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Review Article

Systemic Mastocytosis: Radiological Point of View

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Abstract. Radiological diagnosis of systemic mastocytosis (SM) can be hard to establish. This difficulty is mainly due to the variable radiological features involving many organ systems (e.g., respiratory, cardiovascular, lympho-reticular, digestive systems, and most commonly skin), and above all, to the broad spectrum of skeletal findings. Skeletal involvement is the most common and prominent imaging feature in patients with SM and represents a prognostic factor as it may entail an aggressive course of the disease. Diagnosis, largely established by histological evaluation of a bone marrow trephine biopsy, supplemented by imaging modalities such as radiography, CT, and magnetic resonance imaging, requires a team approach between the hematologist, radiologist, and pathologist. The general radiologist needs to be familiar with the imaging findings because they may be the first to suggest the correct diagnosis. The primary purpose of this review article was to equip clinicians with pertinent radiological semiotics by presenting relevant radiological features that assist early diagnosis and selection of an effective treatment.

Keywords: Systemic mastocytosis; Radiography - CT - Magnetic resonance imaging.

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Introduction. In systemic mastocytosis (SM), various organ systems, such as the lympho-reticular, respiratory, cardiovascular, gastrointestinal, and skeletal systems, may be involved, with a frequent localization in extracutaneous organs such as the liver spleen, lymph nodes, and gastrointestinal tract.[1] However, skeletal involvement is one of the most important hallmarks of SM in adults occurring in up to 90% of patients;[1,2] bone marrow involvement occurs in virtually all patients with SM.[3,4] Clinical manifestations such as organomegaly, signs of dysplasia, or impaired organ function are due to the destructive accumulation of abnormal mast cells, but mostly to the systemic effect of mast cell-derived mediators.[5] Although diagnosis is mainly based on histological evaluation of a bone marrow biopsy, radiography, CT, magnetic resonance [MR] imaging, and hybrid imaging techniques such as positron emission tomography [PET]/CT, it may be valuable to suggest the diagnosis, to differentiate advanced forms from indolent/smoldering subtypes of SM, and to define response to treatment.[6-8] The prevalence of osteoporosis was reported to range from 8% to 41%;[9,10] thus, a dual-energy x-ray absorptiometry analyzing the lumbar spine and hip should be assessed. The primary purpose of this review article was to equip clinicians with pertinent radiological semiotics by presenting relevant radiological features that assist early diagnosis and selection of an effective treatment.

Imaging Findings.

Musculoskeletal System. Radiological findings are valuable for detecting and characterizing skeletal involvement, the most common radiological change reported in SM.[1,2] There is considerable heterogeneity in the radiological features of SM-related bone involvement. The most common types of skeletal abnormalities comprise: 1) multiple focal sclerotic bone lesions affecting both the axial and appendicular skeleton (**Figure 1**, and **2**) diffuse, well-defined, roundish, sclerotic foci alternating with zones with apparently normal or reduced bone density, predominating in the axial skeleton, ribs, humerus, and femur (**Figure 2**).[11,12] However, when such lesions are radiologically identified, final diagnosis remains extremely challenging since they resemble osteopoikilosis or metastases.[13,14] Osteopoikilosis is an asymptomatic bone dysplasia characterized by numerous bony islands typically clustered around joints within the meta-epiphyseal regions, carpal and tarsal bones, the pelvic ring, and scapulae. It is usually asymptomatic, often discovered incidentally during radiographic examinations made for other reasons, and normally does not demonstrate radiotracer uptake on bone scintigraphy, contrary to what usually occurs in metastasis.[15] Diagnosis of SM is more likely by considering clinical symptoms supported by laboratory parameters (skin lesions, elevated serum tryptase levels, eosinophilia. Diffuse osteosclerosis (**Figure 3**), associated with focal sclerotic bone lesions, characterizes another presentation of SM. Diffuse osteosclerosis, which predominates in the axial skeleton, can simulate numerous other disorders such as fluorosis, renal osteodystrophy, and idiopathic myelofibrosis especially. The latter, however, is characterized by bone marrow fibrosis and extramedullary hematopoiesis.[16] Generalized osteoporosis is frequently encountered in SM; its prevalence ranged from 8% to 41%, with a higher frequency in men than women.[9,10,17,18] Its prompt diagnosis may prevent fragility fractures and decreases mortality and morbidity. In their study of 82 patients with indolent SM, Rossini et al.[18] found osteoporosis in 20% of patients (7 women and 9 men) and vertebral fractures in 21.2 % of patients (5 postmenopausal women and 12 men). The high risk of vertebral fractures in patients with indolent SM, as well as the higher prevalence of osteoporosis in the male population, was confirmed by van der Veer et al..[19] Thus, SM should be considered in patients with unexplained osteoporosis and mast cell mediators release symptoms;[9] furthermore, bone turnover markers and bone mineral density should be evaluated in such patients.[9,18] Single or multicentric osteolysis is a rare radiological finding.[11,19] This uncommon skeletal feature is often associated with osteosclerotic foci or diffuse osteosclerosis in the spine, pelvis, and at the meta-epiphysis of long bones.[12] When skeletal involvement presents as single osteolysis with a well or poorly defined edge or surrounded by a sclerotic" halo" which has been reported as an additional skeletal pattern in SM,[20] its characterization may be challenging (**Figure 4**). It might require a bone lesion biopsy.[21] Furthermore, any

