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EXPERT REVIEW

Update in the imaging study of multiple myeloma

Actualización en el estudio por imágenes del mieloma múltiple

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Abstract

Advances in the diagnosis and treatment of multiple myeloma have led to the modification of diagnostic criteria and initiation of therapy, incorporating myeloma-defining events into the CRAB criteria. Imaging has evolved from radiographic study to whole-body techniques, including low-dose computed tomography (LDCT), 18F-fluorodeoxyglucose positron emission tomography (PET/CT), and whole-body magnetic resonance imaging (MRI), being an important part of the evaluation of myeloma precursors, the staging of the disease and the evaluation of treatment response. LDCT has greater sensitivity in the detection of bone lesions compared to the radiographic study, MRI has the greatest sensitivity in the evaluation of bone marrow infiltration and PET/CT is the method of choice in the evaluation of treatment response. The radiologist must know the morphological characteristics of the lesions originating from myeloma in the different techniques and recognize the advantages and disadvantages of the different types of study.

Keywords: *Multiple myeloma. Whole-body magnetic resonance imaging. Full body CT scan. Positron emission tomography.*

Resumen

Los avances en el diagnóstico y el tratamiento del mieloma múltiple han llevado a la modificación de los criterios diagnósticos y de inicio de terapia, incorporándose a los criterios CRAB los eventos definitorios de mieloma. Las imágenes han evolucionado desde el estudio radiográfico hasta las modalidades de cuerpo completo, incluyendo la tomografía computada de baja dosis (TCBD), la tomografía computada por emisión de positrones (PET/CT) con 18F-fluorodesoxiglucosa y la resonancia magnética (RM) de cuerpo completo, siendo parte importante de la evaluación de los precursores del mieloma, de la estadificación de la enfermedad y de la evaluación de la respuesta a tratamiento. La TCBD posee mayor sensibilidad en la detección de lesiones óseas en comparación con el estudio radiográfico, la RM la mayor sensibilidad en la evaluación de la infiltración de la médula ósea y la PET/CT es la modalidad de elección en la valoración de la respuesta al tratamiento. El radiólogo debe conocer las características morfológicas de las lesiones originadas del mieloma en las distintas modalidades y reconocer las ventajas y desventajas de los diferentes tipos de estudio.

Palabras clave: *Mieloma múltiple. Resonancia magnética corporal total. Tomografía computada de cuerpo completo. Tomografía computada por emisión de positrones.*

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Introduction

Multiple myeloma (MM) corresponds to the malignant infiltration and proliferation of monoclonal plasma cells in the bone marrow. This originates from precursor states, such as monoclonal gammopathy of undetermined significance and smoldering or asymptomatic myeloma, which have a risk of annual progression to active disease of approximately 1% and 10%, respectively[1].

The average age at diagnosis is between 66 and 70 years; 37% of patients are under 65 years of age, and less than 1% are under 30 years of age[2].

In an adult patient with multiple osteolytic lesions, the first diagnostic possibility is metastatic disease; in the absence of a primary neoplasm, it is MM.

Diagnostic criteria

For a long time, the diagnosis of active or symptomatic MM required the presence of target organ damage, known by the acronym CRAB (Table 1), a result of the infiltration of plasma cells or excess light chains. However, a subgroup of patients with a high risk of progression to symptomatic disease, potentially beneficiaries of early treatment and greater survival, prior to the occurrence of organ damage, was excluded from therapy. This led to the addition of three new diagnostic criteria, called myeloma-defining events (MDEs) (Table 2). Each of these events is associated with a ≥ 80% risk of developing target organ damage over 2 years.

Currently, the diagnosis of symptomatic MM requires >10% of clonal plasma cells in the bone marrow or a bone or extraosseous plasmacytoma plus a CRAB or MDE criterion.

The presence of one or more osteolytic lesions corresponds to one of the four CRAB criteria, which implies the use of images for their detection, either by radiography, low-dose computed tomography (LDCT) or positron emission tomography/computed tomography (PET/CT). In the MDEs, the detection on magnetic resonance imaging (MRI) of two or more focal lesions ≥ 5 mm[3] was incorporated as a new imaging criterion. It is possible to make the diagnosis of symptomatic MM in the absence of bone lesions, but up to 90% of patients will develop lesions during the course of their illness.

Table 1. CRAB criteria

Hypercalcemia	Serum calcium > 1 mg/dl above the normal range or > 11 mg/dl
Renal failure	Clearance < 40 ml/min or serum creatinine > 2 mg/dl
Anemia	Hemoglobin > 20 g/l below the lower limit of normal or < 100 g/l
Bone lesions	Bone lesions ≥ 1 osteolytic lesion on radiography, CT or PET/CT

Table 2. Myeloma-defining events (MDEs)

≥ 60% clonal plasma cells in bone marrow biopsy
Ratio of free light chains ≥ 100 (absolute value of the altered ≥ 100 mg/l)
1 focal lesion on MRI ≥ 5 mm

Role of imaging

Diagnosis

In a patient with suspected active MM, in the absence of sufficient criteria to confirm it, the detection of osteolytic lesions or more than one focal lesion > 5 mm on MRI allows diagnostic confirmation for the initiation of therapy.

In the study of myeloma precursors, such as solitary plasmacytoma, smoldering myeloma or high-risk monoclonal gammopathy of undetermined significance, the detection of bone lesions modifies the disease status to symptomatic MM, requiring initiation of therapy; on the other hand, the absence of lesions and other CRAB or MDE criteria prevents the initiation of unnecessary toxic treatment[4].

Staging

MM is categorized into three stages according to the Durie-Salmon classification or the *Revised International Staging System* (Table 3). The first includes the absence or presence of bone disease, in addition to serum and urinary parameters, and the second considers serum and cytogenetic parameters, without including bone evaluation[5]. The use of images in staging allows an approximation of the tumor burden: the greater the number of bone lesions, the worse the prognosis and the more advanced the stage of the disease.

