Mast Cell Activation Syndrome Mimicking Breast Cancer: Case Report With Pathophysiologic Considerations

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Clinical Practice Points

- Mast cell activation syndrome (MCAS) represents the common systemic variant (prevalence up to 17%) of mastocytosis, which is associated with an increased risk for breast cancer.
- In MCAS, infiltration of the breast with activated mast cells can induce lesions that may mimic breast cancer in imaging methods using contrast enhancement to exploit tumor-induced angiogenesis for breast cancer detection. The present case is the first demonstrating this frequent phenomenon in patients with MCAS.
- We present the case of a 58-year old woman with MCAS-associated suspicious lesions masked by dense breast tissue, only be visible by breast magnetic resonance (MR) imaging but not by mammography and breast ultrasonography. Minimally invasive MR-guided breast biopsy was required to allow a definite pathologic dignity analysis of biopsies. We discuss the clinical presentation, the imaging characteristics, the pathologic findings, and the pathophysiologic considerations.
- Identification of mast cells in biopsies requires staining with antibodies against CD117 (tyrosine kinase KIT), tryptase, and CD25 (alpha chain of the IL-2 receptor).
- In conclusion, breast MR imaging is the most sensitive imaging technique to visualize mast–cell-related alterations in the female breast of patients with mastocytosis who should be under an increased surveillance because of an increased risk for breast cancer. Pathologic examination of breast biopsies should include specific mast cell staining when the histologic diagnosis of breast cancer is not beyond any doubt with usual staining methods in order to minimize the risk of unnecessary surgical interventions as a result of false-positive findings.

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Introduction

Mast cell (MC) activation syndrome (MCAS) represents the common variant (with a prevalence of at least 17% in Germany)[1] of systemic MC activation disease (MCAD) (ie, a subclass of mastocytosis) (see Supplemental Figure 1 in the online version).[2] MCAD comprises a heterogeneous group of multifactorial, polygenic disorders characterized by aberrant release of variable subsets of MC mediators together with accumulation of either morphologically altered and immunohistochemically identifiable mutated MCs owing to MC proliferation (systemic mastocytosis and MC leukemia) or morphologically ordinary MCs because of decreased apoptosis (MCAS and well-differentiated systemic mastocytosis; for details, see Ref. 2). In a recent retrospective study, the comparison of the frequencies of the malignancies in patients with MCAS with their 10-year prevalence in the German general population revealed, in subsets of the patients with MCAS, a significantly increased prevalence for breast cancer[3] indicating a need for increased surveillance.

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Mammography is recommended for screening women aged 40 to 50 years or older for breast cancer. Limitations of mammographic screening, particularly in women with dense breast tissue, as in our patient described in the following, are decreased sensitivity and specificity to diagnose breast cancer. This is an important disadvantage because two-thirds of women participating in mammographic screening programs will have noninvoluted intermediately dense or extremely dense breast tissue.[4,5] Ultrasonography (US) screening as a nonmammographic screening method is associated with a low positive predictive value.[6-8] Breast magnetic resonance (MR) imaging has recently been shown to exhibit a superior sensitivity (specificity, 97.1%; false-positive rate, 2.9%; positive predictive value, 35.7%) when compared with that of mammographic and US screening in women at high risk as well as at average risk for breast cancer.[9,10] Conventional imaging comprised (1) bilateral digital full-field mammography in 2 views (Selenia Dimensions; Hologic, Bedford, MA) and (2) high-spatial-resolution physician-performed breast US with a 15-MHz probe (IU22 [Philips Medical Systems, Best, the Netherlands] and 3D Aixplorer [SuperSonic, Aix-en-Provence, France]). In the present case, dynamic breast MR imaging was performed with 2 different 1.5-T systems (Philips Achieva, Philips Medical Systems) equipped with a 4-channel breast coil (InVivo, Gainesville, Fla) and a device to immobilize the breast in the craniocaudal (section encoding) direction (Noras, Würzburg, Germany). The standardized protocol was performed in the axial plane and consisted of a T2-weighted turbo spinecho sequence (repetition time msec/echo time msec, 3500/110) performed with a 512 × 512 acquisition matrix, a coronal T1-weighted turbo spin-echo sequence, and a dynamic contrast material-enhanced subtracted series. The latter consisted of 5 dynamic frames, 1 obtained before and 1 obtained after injection of a bolus of gadobutrol (Gadovist; Bayer, Leverkusen, Germany) at 0.1 mmol per kilogram body weight, at 3 mm/second, followed by a saline chaser, and acquired with identical anatomic location as the T2-weighted series, with 250/4.6, flip angle of 90°, and full 512 × 512 acquisition over a 300- to 330-mm field of view. All imaging studies were read in accordance with the Breast Imaging Reporting and Data System (BI-RADS) lexicon.