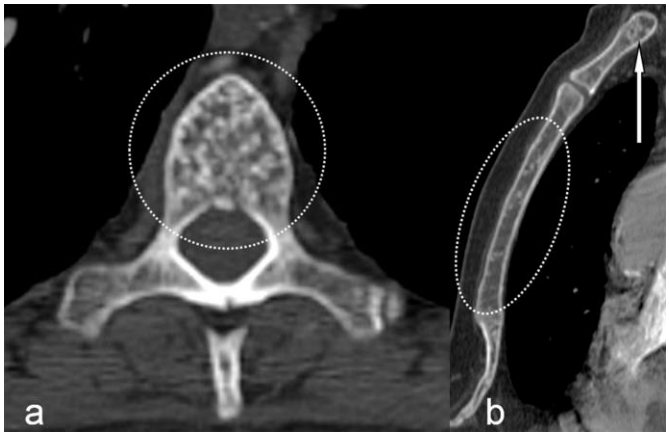

Figure 1. A 48-year-old man with biopsy-proven smoldering SM. **(a)** Axial CT image of a middle thoracic vertebra and **(b)** sagittal reformatted CT image of the sternum show multifocal osteosclerotic lesions in the vertebral body (circle in a) and sternum (arrow and oval in b).

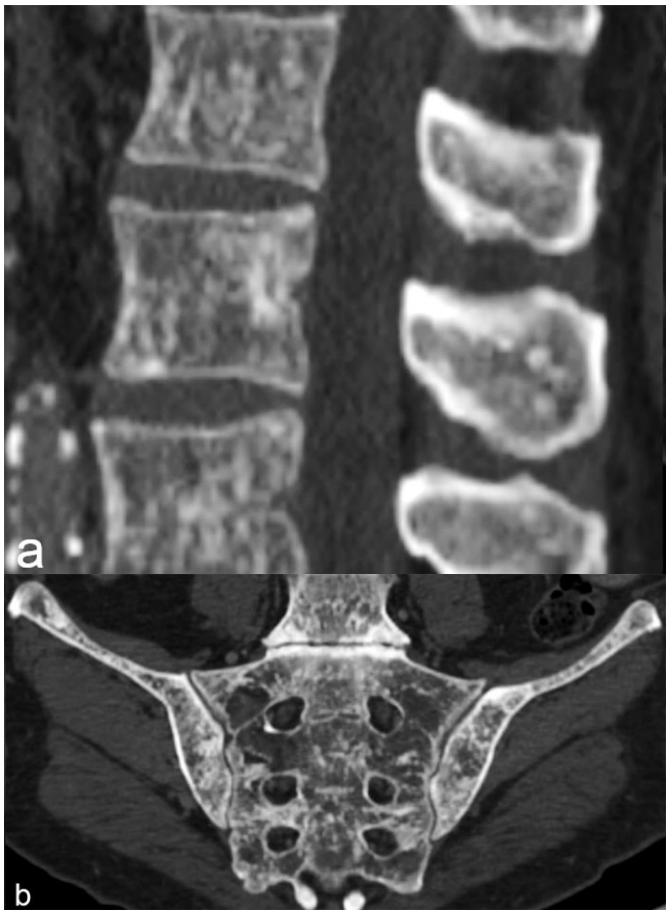

Figure 2. A 67-year-old man with biopsy-proven smoldering SM. **(a)** Sagittal multiplanar reformatted CT image of the lumbar spine, and **(b)** coronal multiplanar reformatted CT image of the sacrum show scattered, countless, well-defined sclerotic foci alternating with zones with apparently reduced bone density.