Evaluation of treatment response

The heterogeneity of disease distribution in the bone marrow and the presence of extramedullary involvement in up to 10% of patients make it necessary to

Table 3. Durie-Salmon Classification and *Revised International Staging System*

Stage	Durie-Salmon	*Revised International Staging System*
I	Hemoglobin > 10 g/dl Normal serum calcium or < 10.5 mg/dl Normal bone structure or solitary plasmacytoma IgG < 5 g/dl; IgGA < 3 g/dl Urinary light chains < 4 g/24 h	β2 serum microglobulin < 3.5 mg/l Serum albumin ≥ 3.5 g/dl Standard risk chromosomal abnormalities normal LDH
II	Does not meet stage I or III criteria	Does not meet stage I or III criteria
III	Hemoglobin < 8.5 g/dl Serum calcium > 12 mg/dl > 3 osteolytic lesions IgG > 7 g/dl; IgA > 5 g/dl Urinary light chains > 12 g/24 h	β2 serum microglobulin > 5.5 mg/l and high-risk chromosomal abnormalities or elevated LDH

Ig: immunoglobulin; LDH: lactate dehydrogenase.

evaluate the disease outside the marrow or standardized biopsy sites, by means of imaging studies. For this reason, in the latest review of the International Myeloma Working Group (IMWG), in 2016, imaging response criteria were incorporated, mainly with the use of PET/CT with 18F-fluorodeoxyglucose (18F-FDG).

The complete response requires a percentage < 5% of clonal plasma cells in bone marrow aspirate, undetectable monoclonal protein in blood and urine, in addition to the resolution of extramedullary plasmacytomas if they exist; for a strict complete response, evaluation of the light chain ratio and the absence of clonal plasma cells in the marrow by immunohistochemistry, is also required. The partial and minimal response requires a ≥ 50% decrease in the sum of the product of perpendicular diameters (SPD) of the extraosseous plasmacytomas, in addition to the evaluation of monoclonal protein, plasma cell and light chain parameters. Among the criteria for progressive disease are the appearance of new focal lesions, ≥ 50% increase in SPD in more than one focal lesion compared with nadir or ≥ 50% increase in the largest diameter of a focal lesion of more than 1 cm in the short axis[6].

There are 1-2% of patients with non-secretory MM, that is, those who do not present detectable monoclonal proteins in blood or urine, in whom monitoring of the disease is carried out exclusively with imaging and bone marrow studies[7].

Suspected relapse

In patients under follow-up with the onset of symptoms or signs of relapse in laboratory studies, the appearance on images of new osteolytic lesions or extramedullary plasmacytomas, or an absolute increase in their size, are part of the criteria for disease relapse[6].

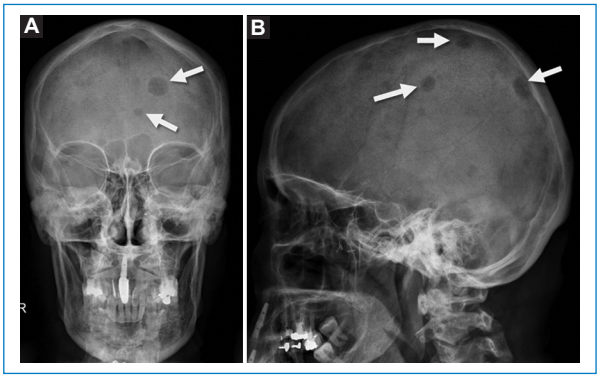

Figure 1. Anteroposterior (**A**) and lateral (**B**) skull radiographs demonstrating osteolytic lesions (arrows) with "punch-out" morphology.

Imaging methods

Radiographic study

Historically, the presence of lytic lesions was evaluated through an extensive radiographic study that included projections of the cervical, thoracic and lumbar spine, skull, thorax, pelvis, humeri and femurs, as well as images focused on symptomatic sites if they existed. For a lytic lesion to be detected on an x-ray, it requires approximately 50% bone destruction; this low sensitivity causes 30-70% of false negatives[8]. The characteristic findings of MM on radiography are osteolytic lesions with endosteal scalloping, multiple small lytic lesions grouped together with a mottled appearance, and "punched out" lytic lesions that correspond to hypodense focal lesions without a sclerotic halo[9] (Fig. 1). Characteristically, myeloma lytic lesions present little or no sclerotic reaction due to an alteration in osteoblastic