In particular, in patients with MCAD, breast cancer screening may be difficult because (1) suspicious lesions may be masked by dense breast tissue, and only visible by contrast-enhanced methods such as breast MR imaging, and because (2) inflammatory changes and MC infiltration caused by MCAD may cause contrast enhancement and thus may mimic breast cancer (Kuhl, Molderings, unpublished observations).[11] In the following case report, we want to point to the diagnostic peculiarities in MCAD that have to be considered in order to minimize the risk of an unnecessary maximal invasive surgical intervention as a result of false-positive findings.

Case Presentation

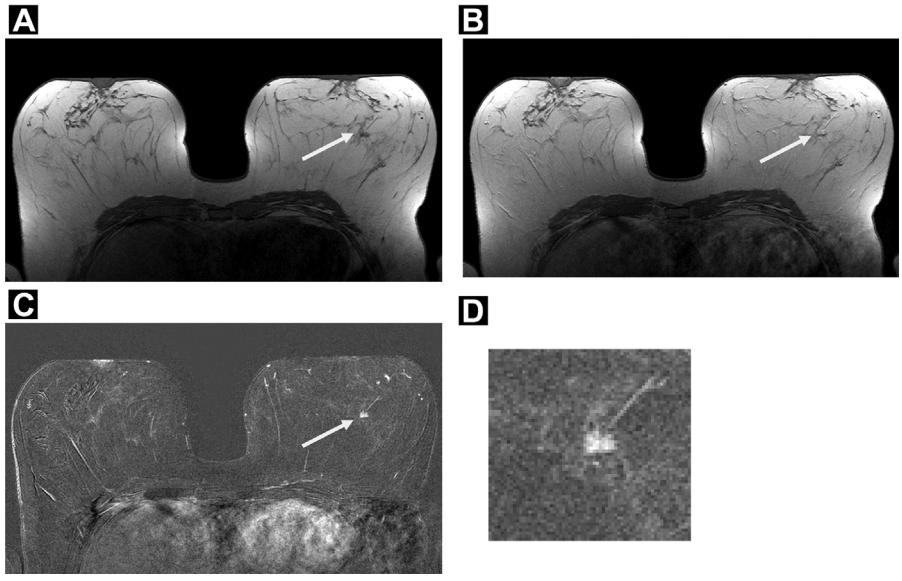
A 58-year-old woman presented to the Klinik für Diagnostische und Interventionelle Radiologie RWTH Aachen for a follow-up examination of a suspicious lesion in her right breast that had been first detected 6 years before and was only visible by dynamic breast MR imaging but not by mammography and breast US. The patient was known to suffer from MCAS diagnosed according to the current international criteria (for details, see Ref. 2). At the time of presentation, her MCAS exhibited rather intense activity reflected by the distinctly increased heparin level in blood (Table 1; MCs are the main source of heparin).[12] She was on medication administered for a reduction of MC activity (rupatadine, ranitidine, ascorbic acid) and on drugs administered to reduce mediator-related symptoms (omeprazol, tranexamic acid, candesartan, diltiazem, hydrochlorothiazide, risedronic acid). Her symptoms and key laboratory results are summarized in Table 1.