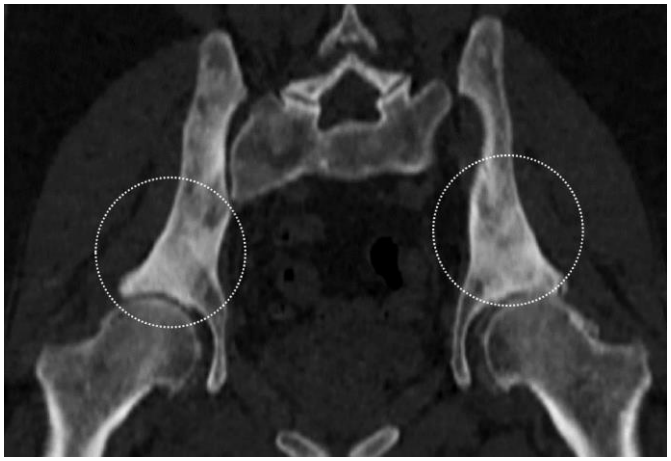

Figure 3. A 61-year-old man with indolent SM. Coronal multiplanar reformatted CT image of the pelvis shows diffuse osteosclerosis (circles).

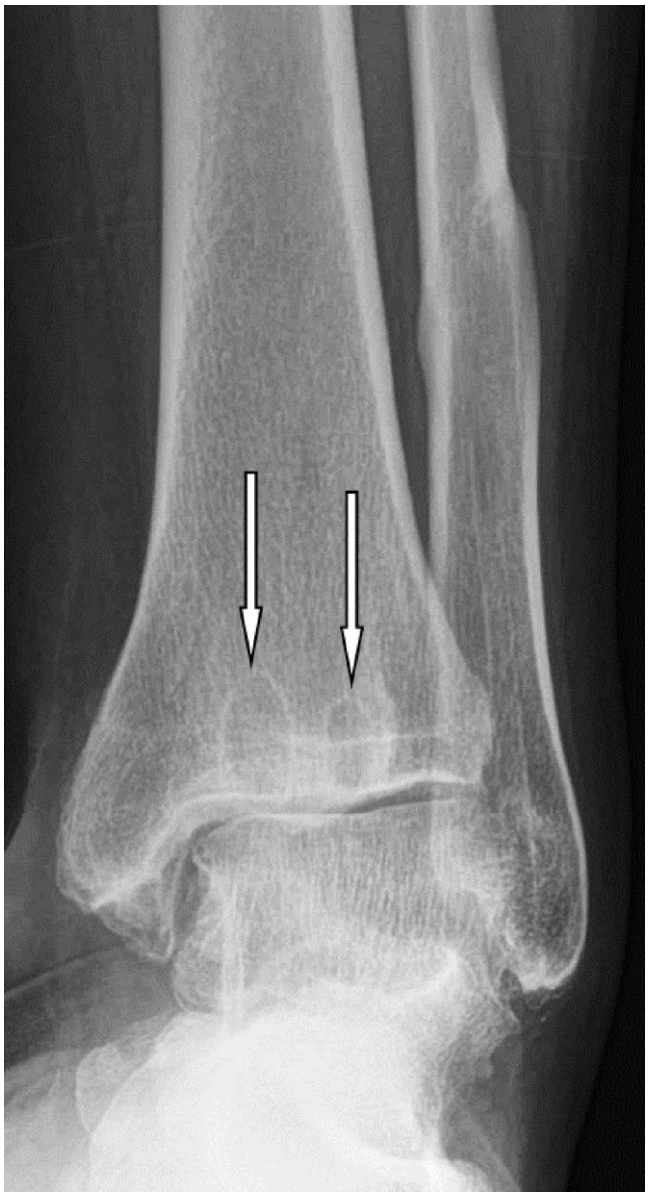

Figure 4. A 36-year-old woman with biopsy-proven SM. The anteroposterior radiograph of the left ankle shows two osteolytic lesions surrounded by a sclerotic" halo" in the distal tibial meta-epiphysis (arrows). However, these findings may be just simple degenerative geodes.

