Diagnostic pitfalls of nonsecretory myeloma manifesting as multiple foci of periosseous plasmacytomas

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Abstract

Nonsecretory myeloma, which comprises 1–5% of all myelomas, is a variant of plasma cell myeloma. It is defined as symptomatic myeloma without detectable monoclonal immunoglobulin levels on serum or urine immunofixation electrophoresis. Here, we report two cases of nonsecretory plasma cell myeloma that manifested as multi-foci periosseous plasmacytomas. Due to the inability to detect monoclonal immunoglobulin on serum or urine immunofixation electrophoresis and the lack of evidence of clonal plasma cells in the bone marrow, it was difficult to establish an early, accurate diagnosis. Misdiagnosing or mislabeling symptomatic myeloma patients with plasmacytoma results in the delay of their systemic treatment. Therefore, comprehensive imaging studies, the detection of free light chains, and histopathological confirmation from different sites and time points are necessary.

Keywords: Multiple myeloma; nonsecretory myeloma; osteolytic lesions; plasma cell disorders; plasmacytoma

1. Introduction

According to the World Health Organization (WHO) classification system, the diagnosis of symptomatic myeloma is based on the pathological proof of plasmacytoma or the presence of bone marrow clonal plasma cells and end-organ damage, such as anemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis, or recurrent infections. For patients that fulfill the above criteria, a minimum level of monoclonal proteins (M-protein) or percentage of bone marrow plasma cells is no longer necessary. Symptomatic myeloma without detectable monoclonal immunoglobulin (Ig) levels on serum or urine immunofixation electrophoresis characterizes nonsecretory myeloma by the WHO definition. This diagnosis constitutes 1–5% of all myeloma patients.1 By immunohistochemical analysis, 85% of patients with cytoplasmic M-protein are nonsecretors and the other 15% are nonproducers. Meanwhile, the detection of free light chains (FLC) has made true nonproducers even rarer than before.2 The proposed pathophysiology includes the diminished capacity to synthesize immunoglobulins, defects in secretion, and the rapid degradation of intracellular immunoglobulins.3 The manifestations of nonsecretory myeloma are similar to those of the secretory types, with the exceptions of improved hemoglobin levels, a less aggressive clinical evolution, lower incidences of renal insufficiency and hypercalcemia, improved Ig levels, and the decreased occurrence of osteolytic lesions.4 The survival outcomes of nonsecretory myeloma patients are comparable to secretors.5 However, because uneven distribution and slow infiltration are not unusual in patients with myeloma, periosseous plasmacytomas...
with multiple foci is classified as symptomatic myeloma. The pitfalls of misdiagnosing nonsecretory myeloma with the manifestations of multi-foci periosseous plasmacytomas are further discussed.

2. Case Report

2.1. Case 1

An 84-year-old man had been previously diagnosed with diabetes mellitus, hypertension, and chronic obstructive pulmonary disease several years prior. He visited our orthopedic outpatient department complaining of painful swelling of his right forearm. Radiography showed a pathological fracture and an osteolytic lesion measuring 2 cm in diameter on the right distal radius (Fig. 1A). Further studies were conducted because malignancy was highly suspected. Computed tomography (CT) of the abdomen revealed lytic bone lesions with multiple foci. A whole-body bone scan demonstrated abnormal uptake into the thoracic spine at the T8, T11, and T12 vertebral bodies, the lumbar spine at the L1, L2, and L3 vertebral bodies, the left acetabulum, and the left posterior 11th rib and suspicious focal uptake into the anterior surface of the sacrum. Magnetic resonance imaging (MRI) revealed a bulging soft-tissue mass, measuring approximately 18 mm in size, with central necrosis and a pathological fracture in the right distal radial shaft. A CT scan of the chest showed multiple osteolytic lesions on the T-spine without any suspicious lung masses. The patient’s tumor markers were all within normal limits. The patient received curettage of the tumor mass and open reduction and internal fixation surgery. Pathological examination of the tumor demonstrated diffuse infiltration of large neoplastic cells with eccentric nuclei and prominent nucleoli. Immunohistochemical studies were positive for vimentin and CD138, focally positive for CD56, and negative for leukocyte common antigen, CD3, CD20, S100, and cytokeratin. Based on these results, plasma cell disorder was suspected and further studies were performed. The patient’s laboratory data are summarized in Table 1. A low IgM level (45.5 mg/dL; reference range: 46–304 mg/dL), a high serum free light chain ratio (2.29; reference range: 0.26–1.65), and a high beta2-microglobulin level (1457 mg/L; reference range: 670–1310 mg/L) were noted as abnormal findings. However, M-proteins were not detected on serum or urine protein immunofixation electrophoresis. A bone marrow biopsy from the bilateral posterior superior iliac crests showed no evidence of clonal plasma cells. In order to reconfirm these results, a CT-guided biopsy of the mass lesion at the L3 vertebral body was performed, and the pathological results