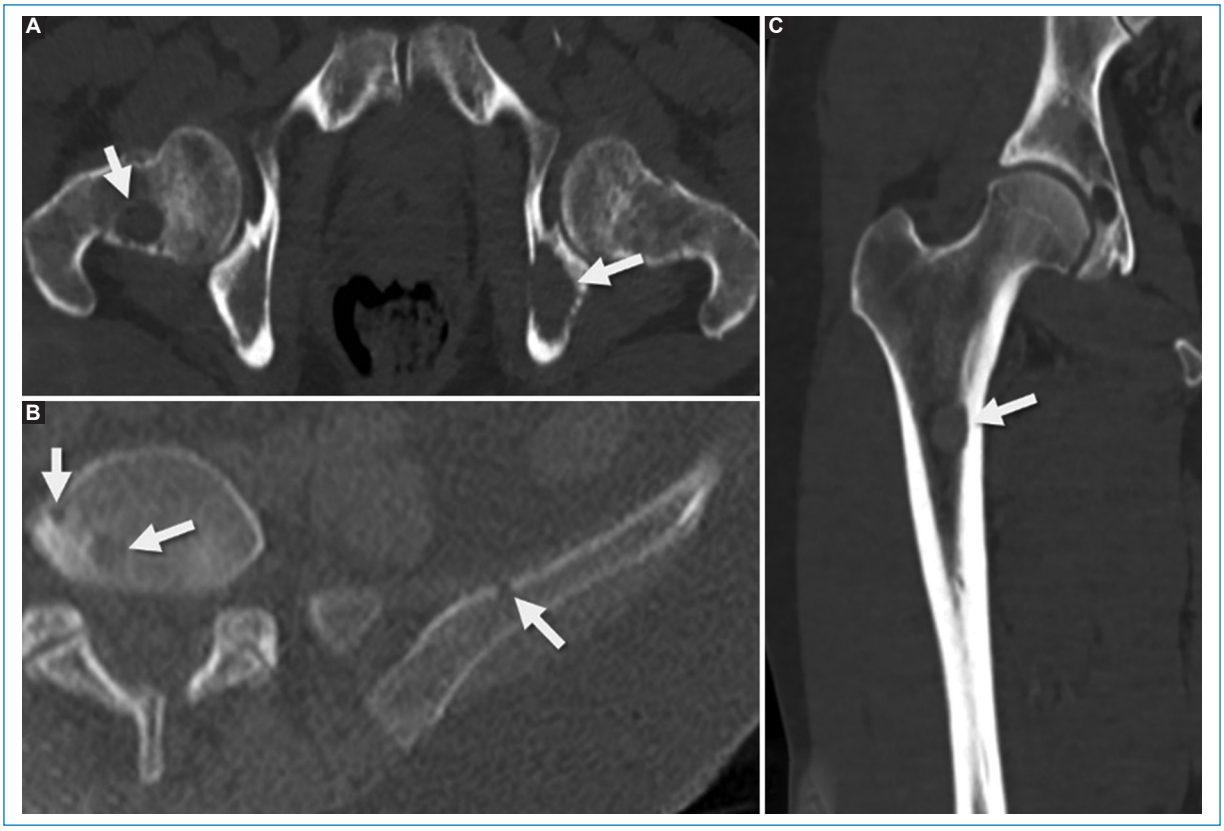

Figure 2. Axial CT of the pelvis (**A** and **B**) with osteolytic lesions without sclerotic halo (arrows) and coronal CT of the femur. **C:** with nodular focus of increased bone marrow density that determines endosteal scalloping (arrow).

activity, and therefore evaluation with bone scintigraphy is not recommended[10]. These findings are frequently associated with diffuse osteopenia and fractures, especially of the vertebral bodies, but these are not part of the diagnostic criteria for MM[3].

In addition to the low sensitivity in the detection of focal lesions, radiography is not useful in the evaluation of treatment response, since the deregulation of osteoblastic activity makes it difficult to repair the lesions, which may remain unchanged despite a favorable evolution. Currently, radiographic study is not part of the myeloma evaluation and has been replaced by new techniques; it is only indicated in places that do not have other alternatives[11].

LDCT

It has greater sensitivity than the radiographic study in the detection of bone lesions, requires less than 5%

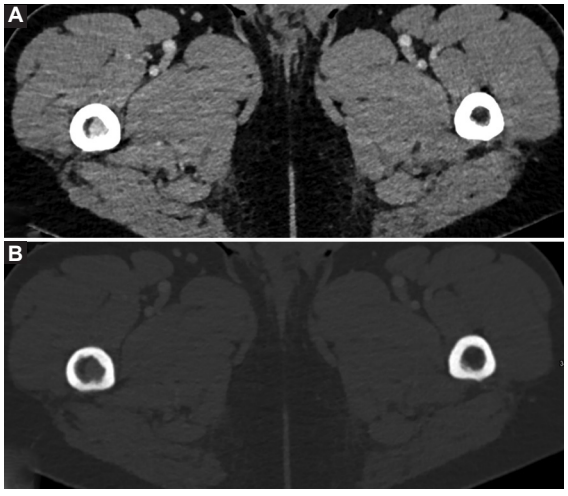

Figure 3. Axial CT of femoral shafts with soft tissue window (**A**) and bone (**B**) showing increased density of the right femoral medullary cavity, compared to the contralateral one with adipose density.

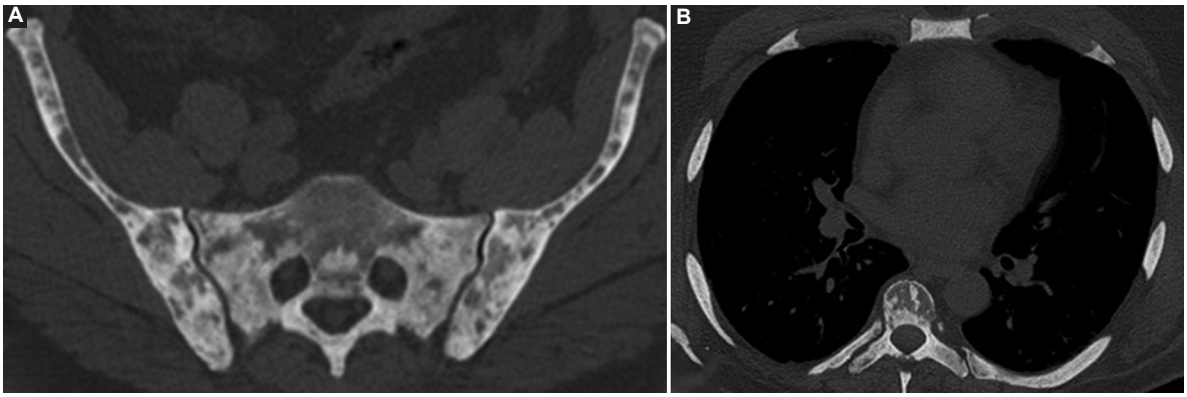

Figure 4. Axial CT of the pelvis (**A**) and thorax (**B**) with extensive heterogeneous increase in bone density in a patient with osteosclerotic myeloma.