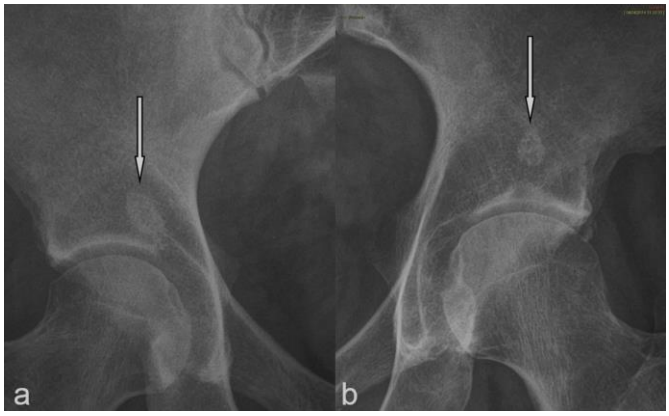

Figure 5. (a, b) Radiographic anteroposterior views of two patients with indolent SM showing focal supra-acetabular osteosclerotic lesions (arrow in a, and b).

sclerotic or lytic bone lesion may change its appearance over time or by treatment; focal lesions may become diffuse later on,[22] and any bony change may be reversed because of treatment.[23]

Radiography and *Dual-Energy X-Ray Absorptiometry*. Because of its simplicity, low expense, and wide availability, radiography should be the first-line imaging modality in diagnosing and assessing skeletal abnormalities. Although its sensitivity and specificity are rather low,[24] once a bone lesion is evident radiographically, the likelihood that it truly exists is high (**Figure 5**). Nevertheless, it should be kept in mind that radiography is not suitable for detecting bone marrow changes. Furthermore, its role in detecting and characterizing osteoporosis is limited as more than 30%-50% bone loss is required to appreciate decreased bone density radiography. Nowadays, dual-energy x-ray absorptiometry (DEXA) at the lumbar spine and hip is the reference standard for diagnosing osteoporosis and predicting fracture risk.[19,25] Thus, DEXA should be assessed in patients with idiopathic osteoporosis and mast-cell mediator release symptoms and in all SM patients at diagnosis and during follow-up to detect those who may benefit from an anti-osteoporotic treatment.[26-29] Meyer et al.,[27] analyzing DEXA data, records, clinical data, and bone marrow biopsies of 39 patients with SM, retrospectively, reported that DEXA findings are positively associated with tryptase level and mast cell amount in bone marrow biopsies. In their study of 61 patients with SM, Riffel et al.[29] correlated the prevalence of osteoporosis, increased bone mineral density (BMD), and osteosclerosis with clinical parameters, disease type, and prognosis. The authors found that an increased BMD and osteosclerosis are frequently present in advanced SM but not in indolent SM; furthermore, in advanced SM, a high BMD and osteosclerosis are associated with a more aggressive phenotype, high-risk molecular aberrations, and inferior survival.

CT. CT is more sensitive and reliable than radiography in revealing and providing a detailed view of small lesions, especially in areas that may be poorly evaluated radiographically, because of their complex anatomy, such as the craniocervical and cervicothoracic junctions, anterior chest wall (**Figure 1b**), pelvic ring (**Figure 2b**), and acetabulum.[30] CT is helpful in patients with SM and nonspecific radiographic findings or patients with a clinically suspected diagnosis of SM and atypical skin involvement. Furthermore, it has been reported that the assessment of differences in attenuation values within the medullary cavity at CT may be useful in identifying bone marrow infiltration, particularly in the setting where MR imaging is contraindicated.[31] Axial quantitative CT that can be conducted on conventional CT examination allows establishing the true volumetric mineral density in calcium hydroxyapatite milligrams per cubic centimeter of trabecular and cortical bone. Quantitative CT has an excellent capability to measure BMD, generally with better sensitivity than DEXA.[6]

MR Imaging. MR imaging is the most sensitive imaging modality to assess bone marrow cellular infiltration because of its high tissue contrast.[32,33] Lesions with high cellularity are readily visible as decreased bone marrow signal intensity on T1-weighted images and high marrow signal intensity on fluid-sensitive fat-suppressed sequences (**Figure 6**). However, these MR imaging findings are nonspecific, and the differential diagnosis includes leukemia, myeloma, and Gaucher's disease.[14] Osteosclerotic lesions are constantly hypointense on both T1 and fluid-sensitive images.[33] Routine MR evaluation of bone marrow is not well suited for assessing the effectiveness of the therapeutic agents; however, decreasing fluid-sensitive and increasing T1-weighted signals usually indicate a response to treatment.[34] Whole-body (WB)-MR imaging has become a modality that, allowing assessment of the entire skeleton with high sensitivity for bone marrow changes, enhances diagnostic performance and represents a valuable tool for screening, detecting the extent of disease, and monitoring therapy in many oncologic disorders.[35] Riffel et al.,[11] analyzing the bone marrow pattern of 115 patients with different forms of SM through WB-MR imaging including T1-weighted, and turbo inversion recovery magnitude (TIRM)-sequences, demonstrated the following five distinct MR patterns:

1. Normal bone marrow.
2. Activated bone marrow (diffusely T1 hypointense, TIRM hyperintense).
3. Diffuse sclerotic bone marrow (diffusely T1 hypointense, TIRM hypointense).
4. Small-spotted sclerotic bone marrow (small-spotted T1 hypointense, TIRM hypointense).
5. Osteolytic lesions (sharply demarcated T1 hypointense, TIRM hyperintense).

