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Multiple myeloma – usefulness of imaging techniques in diagnostics

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Summary

Background: Multiple myeloma is the most common generalized primary neoplasm of the bones. The cause of this pathology is the monoclonal proliferation of plasma B cells, resulting in marrow infiltration. Multiple osteolytic lesions throughout the skeleton are characteristic for multiple myeloma in radiological examinations.

Material/Methods: This analysis involved twenty-two patients with multiple myeloma, hospitalized in the period between the year 2009 and 2014 in the Hematologic Department, examined with diagnostic imaging techniques.

Results: In all cases, standard X-ray examinations were performed to visualize lytic areas. CT and MRI examinations were carried out when plain X-rays showed no abnormalities in symptomatic areas of the skeleton and to examine parts of the skeleton which cannot be accurately visualized with this method (ribs, sternum). MR imaging was used in twelve patients with neurological symptoms and in two cases it showed cord compression by multiple myeloma infiltration.

Conclusions: The preferred initial imaging method for the diagnosis and staging of multiple myeloma remains the standard X-ray examination. Although it is a conventional examination, it has its limitations. CT should be used to explain ambiguous findings in plain X-rays especially in parts of the skeleton that are difficult to visualize in the standard method, such as ribs, sternum and scapulae. CT and MRI examinations can accurately show the presence and extent of associated soft tissue changes and are useful in the planning of radiotherapy. MRI is the technique of choice for explaining reasons of neurological symptoms suggestive of cord compression. It provides accurate assessment of the level and extent of cord or nerve root compression, size of the tumor and the degree of meningeal infiltration.

MeSH Keywords: Magnetic Resonance Imaging • Multiple Myeloma • Tomography Scanners, X-Ray Computed

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Background

Multiple myeloma (myeloma multiple, MM) is the most common generalized primary neoplasm of the bones and bone marrow. Annual incidence rate of multiple myeloma in Europe is about 4.5 per 100,000 individuals. In Poland there are about 1,500 new cases annually and this number grows each year. MM constitutes about 10–15% of hematologic neoplasms and approximately 1–2% of all malignant diseases [1]. Myeloma has a twice higher incidence in African Americans compared to American and European Caucasians. Furthermore, a slight male gender predilection is visible (M:F – 1.4:1) [2]. Peak incidence is between the fifth and seventh decade of life but it may also occur at any other age: about 15% of patients are younger than 60 and less than 2% are under 40 years of age [3]. It does not occur in children and is extremely rare in people younger than 30 [4].

Multiple myeloma is a monoclonal gammopathy in which atypical plasmocytes proliferate and produce monoclonal protein (IgA, IgG, IgD, IgE and/or light chains λ and κ) leading to bone marrow infiltration. The disease develops in several stages: in some patients due to chromosomal translocation immunoglobulin gene enhancers and oncogenes

Table 1. Criteria of identifying monoclonal gammopathy according to recommendations of International Myeloma Working Group (IMWG) [1,5].

Monoclonal gammopathy of undetermined significance (MGUS)	All criteria must be fulfilled: 1) monoclonal protein concentration in serum <3 g/dL and/or <200 mg/24 h in a daily urine collection, 2) <10% of clonal plasma cells in a trephine biopsy, 3) no myeloma-related organ destruction which may result from plasmocyte proliferation (CRAB)
Smoldering multiple myeloma (SMM)	Necessary to fulfill criteria of monoclonal protein presence and plasma cells in bone marrow as in symptomatic myeloma. No myeloma-related organ impairment (CRAB)
Symptomatic myeloma	All criteria must be fulfilled: 1) monoclonal protein in serum at least 3 g/dl and/or at least 200 mg/24 h in a daily urine collection (except for nonsecretory myeloma), 2) at least 10% of plasmocytes of confirmed clonality in a trephine biopsy, 3) at least one of the symptoms of organ impairment directly related to clonal plasmocyte proliferation, so called CRAB
Solitary plasmacytoma	All criteria must be fulfilled: 1) bone or extraosseal tissue plasmocyte infiltration confirmed with biopsy, 2) lack of bone marrow infiltration, 3) normal results of bone imaging studies (except for infiltrated tissue), 4) no myeloma-related tissue impairment in the course of clonal plasmocyte proliferation (CRAB)

