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Breast Implant Illness May Be Rooted in Mast Cell Activation

A Case-Controlled Retrospective Analysis

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Objective: To investigate the possible association between breast implant illness (BII) and mast cell activation syndrome (MCAS), which often manifests increased mast cells (MCs) in assorted tissues and may explain BII symptoms.

Background: Mechanisms by which implants cause BII symptoms remain unclear, but BII and MCAS symptom profiles heavily overlap, warranting investigation of potential linkage.

Methods: We retrospectively analyzed 20 implant patients who underwent explantation and total capsulectomy; 15 self-reported preoperatively they had BII (subject group); 5 felt they did not [control group 1 (CG1)]. Five prophylactic mastectomy patients constituted control group 2 (CG2). Subjects and CG1 patients completed BII symptom questionnaires preoperatively and multiple points postoperatively. With CD117 staining, average and maximum mast cell counts (MCCs) in resected tissues were determined.

Results: Mean BII symptom score 2 weeks postexplantation was reduced by 77% ($P < 0.0001$), and 85% by 9 months. Analysis suggested BII in CG1 patients, too, who improved similarly. Among CG2 patients, healthy breast tissue showed mean and maximum MCCs of 5.0/hpf and 6.9/hpf. Mean and maximum MCCs in capsules in BII patients were 11.7/hpf and 16.3/hpf, and 7.6/hpf and 13.3/hpf in CG1 patients. All intergroup comparisons were significantly different ($P < 0.0001$).

Conclusions: MCCs in peri-implant capsules in BII patients are increased; some implanted patients appear to have unrecognized BII. Given that neoantigenic/xenobiotic exposures commonly trigger dysfunctional MCs in MCAS to heighten aberrant mediator expression driving inflammatory and other issues, further investigation of whether BII represents an implant-driven escalation of pre-existing MCAS and whether an MCAS diagnosis flags risk for BII seems warranted.

Keywords: breast implant illness, mast cell activation disease, mast cell activation syndrome

INTRODUCTION

The US Food and Drug Administration ("FDA") lists "systemic symptoms" as some of the risks associated with the use of breast implants.[1] More commonly, this group of symptoms, in the context of having developed following placement of breast implants, is labeled breast implant illness (BII). It is unknown what the incidence of BII is, but it is reported that women are 8 times more likely to develop an autoimmune disorder following reconstruction or breast augmentation using breast implants.[2] Some social media support groups focused on BII now count hundreds of thousands of members.[3]

It has been suggested that individuals who already have autoimmune diseases or hyperactive immune systems reconsider the use of breast implants.[3] The most common BII symptoms are fatigue, joint pain, cognitive issues (general "brain fog," poor concentration, and word-finding difficulties), depression, anxiety, hair loss, autoimmune diseases, rash, headaches, and inflammation.[4] The time span between implant placement and the onset of symptoms in BII patients ranges from immediately to several years.[5] In most cases, the onset of symptoms is subtle, with mild allergy-like reactions initially (sinusitis, rashes, itching), commonly followed by a steady increase in the number and severity of symptoms. As BII is a relatively new condition, the average patient sees multiple healthcare professionals about her unexplained symptoms before arriving at the conclusion that these symptoms may be related to the implants.

Another chronic multisystem inflammatory disease with symptom profiles significantly overlapping those seen in BII is mast cell activation syndrome (MCAS). MCAS is a complex chronic multisystem disease of aberrant constitutive and reactive mast cell (MC) mediator release causing highly heterogeneous menageries of symptoms of generally inflammatory, allergic, and dystrophic themes.[6] Preliminary epidemiologic research is increasingly demonstrating MCAS is quite prevalent, in as much as 17%–20% of the general population.[7–9] For BII patients, MCAS may be present before implantation surgery, but symptoms and signs of the disease in the years (even decades) before surgery may be mild or even subclinical (eg, allergic rhinitis, or intermittent unexplained modest elevations in serum transaminase levels). For these patients, it is the introduction of the implants to the immune system that may lead to further