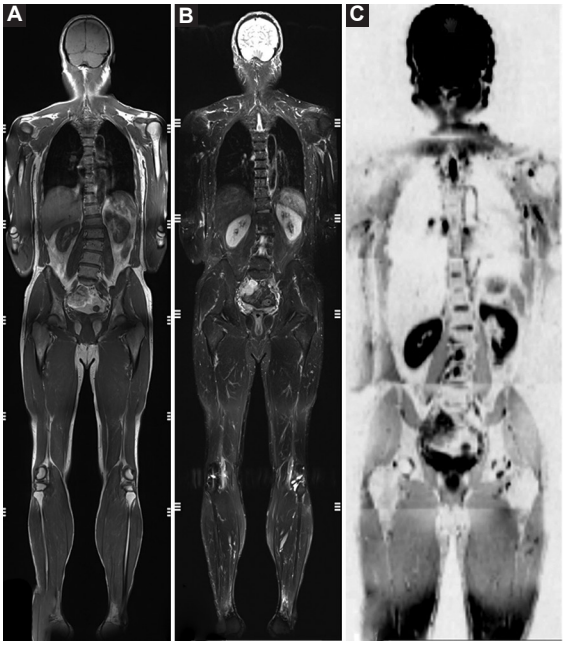

Figure 5. Whole body MRI protocol: coronal T1 whole body (**A**), coronal STIR (**B**) and coronal diffusion with inverted gray scale (**C**).

of trabecular destruction, is tolerated better and is faster, and is a cost-effective study.

Although it can detect extramedullary lesions, as it is a study usually without intravenous contrast, and not focused on the evaluation of the soft tissues, it is not the method of choice for its detection. It allows estimating the risk of fracture or instability, in addition to performing multiplanar reconstructions. Although it has a high positive predictive value (94.1%), it presents a low negative predictive value (58.8%)[12]. High spontaneous bone contrast allows reduction of radiation dose compared to studies requiring soft tissue evaluation, while preserving sufficient image quality. By decreasing tube currents and automatic dose modulation, a significant reduction in radiation dose can be achieved, to values of around 5 mSv[13].

Bone lesions on LDCT present characteristics similar to those described in radiograph: they manifest as osteolytic lesions, frequently with the absence of peripheral sclerosis, with disruption of the cortical or extramedullary soft tissue component and endosteal scalloping (in case of central location in tubular bones), and can also be associated with osteopenia and osteoporotic fractures (Fig. 2). LDCT has low sensitivity in detecting marrow infiltration without bone destruction; it can be observed as an increase in the focal or diffuse density of the spinal canal in long bones, although it is not a specific finding[14] (Fig. 3).

Osteosclerotic myeloma is a rare manifestation of the disease that presents as multiple sclerotic lesions or areas of diffuse sclerosis, frequently associated with POEMS syndrome (*Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes*)[15] (Fig. 4).

LDCT is not recommended in the evaluation of treatment response, since morphological changes are late and in many cases non-existent, despite a complete remission, due to the alteration of osteoblastic function.

Whole body MRI

MRI is the most sensitive method for detecting focal or diffuse bone marrow infiltration, prior to bone

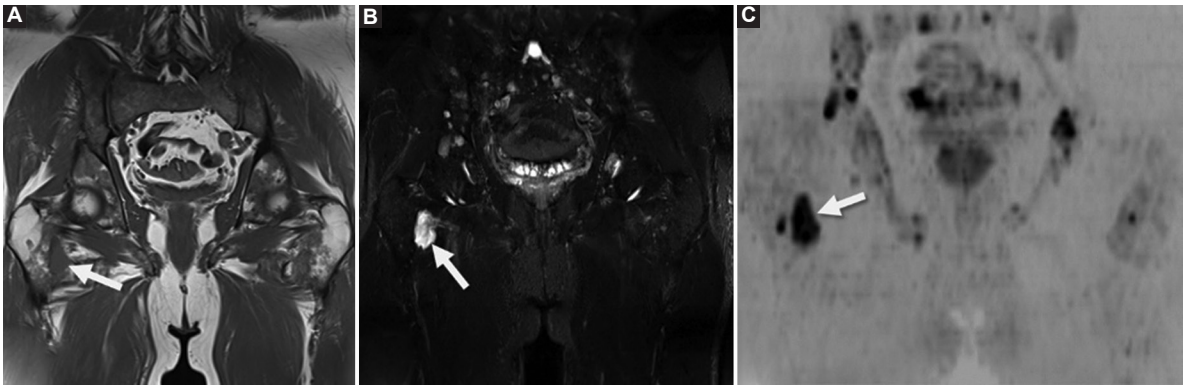

Figure 6. MRI of the pelvis, coronal T1 sequence (**A**) demonstrating multiple hypointense lesions, the dominant one in the lesser trochanter of the right femur, hyperintense on STIR (**B**), that restricts on diffusion (**C**) (arrows), compatible with foci of medullary infiltration.

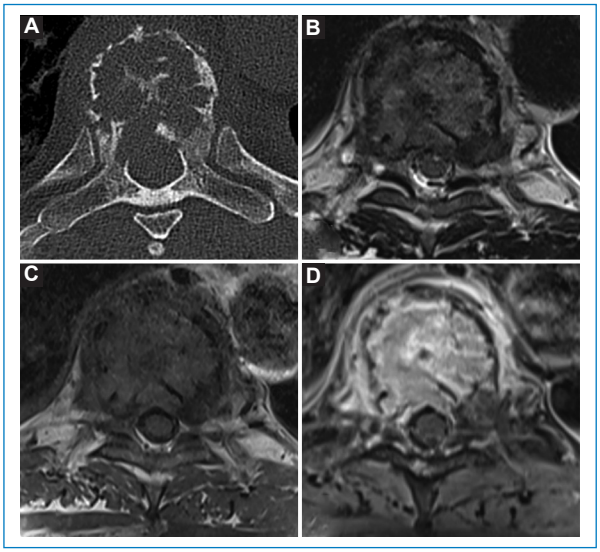

Figure 7. Axial CT of the dorsal column showing an osteolytic lesion with some dense bands that occupies a large part of the vertebral body, with *mini-brain* morphology, compatible with plasmacytoma (**A**), and MRI of the dorsal column of the same lesion, with mild T2 hypersignal and hypointense bands (**B**), isosignal compared to the muscle on T1 (**C**) and intense enhancement with intravenous contrast, with the perivertebral soft tissue component being more evident (**D**).

destruction[16]. It is the method of choice in the study of complications such as spinal compression or to distinguish between osteoporotic fracture or pathological bone fracture.