CRAB: a. (C – Calcium) hypercalcaemia (above 11.5 g/dL); b. (R – Renal failure) renal insufficiency and creatinine in serum >2 mg/dL; c. (A – Anemia) normocytic, normochromic anemia with hemoglobin in serum <10 g/dL or decrease of at least 2 g/dL below the reference value of a given laboratory; d. (B – Bones lesions) osteolytic lesions or pathological fractures or generalised osteopenia in X-rays; e. at least two severe infections during past 12 months; f. hyperviscosity; g. amyloidosis.

are combined which results in monoclonal gammopathy of undetermined significance (MGUS). In case of additional genetic aberrations stable MGUS may transform into plasmacytic myeloma [3]. The risk of MGUS progression into myeloma, of amyloidosis and Waldenstrom's macroglobulinemia persists throughout life and amounts to about 1% per year [2,4]. Etiology of the disease is unknown and potential causes may include ionizing radiation or chemical substances such as asbestos, and benzene exposure [3].

Myeloma can be asymptomatic as smoldering multiple myeloma (SMM), solitary plasmacytoma of bone (SPB) (isolated mass of solitary tumor) or extramedullary plasmacytoma (EP) (beyond the marrow, usually in the nasopharynx, larynx or upper respiratory tract) or be generalized. Apart from bone lesions it causes multiple organ failure, changes in the blood and nervous system [3,5]. Table 1 enumerates diagnostic criteria for MGUS, smoldering myeloma and symptomatic myeloma.

Clinically multiple myeloma may manifest in a broad spectrum of symptoms:
- bone pain – caused by bone lesions (pathological fractures, osteopenia),
- neurological symptoms (compression or lesion caused by neoplasmatic infiltration or pathological fracture of the spinal cord, roots of the spinal nerves or cranial nerves), paralysis or paresis of limbs,
- symptoms of hypercalcemia,
- impaired renal function (toxic damage, nephrocalcinosis, amyloid deposits),
- anaemia (infiltration of hematopoietic marrow with peripheral cytopenia),
- susceptibility to infections (lower concentration of normal globulins),
- haemorrhagic diathesis.

Symptoms of monoclonal gammopathy might be polyneuropathy, organomegaly, endocrinopathy and skin abnormalities comprising so called POEMS syndrome [3].

Differential diagnosis must take into consideration:
- other monoclonal gammopathies e.g. MGUS, Waldenstrom's macroglobulinemia, primary amyloidosis,
- reactive plasmacytic hyperplasia during infection,
- neoplasms metastasizing to bones e.g. breast cancer, kidney cancer, lung cancer, prostate cancer [3].

Multiple myeloma remains incurable. Symptomatic myeloma is treated with chemotherapy, autologous or allogeneic bone marrow transplantation and symptomatically. During induction and combined stage of therapy chemotherapeutics with corticosteroids are used. Patients under 65 years of age with recently diagnosed multiple myeloma undergo bone marrow transplantation (preferably autologous). Some patients require repeated transplantations [3,6,7].

Antianalgetics, bisphosphonates and rehabilitation are used as an adjunctive therapy in bone pain, whereas in multilevel skeletal fractures and osteopenia, neurosurgical, orthopedic therapy or vertebroplasty are implemented. Complications in the course of the disease and basic treatment such as anaemia, infections, and renal failure require symptomatic approach: erythropoietin, antibiotics, dialysis [3].

In solitary plasmacytoma, radiotherapy or surgical operation is the treatment of choice. Smoldering myeloma does not require treatment up to a point of developing marrow lesions [8].

Aim

Diagnostic imaging of multiple myeloma involves bone lesions detection in radiographic examinations or potential extraosseus plasmocytoma manifestations. Estimation of lytic lesions quantity allows to assess the extent of the disease and to choose a proper treatment regimen, therefore the aim of this report is to describe the basic multiple myeloma imaging techniques.

Material and Methods

A retrospective analysis of imaging studies from Provincial Specialized Hospital in Rzeszow between the year 2009 and 2014 was conducted. The study group comprised 22 patients: 14 females, 8 males aged 54 to 85 years (the average age was 63), hospitalized, diagnosed, and treated for multiple myeloma in the local Hematologic Department in the years 2009–2014.

