- Forestier A, Lefebvre G, Leroy X, Husson J, Gay J, Leleu X, et al. Osteolytic lesion with thick sclerotic walls and demyelinating polyneuropathy. *J Rheumatol*. 2012;39(11):2175–6.
- Rahul K, Handa N, Chandrashekara SH, Usha T, Singh A. An atypical case of POEMS syndrome with an osteolytic bone lesion. *J Clin Diagn Res*. 2015;9(6):XD01–2.
- Glazebrook K, Guerra Bonilla FL, Johnson A, Leng S, Dispenzieri A. Computed tomography assessment of bone lesions in patients with POEMS syndrome. *Eur Radiol*. 2015;25(2):497–504.
- Bessler W, Antonucci F, Stamm B, Stuckmann G, Vollrath T. Case report 646. POEMS syndrome. *Skeletal Radiol*. 1991;20(3):212–5.
- Narvaez JA, Majos C, Narvaez J, Valls C, Fernandez-Cabrera L. POEMS syndrome: unusual radiographic, scintigraphic and CT features. *Eur Radiol*. 1998;8(1):134–6.
- Alberti MA, Martinez-Yelamos S, Fernandez A, Vidaller A, Narvaez JA, Cano LM, et al. 18F-FDG PET/CT in the evaluation of POEMS syndrome. *Eur J Radiol*. 2010;76(2):180–2.
- Pan Q, Li J, Li F, Zhou D, Zhu Z. Characterizing POEMS syndrome with 18F-FDG PET/CT. *J Nucl Med*. 2015;56(9):1334–7.
- Shi XF, Hu SD, Li JM, Luo XF, Long ZB, Zhu Y, et al. Multimodal imaging and clinical characteristics of bone lesions in POEMS syndrome. *Int J Clin Exp Med*. 2015;8(5):7467–76.
- An Y, Yoon J, Hong S, Joh C, Yoon S. 18F-FDG PET/CT in POEMS syndrome. *Nucl Med Mol Imaging*. 2007;41(1):66–7.
- Montoriol PF, Cachin F, Michel JL, Soubrier M. Two more cases of evaluation of POEMS syndrome using 18-FDG PET/CT. *Eur J Radiol*. 2011;80(3):861–4.
- Shibuya K, Misawa S, Horikoshi T, Kanai K, Iose S, Nasu S, et al. Detection of bone lesions by CT in POEMS syndrome. *Intern Med*. 2011;50(13):1393–6.
- Chong ST, Beasley HS, Daffner RH. POEMS syndrome: radiographic appearance with MRI correlation. *Skeletal Radiol*. 2006;35(9):690–5.
- Nakanishi T, Sobue I, Toyokura Y, Nishitani H, Kuroiwa Y, Satoyoshi E, et al. The Crow-Fukase syndrome: a study of 102 cases in Japan. *Neurology*. 1984;34(6):712–20.
- Soubrier MJ, Dubost JJ, Sauvezie BJ. POEMS syndrome: a study of 25 cases and a review of the literature. French Study Group on POEMS syndrome. *Am J Med*. 1994;97(6):543–53.
- Li J, Zhou DB, Huang Z, Jiao L, Duan MH, Zhang W, et al. Clinical characteristics and long-term outcome of patients with POEMS syndrome in China. *Ann Hematol*. 2011;90(7):819–26.
- Cui RT, Huang XS, Shi Q, Tian CL, Liu JX, Pu CQ. POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome in China. *Intern Med J*. 2011;41(6):481–5.
- Shi X, Hu S, Luo X, Luo M, You H, Zhu Y, et al. CT characteristics in 24 patients with POEMS syndrome. *Acta Radiol*. 2016;57(1):51–57.
- Wang F, Huang X, Zhang Y, Li J, Zhou D, Jin Z. Bone lesions in Chinese POEMS syndrome patients: imaging characteristics and clinical implications. *PeerJ*. 2016;4:e2294.
- Costelloe CM, Chuang HH, Madewell JE. FDG PET/CT of primary bone tumors. *AJR Am J Roentgenol*. 2014;202(6):W521–31.
- Mauermann ML, Sorenson EJ, Dispenzieri A, Mandrekar J, Suarez GA, Dyck PJ, et al. Uniform demyelination and more severe axonal loss distinguish POEMS syndrome from CIDP. *J Neurol Neurosurg Psychiatry*. 2012;83(5):480–6.