Table 1
Serological parameters used in the diagnoses of the two reported cases.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Reference range</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>13.5–17.8 g/dL</td>
<td>13.8</td>
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<tr>
<td>Creatine</td>
<td>0.7–1.5 mg/dL</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.4–8.4 g/dL</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Globulin</td>
<td>2.3–3.5 gm/dL</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>8.4–10.6 mg/dL</td>
<td>9.3</td>
<td>9.6</td>
</tr>
<tr>
<td>IgG</td>
<td>751–560 mg/dL</td>
<td>1330</td>
<td>1030.0</td>
</tr>
<tr>
<td>IgA</td>
<td>82–453 mg/dL</td>
<td>445</td>
<td>287.0</td>
</tr>
<tr>
<td>IgM</td>
<td>46–304 mg/dL</td>
<td>45.5*</td>
<td>115.0</td>
</tr>
<tr>
<td>Kappa light chain</td>
<td>542–248 mg/dL</td>
<td>874</td>
<td>1000</td>
</tr>
<tr>
<td>Lambda light chain</td>
<td>293–725 mg/dL</td>
<td>382</td>
<td>404</td>
</tr>
<tr>
<td>Serum free light-chain ratio</td>
<td>0.26–1.65</td>
<td>2.29*</td>
<td>2.47*</td>
</tr>
<tr>
<td>Beta2-microglobulin</td>
<td>670–1310 µg/L</td>
<td>1457*</td>
<td>956.1</td>
</tr>
</tbody>
</table>

* abnormal data.

Fig. 1. Images of case 1. (A) One pure osteolytic lesion is clearly visible at the right distal radius with a pathologic fracture (black arrow) (plain film). (B) The magnetic resonance image of lumbar spine reveals discrete lesions at the T11, T12, L2 and L3 vertebral bodies, as indicated by the white arrows.
demonstrated diffuse infiltration of immature plasma cells with frequent conspicuous nucleoli that were positive for CD138 staining and negative for CD3 and CD20 immunostaining. The tumor showed kappa light chain restriction and a single-dot cytoplasmic staining pattern (Fig. 2), which are consistent with plasmacytoma. Also, MRI of the lumbar spine revealed several noncontiguous bone lesions on the T7, T11, T12, L2, and L3 vertebrae and the left iliac bone (Fig. 1B). Based on these findings, systemic chemotherapy with melphalan and prednisolone was prescribed to this patient.