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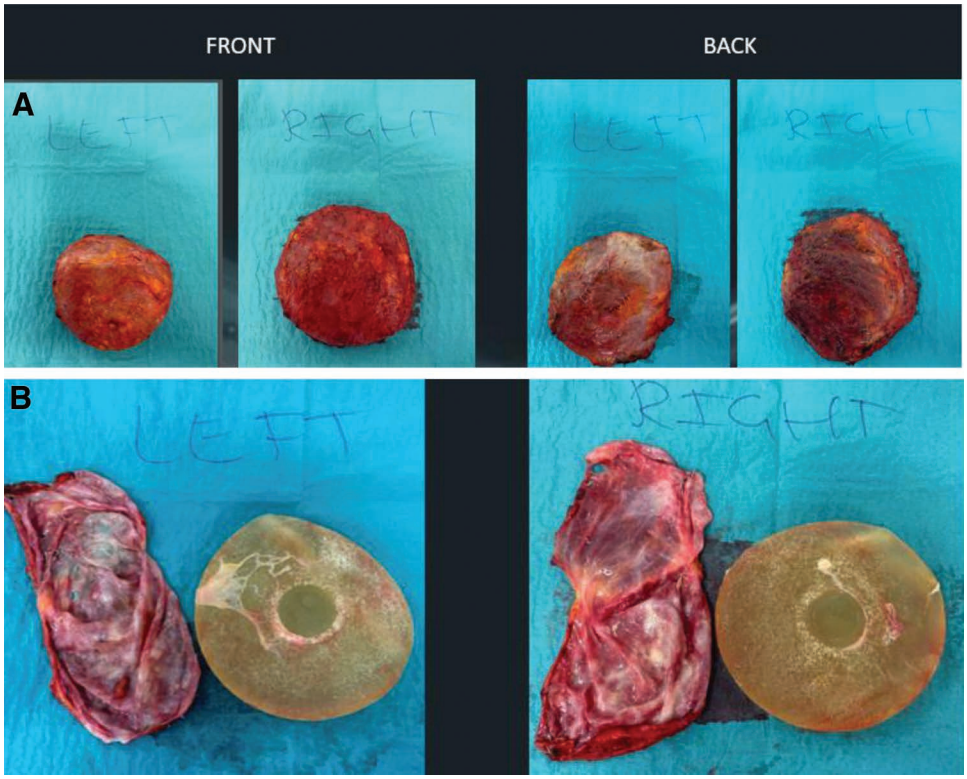

FIGURE 1. A, Anterior and posterior implant photos contained within en bloc capsulectomies (B) Capsules removed separately from implants before placement into formalin.

heightening of activation of dysfunctional MCs,[10] in turn, leading to increased release of many mediators which directly and/or indirectly drive, or at least contribute to, the symptoms associated with BII. Though no causative pathways have been researched yet, associations indeed have been found between MCAS and a wide range of other idiopathic chronic multisystem inflammatory diseases.[11]

There have been multiple publications of the improvement in, and even complete resolution of, BII symptoms once the implant and capsules were removed,[4,12] further illustrating the immunogenic stimulus that silicone may pose in the body. Recent literature, too, has suggested a linkage between illness from exposure to xenobiotical chemicals and the development or worsening of MCAS.[13] Furthermore, MC disorders are known to increase the risk for, and severity/aggression of, liquid and solid tumors,[14,15] and a case report has shown improvement in multiple myeloma in a patient when silicone implants were removed.[16]

Given our observation in practice of the similarity of the symptom profiles in BII and MCAS, and given the commonly observed natural history in MCAS of worsened MC activation upon exposure to novel antigens, we hypothesized that many patients who experience BII may actually suffer from MCAS. We performed a preliminary assessment for evidence of MCAS in a small series of BII patients who underwent explant surgery with total capsulectomies, as compared against potential control groups.

METHODS

Under ethics approval, 0127E_2023 by National Institute of Integrative Medicine HREC (EC00436), the cases of fifteen BII patients (the subject group, who all reported preoperatively they had BII), 5 "Non-BII" patients (ie, patients who preoperatively did not feel they had BII) with breast implants [control group 1 (CG1)], and 5 prophylactic mastectomy patients [control group 2 (CG2)] were reviewed for this pilot retrospective study. Data was accessed through Clinic 2 Cloud Software and patients' personal details were deidentified during analysis. BII patients ranged in age from 31 years to 62 years (mean age: 42 years). Implant duration ranged from 3 years to 19 years (mean duration: 10 years). CG1 patients ranged in age from 29 years to 54 years (mean age: 44 years), and their implant duration ranged from 5 years to 24 years (mean duration: 15 years). CG2 patients ranged in age from 28 years to 61 years (mean age: 47 years). All BII and CG1 patients had explant and total capsulectomies and pectoralis muscle repair if their implants were originally placed subpectorally. All patients received regional anesthesia in conjunction with general anesthesia, allowing patients to be safely discharged within 48 hours of surgery. All patients had immediate mobile phone access to the surgeon to address any concerns.