Table 1 Symptoms and Key Laboratory Results

Symptoms	Key Laboratory Results (Normal Range)
Fatigue, malaise, asthenia, feeling cold much of the time, frequent headache, word finding difficulties, "brain fog," multiple small lesions in brain white matter (increasing in number), insomnia, constant bilateral tinnitus, irritated eyes, nasal irritation and copious coryza, wheezing, irritated throat during flares, dyspnea, chest discomfort/heaviness, palpitations, hot flash, arterial hypertension, secondary Raynaud's syndrome, "easy" bruising/bleeding, nausea, diarrhea, marked abdominal bloating, hypercholesterolemia, heartburn, diffuse edema with weight gain for several days, diffusely migratory paresthesias and pain (fibromyalgia), rheumatoid arthritis-like symptoms, osteopenia, waxing/waning bilateral sore throat, chronic kidney failure grade 1, interstitial cystitis, progressive deterioration of dentition despite good hygiene, alopecia, dermatographism, longitudinal ridging in all nails, mood disturbances, progressive bilateral breast hypertrophy (cup size B → E)	Serum tryptase: 5.5 μg/L (<11.5 μg/L) Plasma heparin: 0.22 IU/mL (≤0.05 IU/mL; progressively increasing since the time of diagnosis) Clotting factor VIII: 225.1% (67%-220%) Trigger-induced PgD_2 values increased Chromogranin A 95 mg/L (19-98 μg/L) Mutation analysis of genomic DNA of leukocytes from peripheral blood by next generation sequencing: Germline mutations in coding sequences: KIT^{M541L} (heterozygously) $IL13^{Q144R}$ (homozygously) $JAK2^{R1063H}$ (heterozygously) $TP53^{P72R}$ (homozygously) $SETBP1^{A222T,\ T228Sfs*8}$ (heterozygously) $ASXL1^{G652S}$ (heterozygously) No somatic KIT^{D816V} mutation

Her breast examination showed no cutaneous or nipple lesions and revealed no tenderness and no palpable masses. No pathologically enlarged axillary lymph nodes were observed, either in the axillary or the parasternal or jugular region. On dynamic breast MR imaging, there was only minimal parenchymal enhancement after contrast agent (gadobutrol 0.1 mL/kg b.w.) (MR-ACFR I). On the breast MRI study in 2017, there was focal non-mass enhancement (5 × 5 mm) in the right breast, with inhomogenous internal enhancement and a washout time course (Figure 1). Similar findings were seen in the central and caudal parts of the right breast. All findings appeared stable compared with the previous scan performed 6 years prior (ie, 2011). In the left breast, there was an enhancing area, 8 × 5 mm in size, located centrally behind the nipple, with irregular shape and spiculated margins, and early, inhomogeneous enhancement. The lesion was new compared with the previous MR imaging. Still, and in spite of the suggestive lesion shape and margins, the lack of any mass effect and the hazy type of contrast enhancement suggested presence of an inflammatory lesion rather than that of a breast cancer. Accordingly, the lesion was categorized as BIRADS4 (possibly malignant) There were further enhancing foci, with similar MR findings as the ones in the contralateral breast, all suggestive of adenosis. A bilateral 2-view digital breast

Figure 1 Findings in Dynamic Breast Magnetic Resonance Imaging of Left and Right Breast, Which Were Not Visible by Mammography and Breast Ultrasound. A, Dynamic Series, Precontrast T1-Weighted Image Exhibits an Irregular Mass in the Left Breast (Arrow). B, First Post-contrast Dynamic T1-Weighted Image Exhibits Strong Enhancement of the Mass (Arrow). C, Subtraction Image (B Minus A) Reveals Irregular, Spiculated Mass Margins (Arrow). D, Close-up of C. Note Irregular Margins



tomosynthesis and bilateral high-resolution (15 MHz) second-look ultrasound was performed; none of the enhancing lesions exhibited a correlate on these imaging studies.