2.2. Case 2

A 32-year-old man was healthy until two months prior to admission. He found a painful mass over his anterior sternum. He visited another hospital where a chest CT scan identified a tumor arising from the distal sternum, but a definite diagnosis could not be made. Therefore, he was admitted to our hospital for additional examinations. A bone scan identified a single osteolytic lesion on the distal sternal body. All of the patient’s tumor markers were within normal range. A tiny hepatic hemangioma was observed on abdominal CT. He received a CT-guided biopsy of the sternal mass, and the pathological results showed malignant cells that were positive for synaptophysin, focally positive for cytokeratin, and negative for leukocyte common antigen, chromogranin, and CD5. These tumor cells were also positive for CD138 on polyclonal kappa and lambda immunostaining. The initial diagnosis indicated either a malignant neuroendocrine tumor or plasmacytoma. For further confirmation, the laboratory data were checked, as shown in Table 1. A high serum free light chain ratio (2.47; reference range: 0.26–1.65) was revealed. Later, an open biopsy was performed. The pathological results demonstrated diffuse tumor cells with prominent nucleoli; plasmablast was considered the most likely diagnosis by the morphological results alone. Immunostaining was positive for vimentin and negative for CD20, CD3, PAX-5, CD30, synaptophysin, CD56, S-100, and actin. The patient was focally positive for CD138 and kappa immunostaining, but the lambda staining was negative. The initial false positive results for synaptophysin and lambda immunostaining might have been caused by overstaining the initial, small specimens. Furthermore, the possibility of a neuroendocrine tumor was excluded by a negative CD56 stain. However, neither serum nor urine immunofixation electrophoresis identified a monoclonal band or clonal plasma cells infiltrating the bone marrow. Finally, a positron emission tomography (PET)-CT scan demonstrated fluorodeoxyglucose (FDG)-avid lesions on the sternal body and the right 4th rib (Fig. 3). The right rib lesion had never been identified in the previous bone scan or chest CT. Due to the diagnosis of nonsecretory myeloma, no additional invasive procedures were arranged for diagnosing the right rib lesion. Later, the patient received systemic treatment with thalidomide and dexamethasone instead of curative radiotherapy.

![Fig. 2. In case 1, the L3-mass demonstrates diffuse immature plasma cells with enlarged eccentric nucleoli. Kappa immunostaining shows a dot-like cytoplasmic staining pattern, as indicated by the black arrow. (400× magnification).](image)

![Fig. 3. Images of case 2. Positron emission tomography-computed tomography scan demonstrating fluorodeoxyglucose-avid lesions in (A) the sternal body [Maximal Standard Uptake Value, 7.4] and (B) the lateral right 4th rib [Maximal Standard Uptake Value, 15.2].](image)
3. Discussion

In the largest study on periosseous plasmacytomas performed by the Surveillance, Epidemiology, and End-Results (SEER) program of the National Cancer Institute, only 2.1% of patients (24 of 1164 persons) presented with more than two lesions from 1973–2005. Patients with more than two lesions had significantly lower 5-year survival rates than those with a single lesion (36% vs. 59%; p = 0.032). The diagnosis of multiple plasmacytomas in soft tissues is acceptable, and local treatment with radiation or a separate excision is usually adequate. However, multi-foci periosseous plasmacytoma is regarded as an uncommon presentation of symptomatic myeloma because myelomas tend to infiltrate slowly and are sometimes unevenly distributed. The treatment for myeloma follows the policy of watching and waiting for indolent nature. Systemic immunochemotherapy is reserved for symptomatic myeloma patients; radiotherapy generally only plays a palliative role. Furthermore, misdiagnosing symptomatic myeloma patients with plasmacytoma might delay their frontline systemic treatments. However, the line between asymptomatic and symptomatic myeloma is sometimes blurred, and therefore the limitations of diagnostic tools must be considered.