Furthermore, these authors reported that sclerotic bone lesions were associated with a high mast cells burden, organ damage, and adverse survival; osteolytic lesions rarely resulted.

^{18}Fluorine-Fluorodeoxyglucose-Positron Emission

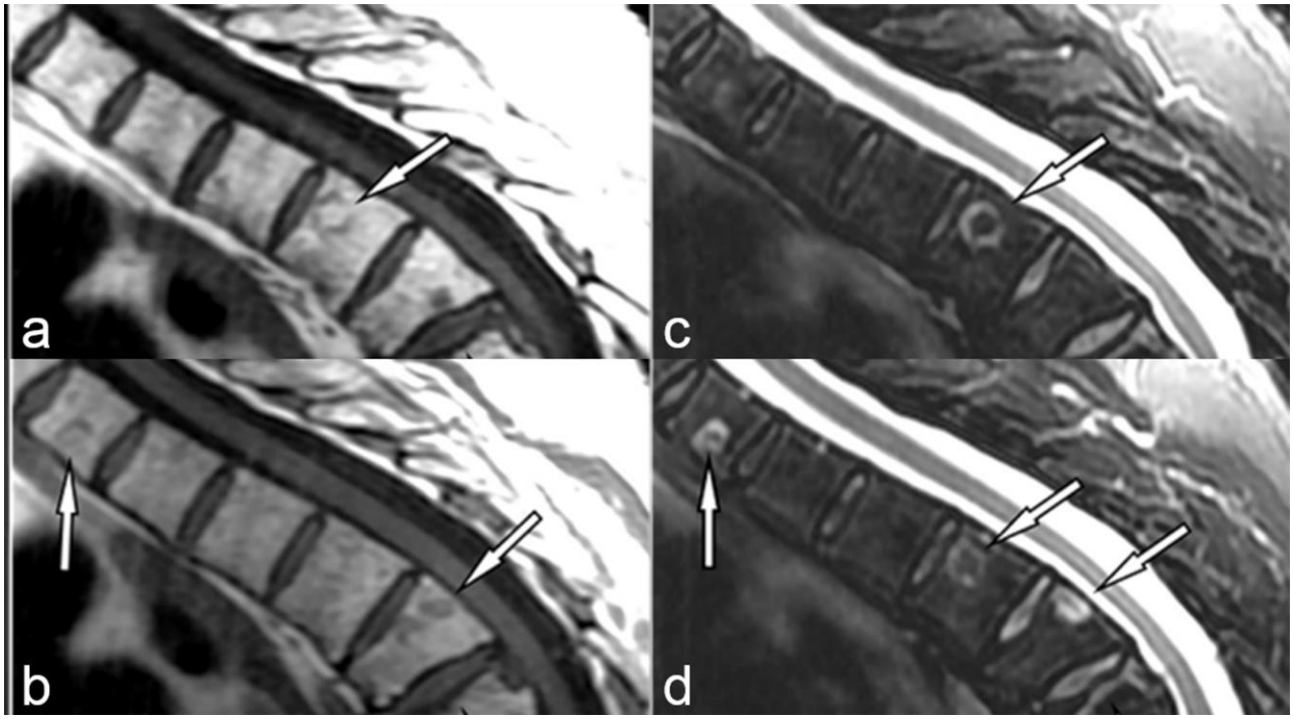

Figure 6. A 60-year-old woman with biopsy-proven SM. **(a, b)** Sagittal T1-weighted and **(c, d)** corresponding T2-fat-suppressed MR images of the thoracic spine show three focal neoplastic lesions due to mast cell infiltration at T2, T5, and T6 vertebral body, respectively (arrows in a, b, c, and d). These findings, however, are nonspecific.

Tomography-CT. Distinguishing malignant from a benign inflammatory process in cases with multiple bony lesions with no skin disease is challenging because both conditions can show increased ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake. In the study of Djelbani-Ahmed et al.,[36] the retrospective analysis of ^{18}F-FDG- positron emission tomography (PET)/CT examinations performed in 19 patients with an established diagnosis of SM demonstrated pathological ^{18}FDG uptake only in the SM with an associated hematologic neoplasm and in mast cell sarcoma cases, suggesting a role of ^{18}FDG-PET in the assessment of these rare forms of SM. However, the current data on the role of this imaging modality in the evaluation of the different SM subtypes has not yet been determined, and further studies are required before its true management value can be determined.