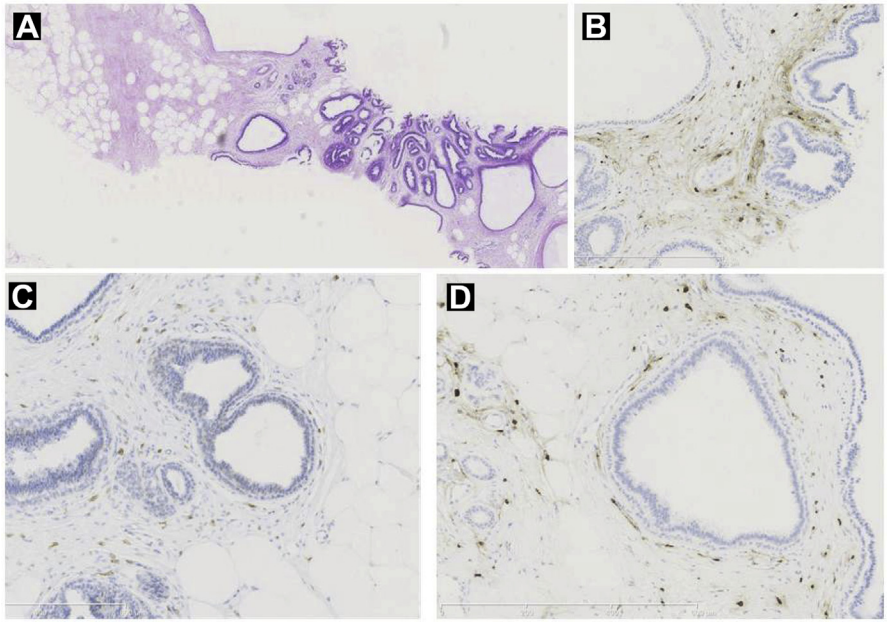
The patient underwent MR-guided vacuum-assisted breast biopsy of the suspicious lesion in the left breast; in the same session, representative MR-guided vacuum biopsy of the benign-appearing focal enhancement in the right breast was performed. MR-guided vacuum-assisted biopsy was performed using a dedicated system (ATEC SUROS; Hologic, Marlborough, MA). As necessary for patients with MCAD, she was premedicated with 80 mg prednisolone, 60 mg fexofenadine, and 50 mg ranitidine to prevent activation of MCs induced by the operation stress.[13] The procedure was performed under general anesthesia with propofol, which has been shown to inhibit MC degranulation.[13]

All specimens were reviewed by an expert breast pathologist (R.K.). To differentiate between ductal hyperplasia and low-grade ductal carcinoma in situ, additional immunohistochemical staining (cytokeratin 5/6 and p63) was performed. To visualize MCs clearly in the biopsies, specimens were immunostained using the avidin-biotin complex method with a monoclonal antibody against MC tryptase (clone AA1, Novocastra, Newcastle upon Tyne, England), an antibody against CD117 (tyrosine kinase KIT; polyclonal rabbit antibody, DAKO), and an antibody against CD25 (alpha chain of the IL-2 receptor; clone IL2 R, Quartett, Berlin, Germany). In the pathologic examination, hematoxylin and eosin and additional Giemsa staining of the biopsies obtained from the right and left breast revealed a mastopathy and slight sclerotic adenosis with slight chronic inflammatory infiltration (Figure 2). Breast cancer was ruled out. There was a moderate increase in MC density, with maximum densities of 35 MCs per mm^2 stained with tryptase antibodies and 40 MCs per mm^2 stained with CD117-antibodies. The MCs were negative for CD25-antibody staining (Figure 2).

Discussion

The present case supports the frequent observation in practice that in patients with MCAD, infiltration of the breast with activated MCs can induce lesions that may mimic breast cancer in imaging methods that use contrast enhancement to exploit tumor-induced angiogenesis for breast cancer detection (ie, contrast-enhanced breast MR imaging). MCAD-associated suspicious lesions can only be visible by breast MR imaging but not by mammography and breast US. Because the inflammatory-like lesions induced by MCAD mimic breast cancer on MR imaging, minimally invasive MR-guided breast biopsy is required to allow a definite pathologic analysis of biopsies. In our patient, MC density in the breast was moderately increased to 35 tryptase-stained MCs per mm^2 and 40 CD117-stained MCs per mm^2. To the best of our knowledge, there is, as yet, no report about the number of MCs in normal breast tissue. In nonneoplastic breast tissue of 104 patients with breast carcinoma,[14] which might serve as equivalent to normal breast tissue, MCs were present only in 76% of the patients, and in these patients, the maximal density was 25 MCs per mm^2 (median, 14 MCs per mm^2). A similar density has been detected in 10 patients with mastopathy (20.5 $\pm$ 9 per mm^2).[15] One may argue that the difference in density of the values in our patient might be too