By definition, the diagnosis of solitary plasmacytoma of the bone is based on excluding other lesions by MRI of the axial skeleton. However, a PET scan of the whole body has the highest sensitivity. The sensitivity of PET, MRI, CT, and plain film scans are 86.3%, 83.3%, 70.4%, and 47.4%, respectively. PET, MRI, and CT scans are optional for determining myeloma, as recommended by the National Comprehensive Cancer Network Guidelines. Although PET imaging was not recommended for routine usage by the International Myeloma Working Group (IMWG) in 2009, it is still a unique tool for the evaluation of nonsecretory myeloma, as shown by case 2 of this study. When cost efficiency is a consideration, MRI seems the most appropriate for diagnosing patients suspected of having nonsecretory myeloma. However, PET is still helpful in some circumstances, such as when negative or equivocal findings are found on an MRI screening. Whenever plasmacytoma is confirmed by histology, either the periosseous or soft tissue variety, or whenever M-proteins are detected, an examination of the other lesions present is necessary. MRI or PET-CT scans are strongly recommended.

The sensitivity levels for protein electrophoresis are about 1–2 g/L, 150–500 mg/L for immunofixation electrophoresis, and less than 1 mg/L for serum FLC immunoassays. Because high levels are often detected on serum FLC in two-thirds of nonsecretory myeloma patients, in addition to extreme FLC ratios, true nonsecretors are very rare and the term “hyposecretors” might be more a suitable descriptor. Serum FLC analysis is recommended for making the diagnosis of nonsecretory myeloma, accessing prognosis, and monitoring a patient’s response to treatment, as recommended by IMWG. The patients described here were both hyposecretors with abnormally high FLC ratios, which is compatible with the clonal kappa plasma cells that were found on immunostaining. In case 1, the low IgM level is indicative of clonal plasma disorder.

Plasma cell myeloma usually involves bones that show active bone marrow hematopoiesis, such as the vertebrae, ribs, skull, and pelvis. The posterior superior iliac crest is the most common site for bone marrow studies, and unilateral biopsy is usually adequate for homogenous infiltration. These two cases described here presented with multi-focal lesions, but there was no evidence of involvement of the bilateral iliac crest. In addition to providing evidence of infiltration into the soft tissue, pathological specimens are also important for differentiating the subtypes of nonsecretory myeloma by immunohistochemical staining, flow cytometry, immunofluorescence, or electron microscopy. In case 1, immunostaining demonstrated dot-like cytoplasmic staining of the kappa light chain. The intracellular aggregation of nonsecreted immunoglobulins is possibly due to the involvement of Russell bodies, which are derived from disruption of the endoplasmic reticulum-associated degradation pathway. In a previous study, a high percentage of t(11;14) in nonsecretory myeloma was reported. However, because cytogenetic studies were unavailable in our hospital (including fluorescence in situ hybridization), we have no information about the cytogenetic statuses of these two patients.

Furthermore, accurate staging is important for prognosis. The staging systems for myeloma include the Durie-Salmon staging system (DSS), the revised Durie-Salmon Plus staging system (DSS-plus), and the International Staging system (ISS). Most end-organ functions are evaluated under the DSS system, which classifies patients with solitary bone lesion as stage 1 and advanced lytic bone lesions as stage 3. The revised DSS-plus takes the results of MRI and/or PET scans into account. Stages 1, 2, and 3 indicate that patients have less than 5, 5–20, or more than 20 focal lesions, respectively, and the assigned stage is in direct proportion to the tumor burden carried by the patient. The ISS is based on serum beta-2 microglobulin and albumin levels. Thirty-six percent of patients are classified as different stages when evaluated using different classification systems. Both of the patients reported here were ISS stage 1; however, case 1 was classified as stage 3A and stage 2A by DSS and DSS-plus, respectively and case 2 was classified as stage 2A and stage 1A by DSS and DSS-plus, respectively. Because nonsecretory myeloma tends to be less involved serologically, ISS played a limited role in the diagnosis of these patients.

In conclusion, misdiagnosing or mislabeling symptomatic myeloma patients with plasmacytoma might delay their systemic treatment. Comprehensive image studies, the detection of free light chains, and histopathological confirmation at different sites and time points are necessary for diagnosing patients suspected of having plasmacytoma, especially those believed to have the nonsecretory variant.

References