Gastrointestinal System. Among all manifestations of SM, symptoms related to gastrointestinal involvement are common, being present in up to 80% of patients with SM but are often nonspecific.[37,38] Involvement of the gastrointestinal system is mostly detected by endoscopic studies and functional studies of absorption. The role of imaging modalities in SM gastrointestinal involvement is limited. Radiological findings in patients with SM include esophageal abnormalities (e.g., hiatus hernia, esophagitis, stricture, varices, and motor incoordination) and peptic ulcer disease. However, the most important imaging features are 1) diffuse thickening and dilation of the stomach, small and large bowel with nonocclusive strictures, 2) gastric, duodenal, and small-bowel thickened folds, 3) mucosal nodular or polypoid lesions, and 4) organomegaly.[39] Thickened folds are due to mast cell proliferation in the lamina propria. Several mucosal nodules are "target" or "bull's-eye" lesions with a central collection of contrast agents on barium examinations. These lesions, however, are nonspecific since they may resemble lymphoma, primary bowel malignancies, and carcinoid tumors.[40] Organomegaly (hepatomegaly and/or splenomegaly), which is a well-known manifestation of SM, may be attributed to tissue infiltration by mast cells (**Figure 7**).[6]

Imaging. Ultrasound is the first-line imaging modality in patients with SM and suspected gastrointestinal involvement. Ultrasound features are not characteristic; differential diagnosis includes amyloidosis, neoplasms, vasculitic disorders, inflammatory bowel disease, and mostly, lymphoma. Nevertheless, the thickened gastric and bowel walls, as well as abdominal lymph adenomegaly, and occasionally hypoechoic mucosa nodules in the bowel wall can be revealed.[41,42] When carefully interpreted together with the clinical presentation and the bone and skin status, these findings can lead to the suspicion of SM.[41] Furthermore, ultrasound, but mostly CT and MR imaging, could be utilized to define hepatic and splenic size.[43-47] Any decrease in hepatic and splenic size in the treatment assessment setting indicates treatment success in SM.[45] Manual CT hepatic volumetry is time-consuming, laborious, and software-dependent; therefore, simplified measuring methods are extremely useful in clinical radiology practice. The longitudinal dimension of the right lobe of the liver as measured in the midclavicular plane is an easy and practical method for routine use. The Hepatomegaly threshold for this parameter was up to 17 cm (**Figure 7**).[46] Verma et al.,[43] correlating retrospectively hepatic measurements on MR imaging and hepatic volume of 116 patients who had undergone post-contrast abdominal MR imaging for conditions unrelated to the hepatobiliary system, reported that simple linear hepatic measurements on MR imaging are good indicators of hepatic volume and a reliable method