A BII symptom questionnaire was formulated by modification of a symptom questionnaire for Lyme patients[1] as symptoms of Lyme disease closely resemble that of patients of BII (and closely resemble symptoms of MCAS, unsurprising given that the *Borrelia* infection underlying Lyme disease is known to drive MC activation[17]). The BII symptom questionnaire was administered 2 weeks before explantation in the BII subject group and the CG1 group and at 2 weeks, 3 months, 6 months, and 9 months postexplantation. A questionnaire's total score was determined by summing (1) the number of symptoms self-rated by the patient as being suffered at the time of the assessment only "mildly," (2) the number of symptoms self-rated as being suffered "moderately" and multiplying by 2, and (3) the number of symptoms self-rated as being suffered "severely" and multiplying by 3.

Capsules removed during surgery in BII and CG1 patients (Figs. 1A, B), and healthy breast tissue from prophylactic mastectomy CG2 patients, were placed in formalin and sent for standard histopathological hematoxylin and eosin staining.

CD117 stains, too, were performed on the capsules of BII and CG1 patients to highlight mast cell counts (MCCs) specifically.[18]

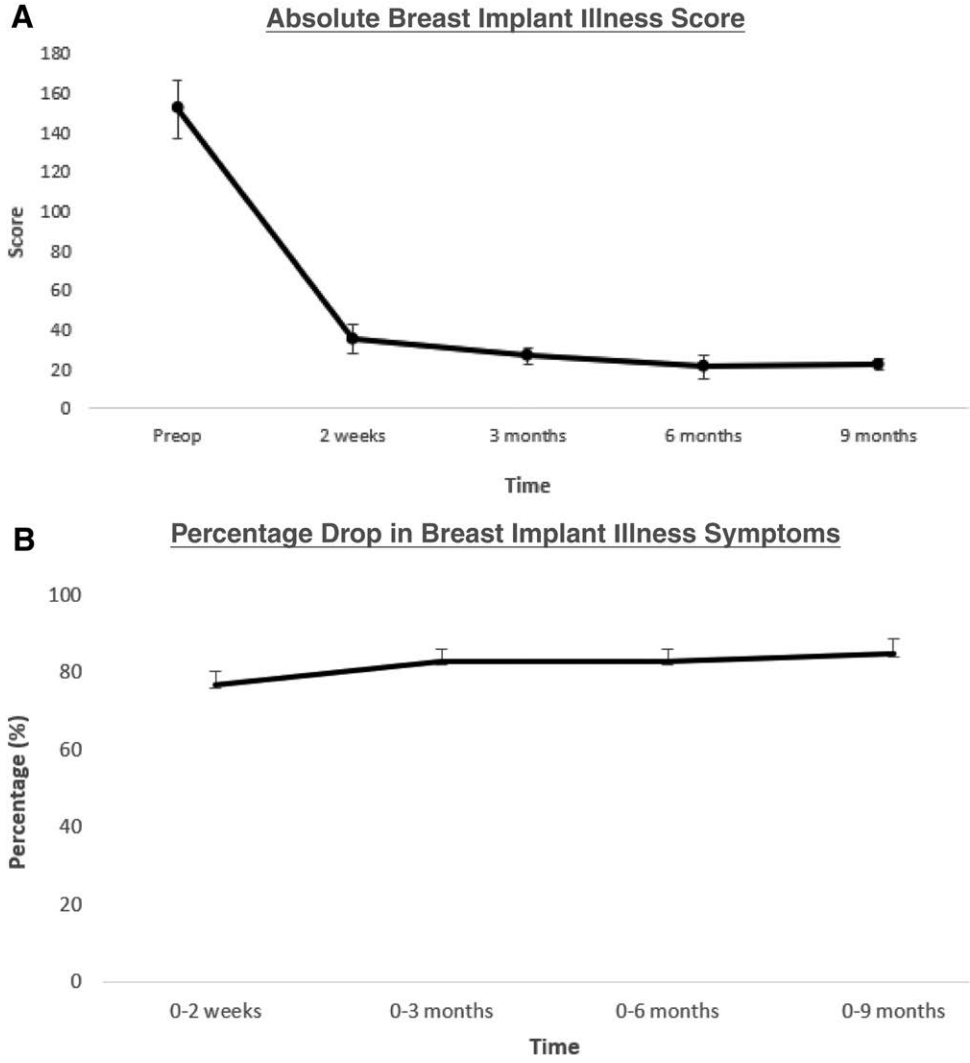

FIGURE 2. A, Absolute breast implant illness score over time (breast implant patient cohort) (average ± SEM). B, Percentage drop in absolute breast implant illness scores over time (breast implant patient cohort) (average ± SEM).

An average count for any given section was determined from examining 5 randomly selected high-power fields (HPFs; 40× objective × 10× ocular = 400× magnification), and the maximum count for that section was determined by counting the MCs in the 1 HPF showing the greatest number of bright-CD117-stained cells. Similar average and maximum counts were determined in CD117 stains of random breast tissue samples of CG2 patients undergoing mastectomies either prophylactically or for breast cancer (only healthy noncancer side analyzed).

BII absolute and reduction symptom scores were analyzed between subject group and CG1 group using student *t* test. MCCs were analyzed amongst all 3 groups using one-way ANOVA test results.