During multiple hospitalizations several types of radiological diagnostic imaging were performed in the abovementioned group: standard bone X-rays (in all cases), computed tomography (CT) bone scans (12 cases), CT of other regions depending on the type of symptoms (10 cases) and magnetic resonance imaging (MR) of various body locations also depending on clinical symptoms (12 cases).

Results

Members of the study group were in the fifth, sixth, seventh and eighth decade of life. Most of them suffered from stage III myeloma according to Durie-Salmon staging system (stage III – 11 cases, stage II – 7 cases, stage I – 3 cases) at the time of diagnosis. In one case of solitary plasmacytoma located in mesogastrium no other bone changes were found in the imaging.

In chosen cases (except for a patient with extraosseus manifestation) standard bone X-rays revealed myelomatous changes in bones in a form of lytic lesions with very well-defined edges, deformation of the internal lamina of compact bone, extensive osteoporotic and osteolytic changes, pathological fractures of vertebra and long bones and expansive osteolytic changes (ribs, pelvis, long bones) (Figure 1).

CT bone scans (12 cases) and CT scans of other regions, depending on the clinical manifestation (10 cases), enabled detection of focal lytic lesions, assessment of the extent of myelomatous bone changes and additionally allowed to detect a tumor in soft tissues surrounding bone destruction (Figure 2).

In the evaluated material 4 patients had a chest CT scan:

1. Before and after administering the contrast agent in order to better visualize the extent of thoracic organ infiltration by pathologic soft-tissue myelomatous mass causing bone destruction in the sternum visible in the standard bone X-ray in the lateral projection (Figure 3).
2. Due to a strong pain in the chest which turned out to result from compression fractures of numerous thoracic vertebrae.

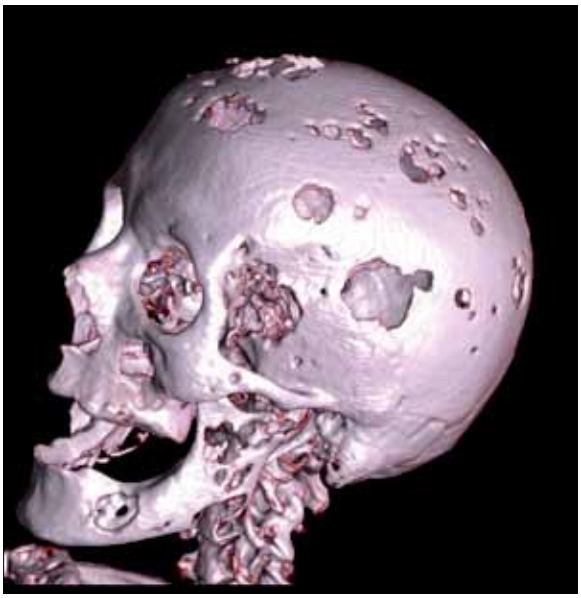

Figure 1. CT examination. 3D reconstruction. Disseminated focal lytic lesions in facial and calvarial bones

3. Due to a strong pain in the chest where the myelomatous mass embraced the 8th left rib extending into the vertebral canal and infiltrated the left lung.
4. Due to a strong bone pain of the left shoulder and right ribs caused by lytic lesions at sternal ends of the clavicles, both heads of humeri and scapuale.

In three cases the CT scan of the thoracic spine was performed, and in four cases the lumbosacral CT scan due to strong pain in those regions.

In order to better assess the extent of soft-tissue lesions projecting from destroyed bone structures in one case CT scan of the head and face was performed and orbit CT scan in another.

Multiphase CT scan of the abdomen and pelvis was performed in one patient with extraosseal manifestation of multiple myeloma.

Magnetic resonance imaging was conducted in 12 patient. In some cases it comprised two sections of the spine. In the majority of cases the cause of extended diagnostics was neurological symptoms in physical examination which suggested spinal cord involvement (Figure 4). In three cases it was MRI of the cervical spine, thoracic spine in 6 and lumbosacral spine in 7 patients. Infiltration of the spinal cord in the course of the underlying disease was confirmed in two patients. One scan did not reveal any myelomatous lesions.