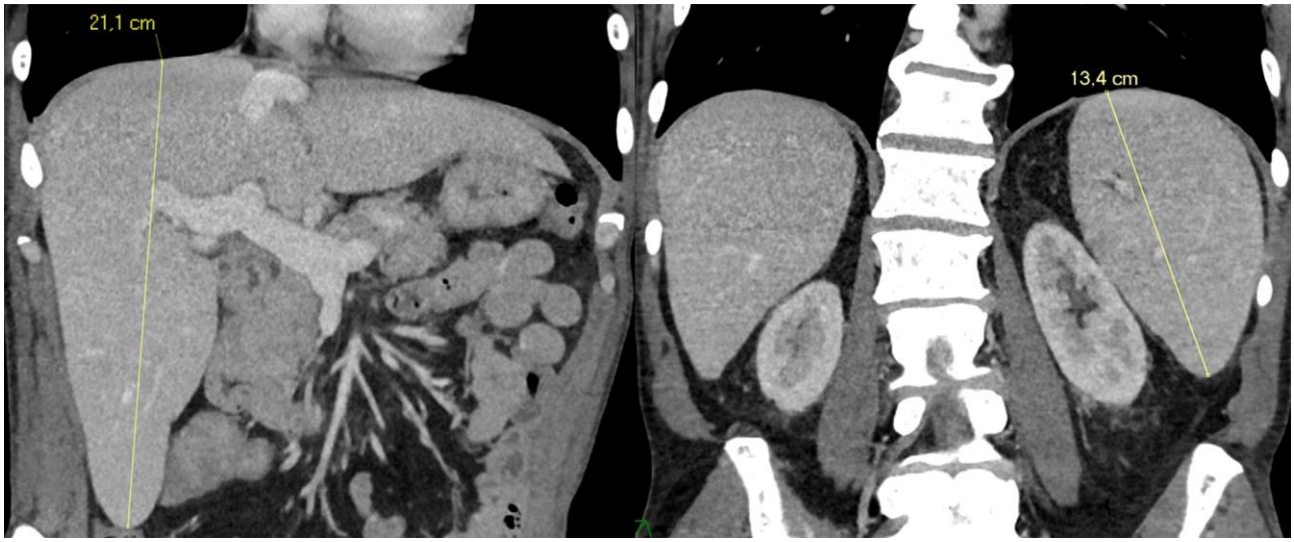

Figure 7. A 58-year-old man with biopsy-proven aggressive SM. **(a, b)** Coronal reformatted CT images showing hepatomegaly (arrow in a) and splenomegaly (arrow in b). Liver and spleen vertical heights were 21.1 and 13.4 mm, respectively.

for monitoring the liver volume. There are complex methods of defining splenomegaly;[47] however, in their retrospective study of 264 abdominal CT examinations, Kucybala et al.[44] found that the strongest correlation with splenic volume, using a single linear measurement, was the maximal height with a threshold for this parameter of 12 cm (**Figure 7**). Epelboym et al.,[48] analyzing 29 patients with confirmed mastocytosis, found that patients with non-indolent mastocytosis were statistically more likely to have hepatomegaly, splenomegaly, or lymphadenopathy on CT imaging as compared to the indolent cohort. Hepatic and splenic involvements are often characterized by prominent portal fibrosis, focal (perivascular) or diffuse, respectively. Liver fibrosis, characterized by the excessive accumulation of extracellular matrix proteins, leads to portal hypertension and ultimately to cirrhosis. Conventional ultrasound and cross-sectional imaging modalities have limited capability to demonstrate liver fibrosis. Thus, diagnosis and staging of hepatic fibrosis are currently performed by liver biopsy. However, other imaging modalities such as ultrasonography-based transient elastography, CT-based texture analysis, and diverse MR imaging-based techniques have been proposed for noninvasive diagnosis and grading of hepatic fibrosis.[49-51] MR imaging-based techniques include conventional post-contrast MR imaging, double contrast-enhanced MR imaging, MR elastography, diffusion-weighted, and MR perfusion imaging. Granted that a detailed discussion of MR imaging physical phenomena is beyond the scope of this article, these MR techniques may play a central role in treatment response monitoring and the clinical management of patients with liver fibrosis.[51]

Lymphadenopathy. Another central pathological feature is systemic infiltration and proliferation of mast cells in lymph nodes (**Figure 8**). Unfortunately, the radiological appearances of lymphadenomegaly (a short axis measurement ≥ 1.0 cm) in mastocytosis cannot be distinguished from those in lymphoma.[52,53]

Respiratory System. Mast cells have been implicated in causing fibrosis since they could stimulate fibroblasts proliferation, recruitment, and activity (e.g., transforming growth factor-β production).[54] However, although the huge burden of mast cells within the lungs, pulmonary involvement in SM and pulmonary fibrosis, in particular, are rare.

Imaging. Chest radiographic findings include perihilar or diffuse interstitial fibrosis, cysts, lung nodules, and mediastinal lymphadenopathy. Pulmonary involvement occurs in less than 20% of patients. Travis et al.,[2] evaluating 58 patients with SM, found focal or scattered areas of fibrosis, bilateral interstitial fibrosis, and multiple pulmonary nodules in 16% of patients; however, none was with biopsy-proven pulmonary mastocytosis. Hermans et al.[55] described the case of a young Caucasian female with SM associated with pulmonary interstitial disease. The latter was directly related to SM because of the presence of mast cells in bronchoalveolar lavage. Concerning chest CT findings in SM patients, only a few case reports have been published in English literature. Schmidt et al.[56] described a case of a 54-year- old man with biopsy-proven mast cell infiltration of the lung. Corresponding chest CT showed multiple lymphadenopathies of the mediastinum and