Figure 2 Breast Biopsy With Increased Mast Cell Density: A, Overview, Hematoxylin and Eosin Staining: Adenosis With Cysts Is Seen in Parallel to an Increased Fibrosis Also Affecting the Adjacent Fatty Tissue (Left Part of Biopsy). B, Mast Cell Tryptase Staining of This Biopsy Indicates the Increase in Mast Cells Related to the Periductal Fibrosis. Comparison of CD117 Staining (C) and Mast Cell Tryptase Staining (D) in Similar Areas of the Biopsy, Whereas CD25 Was Found Negative in All Samples (Data Not Shown)



moderate to be implicated in the involvement of the lesions in our patient. However, evidence has accumulated that it is rather the activity of the MCs and not their mere number is important for the pathogenesis.[16] As an estimation of the MC activity, the difference in the number of CD117-positive MCs and tryptase-positive MCs can serve: tryptase as component of the granula is excreted by activated MCs by degranulation so that only a faint, if at all, staining of degranulated MCs with the tryptase antibody can be seen. In contrast, staining with CD117 antibodies is not influenced by degranulation, because tyrosine kinase KIT is a membranous enzyme of the cell membrane. In fact, there is a difference of 5 MCs per mm^2 between MC density determined by tryptase and CD117 staining, respectively, indicating the presence of activated MCs, which is in agreement with the intense activity of the patient's MCAS as indicated by the highly increased heparin blood level. In this context, it should be noted that, in patients with MCAD, it can be difficult to distinguish MC mediator-induced benign alterations in the breast from malignant lesions, so that in a given case, extensive immunohistochemical tests can be necessary (unpublished data).

In our patient, a progressive bilateral breast hypertrophy (cup size B → E) has occurred over about 10 years; this was paralleled by her increase in MCAS activity. It would be plausible that the MC accumulation identified in the patient's breast tissue may have caused her bilateral breast hypertrophy. It has been postulated that benign fibrocystic changes of the breast were the sequelae of biochemical events initiated by MCs.[17] Wood et al[18] reported a case of a fibrous mastocytoma in a patient with generalized cutaneous mastocytosis. It has been suggested that hyperplasia of MCs may contribute to increased collagen synthesis causing fibrosis induced by therapeutic irradiation.[19] MCs have been shown to play an important role in various fibroproliferative diseases by release of a variety of pro-fibrotic mediators such as histamine, tryptase, transforming growth factor ß1, platelet-derived growth factor, basic fibroblast growth factor, and angiotensin II (formed by released chymase), which are capable of stimulating fibroblast proliferation and collagen synthesis.[20] In fact, in women with fibrocystic changes of the breast, blood serum concentrations of histamine were significantly higher than in women without any changes in their breasts (control group).[21] This elevated histamine concentration in the blood serum may suggest a higher concentration of histamine also in the breast tissue, where it may promote proliferation by activation of H_2 histamine receptors.[22]

Conclusion

In conclusion, breast MR imaging is the most sensitive imaging technique to visualize MC-related alterations in the female breast of patients with MCAD who should be under increased surveillance because of an increased risk for breast cancer. Considering the high prevalence of (the majority of which is unrecognized) MCAS at least in the German population, pathologic examination of breast biopsies should include specific MC

staining when the histologic diagnosis of breast cancer is not beyond any doubt with the usual staining methods, to minimize the risk of unnecessary surgical interventions as a result of false-positive findings.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2017.12.004.

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Supplemental Figure 1 Current Classification of Primary Mastocytosis

Mastocytosis			
Systemic mast cell activation disease (MCAD)		**Cutaneous mastocytoses (CM)**	**Mast cell sarcoma**
Systemic Mastocytosis (SM)	**Mast Cell Activation Syndrome (MCAS)**		
• indolent SM • well-differentiated indolent SM • smoldering SM • aggressive SM • SM with an associated hematological neoplasia ("leukemia") • Mast cell leukemia	• with hypertryptasemia • without hypertryptasemia	• maculopapular mastocytosis = urticaria pigmentosa (UP) • diffuse CM • solitary cutaneous mastocytoma • telangiectasia macularis eruptiva perstans	

Abbreviations: CM = cutaneous mastozytoses; MCAD = mast cell activation disease; MCAS = mast cell activation syndrome; SM = systematic mastocytosis; UP = urticarial pigmentosa.