RESULTS

Mean BII symptom score in BII patients was 152 [standard error of mean (SEM): 15.9] preoperatively. The mean BII symptom score as early as 2 weeks postexplantation was significantly reduced to 35 (SEM: 7.6; $P < 0.0001$) (Fig. 2A). The drop in BII symptom score from preoperatively to postoperatively was significant ($P < 0.0001$) at each postoperative time point.

Analyzing score reduction by percentage [(preoperative BII score vs week 2 postoperative BII score) × 100], there was a 77% decrease in the burden of assessed BII symptoms within the first 2 weeks after explantation surgery (preoperative BII score vs week 2 postoperative BII score; $P < 0.0001$) (Fig. 2B). Gradual improvement continued over the next 9 months, resulting in 85% decrease in BII symptom burden (preoperative vs 9 months postoperative; $P < 0.0001$) (Fig. 2B). The BII score reduction by percentage from preoperative to postoperative was significant ($P < 0.0001$) at each postoperative time point. No patient had a relapse of symptoms within the duration of the study, and all patients had a statistically significant improvement in their disease severity.

Informal symptom review for 3 BII patients who were 2 years from surgery (though without the BII questionnaire administered) did not find any relapse in their BII symptoms.

CG1 patients at initial consultation who were removing implants purely for improvement in cosmesis or capsular contracture self-reported they believed they did not have BII. However, on analysis of the BII questionnaire scores, there was evidence of BII-related symptoms, with similarly rapid and marked improvement postexplantation as in the BII Group (Fig. 3A). Similar to the BII Group, the greatest improvement occurred in the first 2 weeks with 70% symptom reduction, with further improvement at 9 months: 77% decrease in disease severity compared to the preoperative state (Fig. 3B). The drop in BII symptom score from preoperatively to postoperatively was significant ($P < 0.0005$) at each postoperative time point.