Currently, it is possible to perform whole body MRI studies in less than 60 minutes, with combinations of coronal T1, coronal STIR (*Short Tau Inversion Recovery*) and axial diffusion sequences, incorporating or not incorporating sagittal sequences, usually without the use of intravenous contrast media (Fig. 5). If a whole body study is not available, as an alternative it is possible to perform an MRI of the entire spine and pelvis, considering that the majority of the lesions are located in the axial skeleton, with the risk of omitting lesions of the appendicular skeleton, which can be found exclusively in 10% of patients[17].

MM lesions manifest with iso- to hypo- T1 signal compared to the muscle signal, moderate to high signal in T2 and T2 STIR, with diffusion restriction and contrast enhancement if used (Fig. 6). Vertebral plasmacytomas with *mini-brain*-type morphology can also be observed, corresponding to expansive lesions with hypointense curvilinear bands that resemble brain sulci[18] (Fig. 7).

There may be greater difficulty in interpretation in the case of bone marrow reconversion, whether due to anemia, chemotherapy or colony stimulators, with the yellow bone marrow being replaced by hematopoietic marrow, which presents signal characteristics close to those of the infiltrated marrow, making focal lesions less conspicuous. Repeated transfusions and bone marrow transplantation can cause iron overload and decreased marrow signal even in diffusion-weighted sequences. Normal bone marrow has low ADC values, since yellow marrow contains little water, large hydrophobic lipid cells and little irrigation, which restricts water movement, and for this reason tumor lesions may present higher levels of ADC compared to the normal marrow[12].

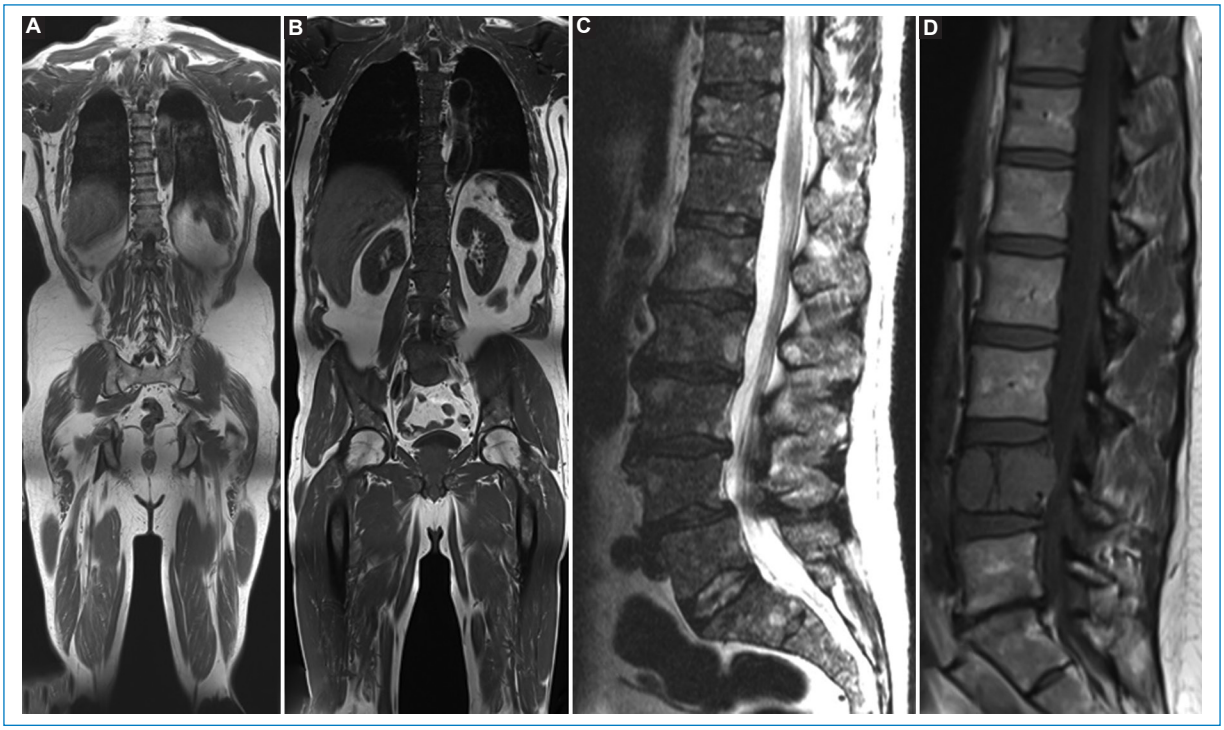

Figure 8. Coronal whole body MRI with T1 hypersignal characteristic of normal fatty bone marrow (**A**), coronal body MRI with diffuse T1 hyposignal of the spine and pelvis, and normal signal of the femoral heads, in the context of a diffuse infiltrative pattern (**B**), sagittal T2 MRI of the lumbar spine with heterogeneous "salt and pepper" signal (**C**) and sagittal T1 MRI of the lumbar spine with an expansile lesion that replaces the L4 vertebral body, hypointense, compatible with plasmacytoma and focal pattern (**D**).

Five patterns of bone marrow infiltration have been described on MRI, with the diffuse or focal pattern, or the combination of focal and diffuse, having a worse prognosis compared to the normal or "salt and pepper" pattern (Fig. 8). Despite its worse prognosis, the diffuse pattern is not considered within the diagnostic criteria in current clinical guidelines. Another poor prognostic factor is the detection of more than seven focal lesions[19].

The detection on MRI of more than one compatible focal lesion ≥ 5 mm modifies the management of the disease, allowing the initiation of therapy before the appearance of symptoms. In the case of questionable focal lesions, an isolated lesion, lesions < 5 mm, or a diffuse infiltration pattern, it is recommended to reevaluate in 3 to 6 months.

MRI has some limitations in the evaluation of treatment response. The bone marrow signal takes time to vary after the start of therapy and has less specificity in differentiating between viable disease or bone remodeling compared to PET/CT[6].