Discussion

The most common location of the disease is the axial skeleton: skull, vertebral column, ribs and pelvis but any bone may be involved. One of the methods of visualization and monitoring of multiple myeloma is imaging of the skeletal system.

Currently standard bone X-rays: a lateral and anterior-posterior (AP) skull X-ray, anterior-posterior (AP) and

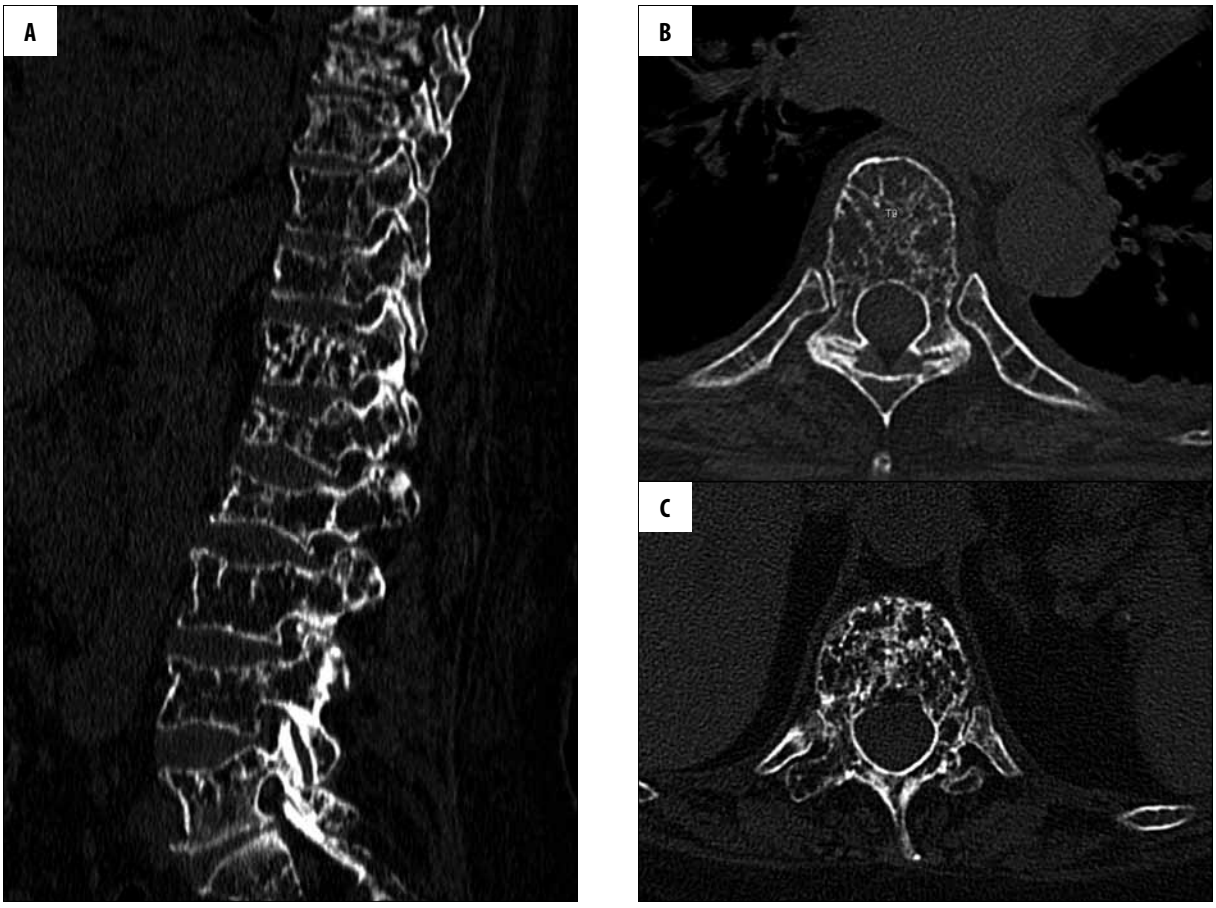

Figure 2. CT scan. (**A**) MPR reconstruction. (**B**) Axial plane at the level of T9 vertebra. (**C**) Axial plane at the level of L1 vertebra. Multiple lytic lesions throughout the spinal column, typical for disseminated myeloma with pathological fractures.