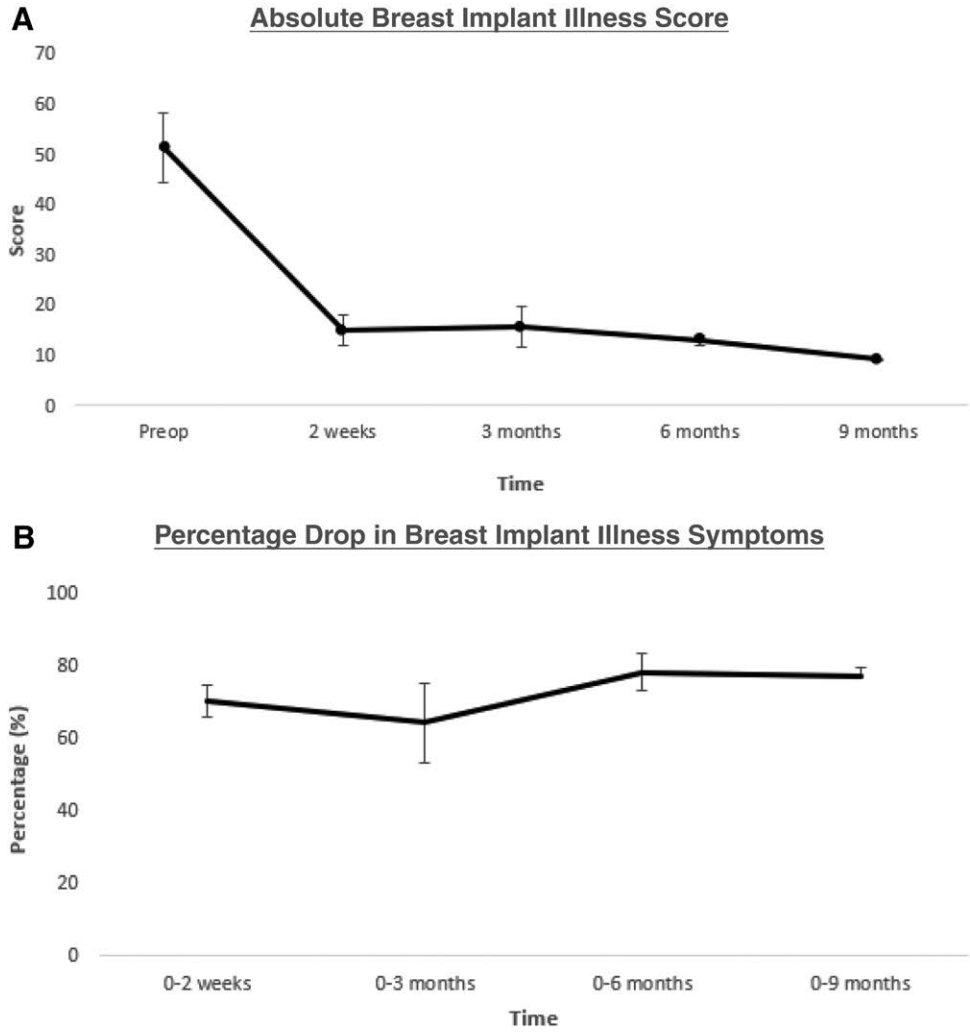

FIGURE 3. A, Absolute breast implant illness score over time [nonbreast implant illness patient (CG1) cohort] (average ± SEM). B, Percentage drop in absolute breast implant illness scores over time [nonbreast implant illness patient (CG1) cohort] (average ± SEM).