There is a proposal to standardize the evaluation of the disease and the treatment response with whole-body MRI, called MY-RADS (*Myeloma Response Assessment and Diagnosis System*), in an attempt to unify criteria[20].

In the case of evident modification of the infiltration pattern, resolution or increase in number or size of focal lesions, the interpretation of the imaging response as complete, partial or progressive is correct, but morphological stability should not be interpreted as stable disease, since there may be non-viable involvement without imaging variation[21]. The appearance of high T1 signal in the periphery or inside a focal lesion, the loss of definition and the lower impregnation reflect a partial response[12] (Fig. 9). Some studies have incorporated dynamic perfusion in the evaluation of treatment response, obtaining intensity curves, increasing study times, which is currently not included in the response criteria of clinical guidelines.

18F-FDG PET/CT

PET/CT, as it has a whole-body CT, is one of the options for the detection of lytic lesions in patients with

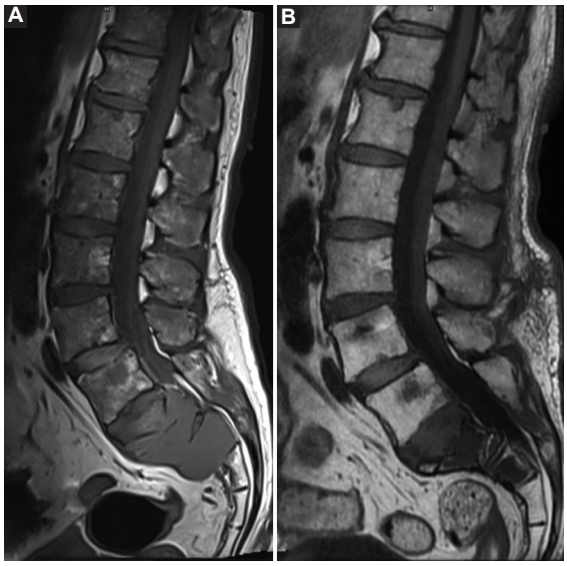

Figure 9. Pretreatment T1 sagittal MRI of the lumbar spine (**A**) showing expansive lesions in S1 and S2, isointense to the muscle, with fracture in the pathological bone of S1, in addition to a "salt and pepper" infiltrative pattern in the remaining vertebral bodies, and sagittal MRI of the lumbar spine T1 after treatment (**B**) with normalization of the T1 signal of the lumbar bone marrow, decreased signal of the sacral lesions and appearance of high T1 signal edges, compatible with complete or partial response.

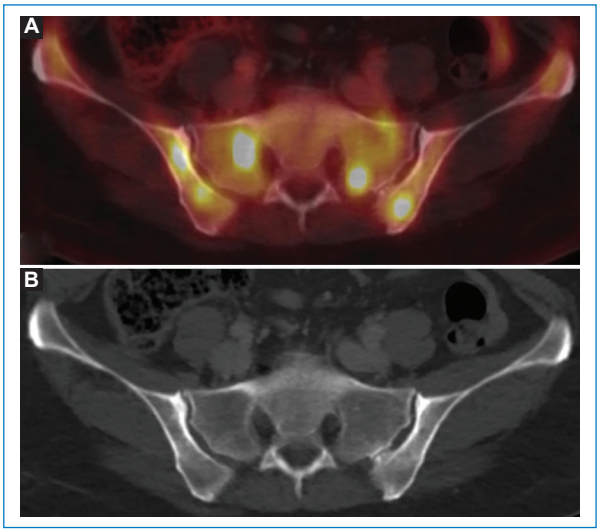

Figure 10. Axial FDG PET/CT fusion showing multiple hypermetabolic foci in the bone marrow of the pelvic bones (**A**) without representation on axial CT of the pelvis (**B**), compatible with multiple myeloma involvement.

MM precursors. Osteolytic lesions detected with this method are considered within the CRAB criteria; however, bone hypermetabolic foci, without anatomical representation, are not part of the diagnostic criteria (Fig. 10). One of the advantages of PET/CT is the ability to detect extramedullary disease, a finding with a poor prognosis, which manifests as soft tissue masses with defined margins and homogeneous impregnation (Fig. 11). Other poor prognostic factors are the detection of more than three focal lesions and hypermetabolic focal lesions with high SUV (Standardized Uptake Value) values[22].

No significant differences have been demonstrated in the sensitivity and specificity of whole body MRI and PET/CT in the detection of focal bone lesions[23]; however, MRI shows greater sensitivity in detecting diffuse spinal infiltration.

MM lesions present the characteristics already described for CT, with the addition of radiotracer uptake, which facilitates their detection. However, there are approximately 10% of patients who present focal lesions without significant metabolism (uptake similar to the background), in whom the lesions can only be detected in the anatomical evaluation (Fig. 12). These false negatives in PET have been shown to be associated with low expression of the enzyme hexokinase-2, responsible for the phosphorylation of glucose and therefore FDG. This phosphorylation retains the radiopharmaceutical inside the cell, preventing its return through the cell membrane[24].

There are focal, diffuse or mixed FDG uptake patterns that may not correlate with osteolytic lesions (Fig. 13); findings that are not considered within the diagnostic criteria, but that have a poor prognosis[25].

The advantage of PET/CT is the ability to differentiate between active and inactive lesions in the evaluation of treatment response, with metabolic changes being prior to morphological ones, in addition to the detection of extramedullary disease. Some disadvantages, in addition to its high cost, are false positives due to inflammatory processes or the use of colony stimulators, which determine diffuse uptake of the bone marrow, and the false negatives in focal lesions with little FDG avidity, which make it impossible to assess the metabolic response, only morphological parameters should be used for this.