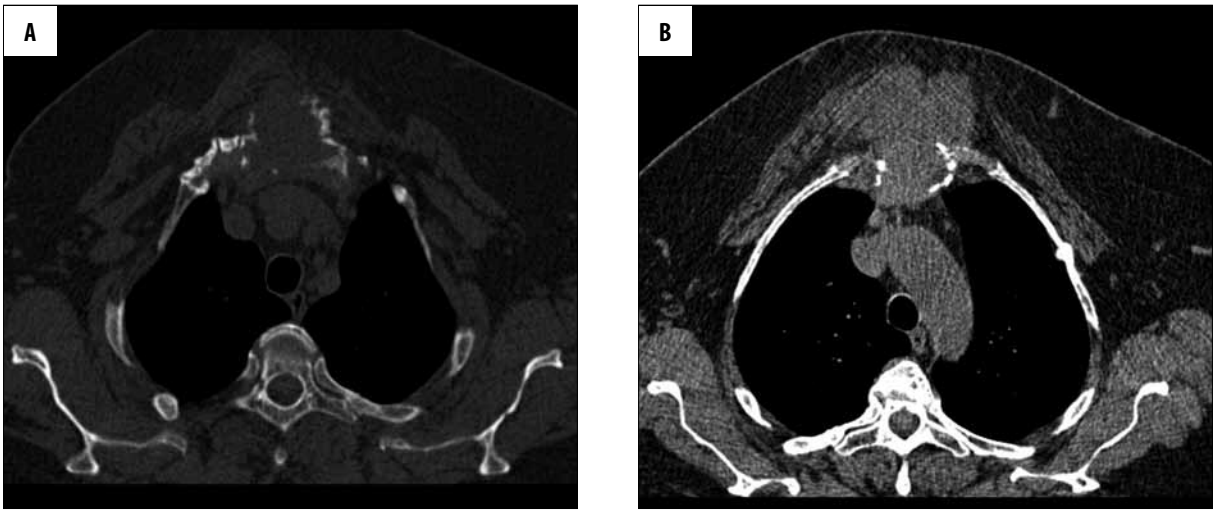

Figure 3. CT scan, axial plane. (**A**) Bone window. (**B**) Mediastinal window. Osteolytic area in the sternum filled with soft-tissue mass extending into chest structures.

lateral view of the cervical, thoracic and lumbar spine, posterior-anterior (PA) chest and anterior-posterior (AP) pelvis, femurs and humeri X-rays allow for detection of advanced lytic lesions and are used as a screening test to visualize basic pathology [9].

According to various suggestions, at least 30% or up to 50% of the cancellous bone must undergo decalcification in order to be visible in standard X-rays [2]. Therefore discovering focal osteolysis with such a method may cause certain difficulties especially when the vertebral column is concerned where due to complicated anatomy and proximity of other structures, only extremely advanced osteolysis