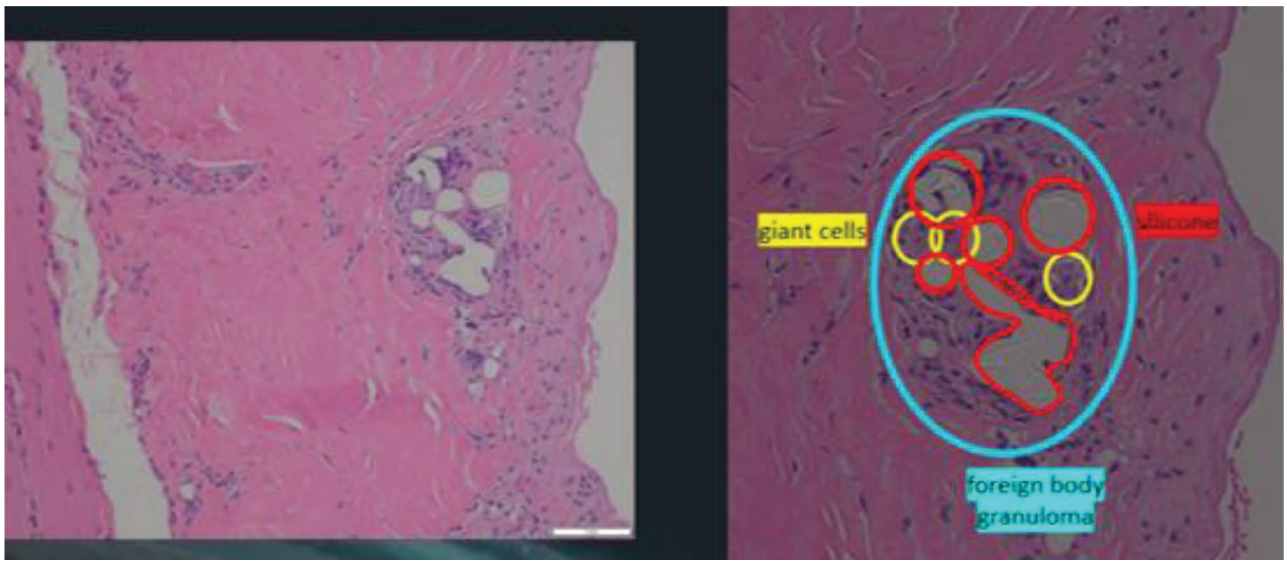

FIGURE 4. Hematoxylin and eosin stains of capsules showing silicone with immune reactive cells.

Overt macroscopic implant rupture was found to have occurred preoperatively on imaging in 3 of 15 BII patients. Histological analysis of the capsules demonstrated silicone fragments in 13 of 15 BII patients, with associated giant cell reaction and granuloma formation, despite no macroscopic rupture (Fig. 4). For the Non-BII CG1 cohort, macroscopic rupture

occurred preoperatively in 1 of 5 patients and microrupture/leak in 4 of 5 patients.

Analyses of MCC using CD117 stain (Fig. 5) in healthy breast parenchymal tissue in CG2 patients showed an average of 5.0 (SEM: 0.3) MCs per HPF and a maximum of 6.9 (SEM: 0.7) MCs per HPF. In capsules of BII patients, the average MCC per HPF was 11.7 (SEM: 0.7) and the maximum MCC per HPF was 16.3 (SEM: 0.9). Similar analyses of capsules for Non-BII CG1 patients showed an average of 7.6 (SEM: 0.8) MCs per HPF and a maximum MCC of 13.3 (SEM: 2.0). MCCs were highest in the BII group, moderately elevated in the CG1 group and lowest in the CG2 group. The MCCs of BII patients were significantly different in maximum ($P < 0.05$) and average numbers ($P < 0.005$) compared to CG1 and CG2 patients using t test analysis. One-way ANOVA testing among all 3 groups showed the maximum and average MCCs for each group were significantly different than in each of the other 2 groups ($P < 0.0001$) (Fig. 6).

The average duration of surgery (including explant, total capsulectomy, and muscle repair) was 4.1 hours (standard deviation: 43 minutes). No immediate or delayed complications occurred, and no representation to the emergency department or hospital, repeated surgery, or other invasive postoperative procedures was needed for any patient.

DISCUSSION

MCAS is a multisystem disease that can manifest a broad set of symptoms, including (but not limited to) chronic fatigue, joint pain, multiple allergies, brain fog, gastrointestinal disturbances, and fibromyalgia. Many BII patients do not experience these symptoms until after breast implants are inserted. Our study was insufficient to establish a definitive diagnosis per published diagnostic criteria[20] of MCAS in our BII and CG1 patients, but the fact that their BII symptom profiles were consistent with what is commonly seen in MCAS, together with the significant and sustained symptomatic improvement upon explantation and total capsulectomy in all of these patients plus the finding of increased MCCs in their capsules, makes it