PET/CT, despite being considered the method of choice for the evaluation of treatment response, does

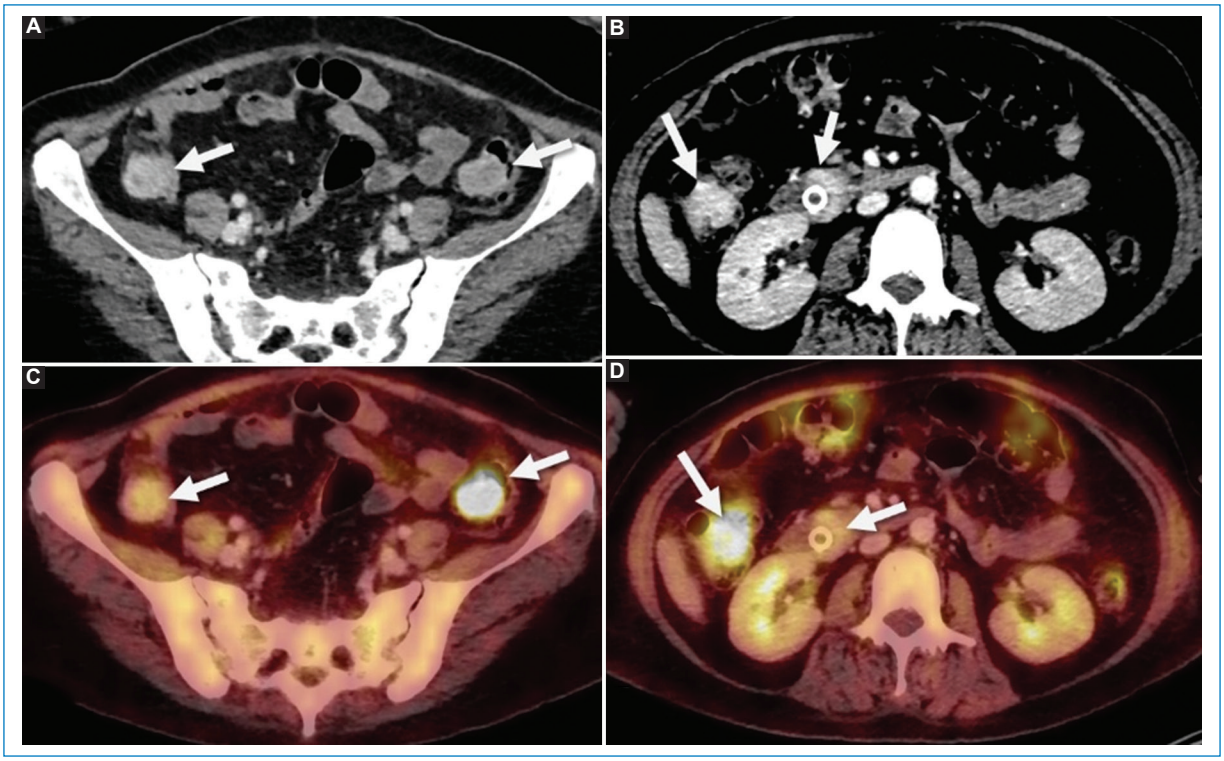

Figure 11. Contrasted CT in venous phase and FDG PET/CT axial fusion of the pelvis and abdomen that shows multiple solid, round, well-defined focal lesions with homogeneous enhancement in the peritoneum of the right iliac fossa and in the serosa of the descending colon in the left iliac fossa (arrows in **A** and **B**), a polypoid lesion in the hepatic flexure of the colon and another lesion in the duodenal papilla with a biliary *stent* (arrows in **C** and **D**), with different affinity for FDG, compatible with extramedullary plasmacytomas.

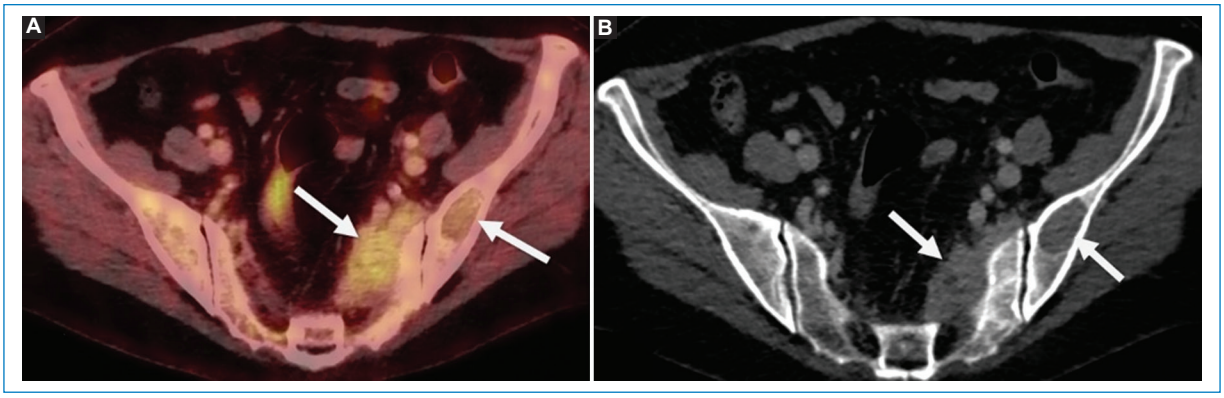

Figure 12. FDG PET/CT fusion and axial CT of the pelvis showing a left iliac osteolytic lesion and a left presacral soft tissue lesion with poor tracer uptake (arrows in **A** and **B**).

not have a standardization like the Deauville scale used in lymphoma. Some studies define the complete metabolic response as a decrease in uptake to similar or lower values compared to vascular structures or the background[26] (Fig. 14).

IMWG recommendations

The latest IMWG consensus, from 2019[27], regarding imaging of monoclonal plasma cell disorders, recommends replacing radiographic study with LDCT.