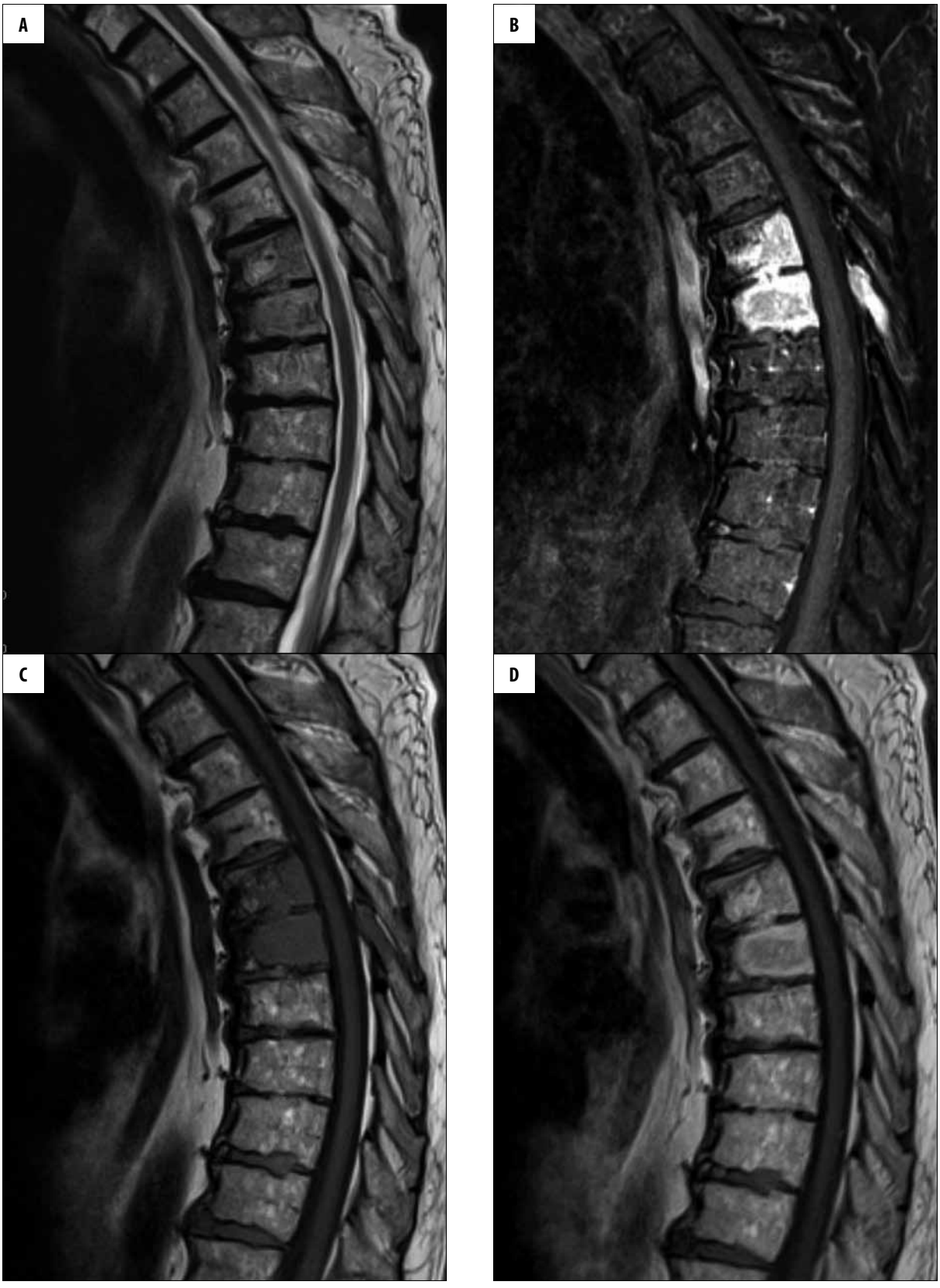

Figure 4. MRI. Myelomatous infiltration of the thoracic spine – T6 and T7 vertebrae. (**A**) T2-weighted image, sagittal plane – increased signal intensity. (**B**) T1-weighted image with fat saturation, sagittal plane – increased signal intensity. (**C**) T1-weighted image, sagittal plane – decreased signal intensity. (**D**) T1-weighted image after intravenous contrast medium administration, sagittal plane. Enhancement of pathological infiltration areas.

Table 2. Staging system according to Durie et Salmon.

Stage I (low cell mass)	All of the following: • Hb concentration >10 g/dL (6,205 mmol/l), • M-protein concentration: IgG <50 g/L, IgA <30 g/L, • serum calcium ≤5.5 mg/dL (2.75 mmol/L), • daily urinary calcium excretion <150 mg (4 mmol/L), • daily urinary light chain M-components <4 g, • normal results or single osteolytic lesions in skeletal imaging
Stage II (intermediate cell mass)	Fulfilling the criteria of neither stage I nor III
Stage III (high cell mass)	At least one of the following: • Hb concentration <8.5 g/dL (5.27 mmol/L), • M-protein concentration: IgG > 70 g/L, IgA >50 g/L, • serum calcium >5.5 mg/dL (2.75 mmol/L), • daily urinary calcium excretion >150 mg (4 mmol/L), • daily urinary light chain excretion >12 g, • multiple osteolytic lesions
Renal function: A. serum creatinine <2 mg/dL (176.9 µmol/L) B. serum creatinine >2 mg/dL (176.9 µmol/L)	

Table 3. Classification Durie/Salmon taking into consideration PET or MRI imaging [3,14].