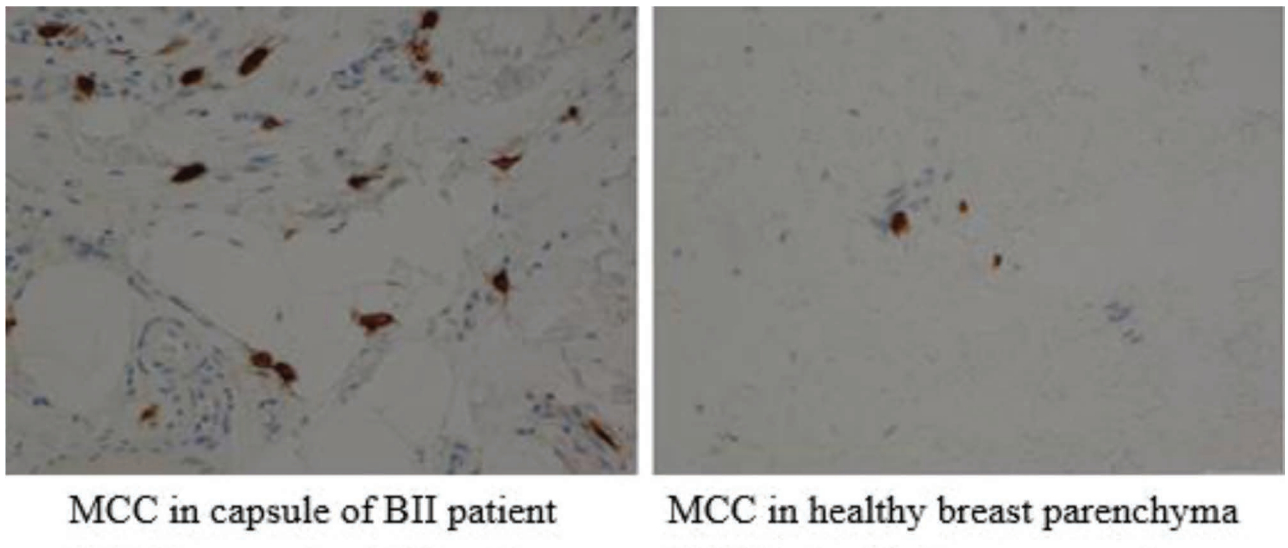

FIGURE 5. CD117 stains from capsule of breast implant illness patient versus healthy parenchymal breast tissue (CG2).

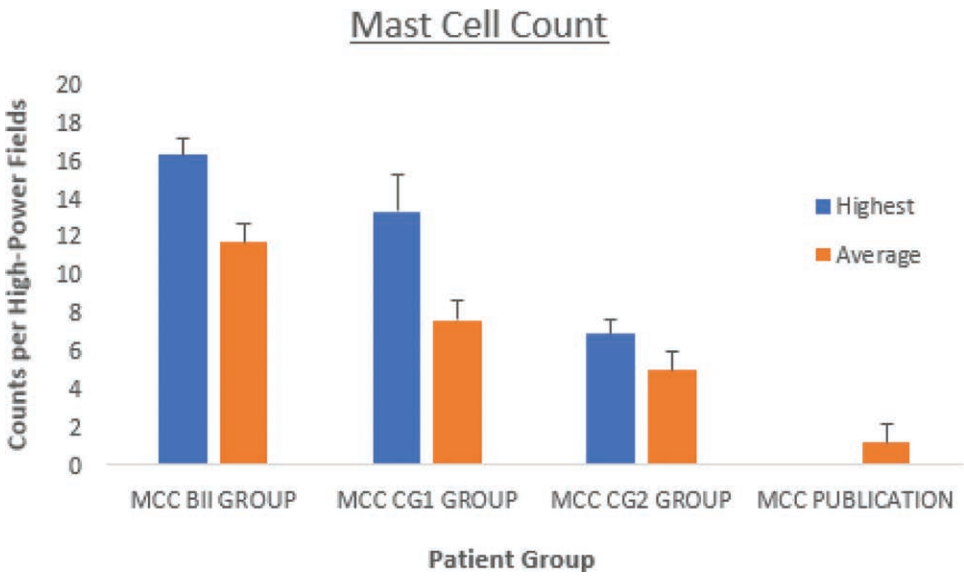

FIGURE 6. Mast cell counts in capsules found in explanted patients versus mast cell counts in healthy breast tissue. Already published normal breast tissue mast cell count added for reference.[19]

likely that the additional laboratory evidence needed for definitive diagnosis of MCAS in these patients would be found if sought.

MCAS is the product of chronic dysfunctional MC activation (ie, inappropriate production and release of mediators with potent local and potentially even distant effects). MCAS usually stems from an assortment, fairly unique to the individual patient and expanding at (typically stressful) points throughout a patient's life, of mostly somatic mutations.[21,22] Sometimes excessive MC proliferation occurs, too, though not anywhere close to the extent, or with the histomorphologic abnormalities, seen in the various types of MC malignancies collectively referred to as mastocytosis.[6] Whilst it is commonly known that mediators such as histamine and tryptase are released via degranulation, there are in fact hundreds of different substances that can be released by a variety of mechanisms,[23] all affecting different responses in different tissues. MCs are present in virtually all tissues but are dominantly sited at the environmental interfaces and abutting vessels and neurons.[24] These factors of the variable mutational menageries, the many involved sites, and the multitudes of direct and indirect effects of the multitudes of MC mediators make it easy to understand how MCAS can present with such a great array of symptoms and such extreme heterogeneity of clinical presentation from one patient to the next.