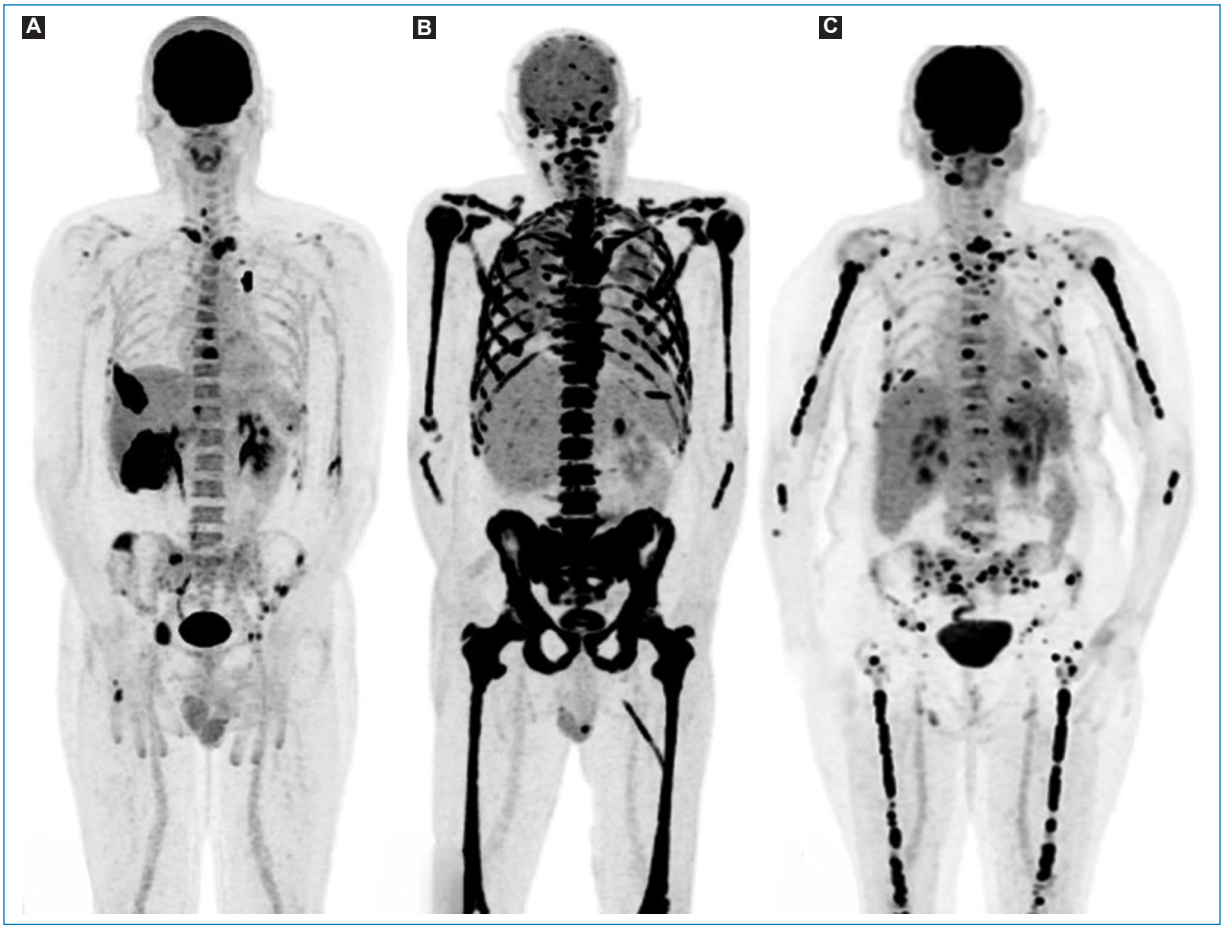

Figure 13. Bone marrow infiltration patterns on FDG PET/CT MIP image: focal pattern with multiple focal hypermetabolic lesions in pelvic bones, ribs and vertebrae (**A**), diffuse pattern with diffusely increased uptake of the axial and appendicular bone marrow (**B**) and mixed pattern with diffuse uptake of the appendicular and multifocal bone marrow in the axial skeleton (**C**).

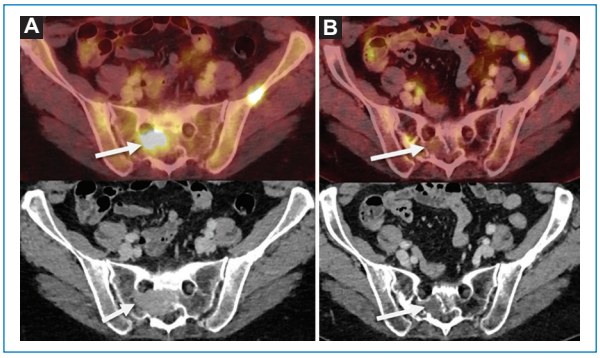

Figure 14. FDG PET/CT fusion and axial CT of venous pelvis for multiple myeloma staging (**A**) showing a sacral hypermetabolic osteolytic lesion with soft tissue density (arrows) and a non-displaced left iliac fracture. In the post-treatment control (**B**), a complete response is observed, characterized by resolution of metabolism, decreased impregnation with contrast, and appearance of sclerotic margins (arrows).

In the case of high-risk non-IgM monoclonal gammopathy of undetermined significance, it is suggested to start the study with LDCT and, if it is negative, maintain annual controls, performing imaging only in symptomatic cases; if the findings are doubtful, complement with whole-body MRI, and in positive cases, perform PET/CT.

In the study of solitary bone plasmacytoma, whole-body MRI is recommended, and in extraosseous plasmacytomas, PET/CT is recommended, with annual controls for 5 years with the same imaging method.

In the evaluation of smoldering myeloma, active MM and in case of suspected relapse recommend LDCT, and if the result is negative or inconclusive, whole-body MRI; however, to assess the treatment response, PET/CT is recommended.

Conclusion

Imaging evaluation of MM is relevant in all stages of the disease, including the study of precursors. Currently radiography, due to its low sensitivity, has been replaced by whole body studies. Although there are multiple imaging techniques and recommendations from clinical guidelines, the choice of the type of study to use will depend on the availability, accessibility and experience of the different working groups.

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Protection of people and animals. The author declares that no experiments have been carried out on humans or animals for this research.

Data confidentiality. The author declares that no patient data appear in this article.

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