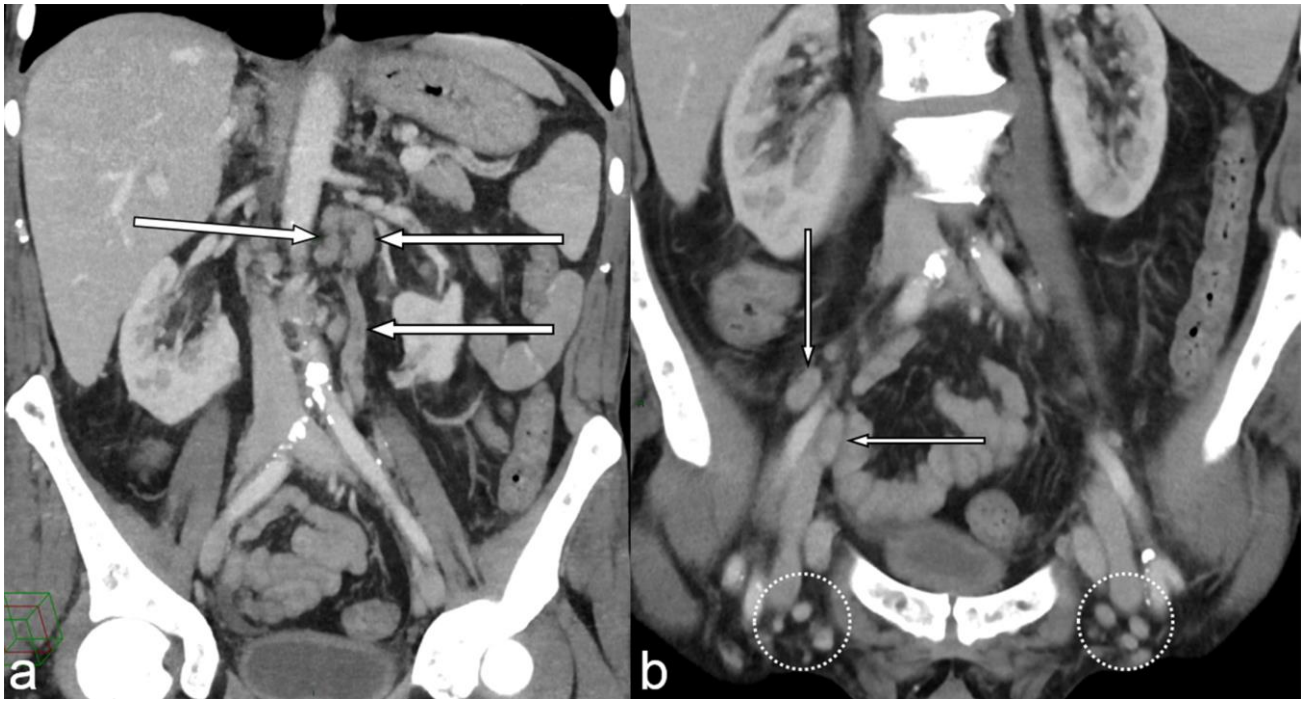

Figure 8. The same patient as in figure 7. **(a, b)** Coronal reformatted CT images show retroperitoneal (arrows in a), iliac (arrows in b), and inguinal (circles in b) lymphadenopathies.

nodular pulmonary lesions.

Central nervous system. Central nervous system involvement is extremely rare in SM. Chronic symptoms such as cognitive impairment and depression-anxiety-like symptoms have been reported by Boddaert et al.;[57] they may be related to tissue mast cell infiltration and mast cell mediator release. Supratentorial and infratentorial ischemic lesions and diffuse brain involvement may be demonstrated on MR imaging, but these features are not characteristic.[58]

Imaging. In the already mentioned prospective and monocentric comparative study of Boddaert et al.,[57] 39 patients with mastocytosis and psycho-cognitive complaints were compared with 33 healthy controls. The authors found a high prevalence (49%) of morphological and functional abnormalities in the brains of mastocytosis patients with neuropsychiatric complaints (depression–anxiety-like symptoms and cognitive impairment). These patients had mainly abnormally punctuated white matter abnormalities and increased perfusion in the putamen demonstrated on MR examinations. However, the specificity of these morphological and functional abnormalities remains to be elucidated.

Conclusions. SM involves many extracutaneous organs systems with a heterogeneous clinical presentation and variable clinical course. For this reason, a variety of imaging modalities such as radiography, CT of the bone, thorax, and abdomen, DEXA, and MR imaging need to be performed to supplement bone biopsy and determine the subtype and extent of disease.

Regardless of the type of SM, bone involvement is the most common presentation and a prognostic factor. The presence of bone lesions may help confirm systemic involvement and, in advanced SM, an increased BMD and osteosclerosis are associated with a more aggressive phenotype and worse outcomes.

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