Durie/Salmon	MRI/PET*
Stage	**Number of bone lesions**
I B	0–4 lesions of small infiltration in WB-MRI/PET
II A or B	5–20 lesions and/or moderate infiltration in WB-MRI/PET
III A or B	>20 lesions and/or extensive, massive infiltration in WB-MRI/PET

A – creatinine <2 mg/dL; B – creatinine >2 mg/dL.

with spinous processes destruction increases the probability of visualization of the lesions. Another obstacle in the diagnostics might be the coexistence of osteoporosis resulting in pathological vertebral fractures similar to those in myeloma [9].

According to the guidelines from 2005 plain X-rays should be performed in newly diagnosed patients, taking into account additional visualization of symptomatic areas [1].

Multiphase CT scan increases myeloma detection due to its high spatial resolution (especially in those parts of the skeletal system that are difficult to visualize precisely in plain X-rays e.g. sternum, ribs, scapualae). Nonetheless it still has a limited sensitivity in the early stages of myeloma which may result in underestimation of the infiltration. Due to side effects of ionizing radiation, the need to visualize the whole skeleton and limited sensitivity, standard radiography and CT scanning are not the only methods of detecting the myelomatous lesions [1].

CT scan is recommended:
– in ambiguous lytic lesions in standard bone X-rays, especially in the region of ribs, sternum, scapuale,
– in clarifying the significance of lesions in symptomatic areas of the skeleton in normal result of the X-ray,
– as a complimentary method in identifying bone lesions in negative MRI results,
– to better detect locations prone to fracture [1].

CT and MRI scans are diagnostic methods used to assess the nature and extent of soft-tissue diseases and are complementary. Moreover, it is possible to perform a tissue biopsy under CT control.

MRI is a method of choice in patients with neurological disorders suggestive of spinal cord involvement. It enables to identify the location, size of lesions and visualize the extent of compression caused by pathological structures, and potential concomitant fractures. It is used in suspected solitary plasmacytoma and in planning radiotherapy. MRI imaging allows to monitor and evaluate the response to treatment, helps to clarify whether the observed lesions are caused by complications in the course of the disease or result from the lack of response to treatment [1,2,6].

According to International Myeloma Working Group (2003), patients with bone disease are classified as "symptomatic" and require treatment even if they do not present clinical

symptoms. To evaluate the stage, prognosis and therapeutic options Durie-Salmon staging system introduced in 1975 is widely used. It takes into account the presence of focal or infiltrating lytic bone lesions in imaging studies (Table 2).

New Durie-Salmon PLUS staging system (MR/PET) described below (Table 3) takes into account detection of lytic regions using MRI or PET which decreases the risk of overlooking myelomatous lesions at their early stage and enables earlier initiation of treatment and delays progression to stage II or III [10].

European Journal of Cancer 42 (2006) recommends conducting X-rays of all flat bones or other imaging studies such as whole-body PET or spine/pelvis MRI and/or MRI of symptomatic regions to establish the diagnosis, stage of the disease and prognosis, and then introducing proper classification [10].

Conclusions

1. Bone destruction assessment is one of the components of the Durie-Salmon staging system from 1975. X-rays visualize lytic lesions in the skeletal system. Plain X-rays are one of the basic methods of diagnosing and monitoring of multiple myeloma.
2. In case of ambiguous lytic lesions in X-rays, especially in regions that are difficult to assess with this method, such as ribs, sternum or scapulae and in negative results of X-ray examination or MRI scan in clinically symptomatic regions it is advisable to perform a CT scan.
3. MRI is recommended for patients with neurological symptoms suggesting spinal cord destruction. It enables to specify the location, size of lesions and visualize the extent of compression caused by pathological structures. It also allows to detect possible concomitant fractures.
4. To assess the type and extent of soft-tissue lesions and in suspected plasmocytoma solitare, both CT and MRI are preferred.

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