Samoszuk et al[19] determined MCCs in healthy breast tissue, finding a mean of 1.2 per HPF. In our study, a slightly higher mean of 5 MCCs was found in healthy breast tissue of CG2 patients. MCC in capsules of BII patients showed significantly higher average and maximum counts than in CG2 patients. This is consistent with what we have observed clinically, with a strong overlap between symptoms of MCAS patients versus what is observed in BII patients. Interestingly, average and maximum MCCs were higher in capsules of Non-BII CG1 patients, too, compared to healthy parenchymal breast tissue of CG2 patients, mirroring their BII questionnaire symptom scores. Whilst CG1 patients did not place emphasis on their fatigue, poor sleep, mild brain fog, muscle and joint pain, and allergies with rashes, for example, and did not attribute these symptoms to their implants, it is evident they have some extent of BII, given their improvement in symptoms postexplantation. Furthermore, their symptom improvement was not only local (ie, reduced breast or chest pain) from removing the capsular contracture, but also systemic. These data suggest BII occurs in more implanted patients than previously suspected by the patients themselves or their doctors.

Analysis of silicone found in capsules despite no macroscopic rupture indicates either the implants are microscopically leaking, or the casing disintegrates over time, as early as 3 years postinsertion based on the briefest duration that the implant was present in this group of patients. It is known that silicone is able to enter lymphatics and can be found in lymph nodes ("snow-storm appearance").[20] In one report of autopsy findings in a patient who died of causes unrelated to her breast implants, not only were ruptured implants found, but also the silicone was found to have spread to many distant sites including the brain, spinal cord, colon, and kidneys.[25] No studies of the long-term consequences of such leakage have emerged yet.

Once complete removal of implants and capsules was performed in our patients, symptoms began improving within hours (based on patient reports and direct observation) and were significantly resolved by 2 weeks postoperatively ($P < 0.0001$). No patient saw any reversal in postoperative improvement of preoperative symptoms or saw new symptoms emerge. This was likely due to the removal of the implant itself and microscopic silicone fragments often found in the capsules, regardless of whether implant macro-rupture was present or not and regardless of whether more widespread microscopic dissemination of silicone to more distant tissues may have occurred. Once a significant extent of the load of the provocative antigen is removed, inappropriate activation of an MCAS patient's dysfunctional MCs would be expected to be reduced (likely bringing reduction in secondary activation of other cells and systems, too), correspondingly reducing, and sometimes even resolving, many BII symptoms. As such, it is total, rather than partial, capsulectomies that would appear to be the better surgeries for such patients, and our experience has been that total capsulectomy, though requiring more time in the operating room than partial capsulectomy, can routinely be performed safely and may bring a postoperative course and outcomes superior to those brought by partial capsulectomy.

The prevalence of BII is unknown, but MCAS is prevalent (if presently underrecognized), and has a strong female predilection (~4–5:1 female:male, possibly a consequence of the known presence of estrogen receptors on the surfaces of MCs which, upon ligand binding, promote MC activation[3,26]), and typically begins manifesting symptoms by no later than adolescence.[27] Although our study did not assess for such, it is conceivable that many women who have breast implants had antecedent MCAS which was antigenically triggered, by one or more materials in the implant's construction (silicone seems likely to be a key offender), to escalate to a worsened state of chronic inappropriate activation (given the chronic presence of the trigger) and begin manifesting, and continue to manifest, more clinically apparent illness. Our data suggest, too, that a proportion of implanted women do not realize their mild systemic symptoms can be attributed to their implants but nevertheless do have a mild form of BII. Therefore, one can speculate there is underreporting of BII. With increased awareness, more women with BII can undergo full implant removal to improve their health. However, given that no biomarker for predicting the probability of developing BII has emerged, perhaps an even greater public health improvement opportunity might lie in assessing whether a diagnosis of (and, thus, preimplantation assessment for) MCAS could serve reliably as a marker of greater likelihood for developing BII and thus prevent performance of unacceptably risky implantations. Of course, if MCAS is a key driver of BII, other questions also emerge as to whether preoperative assessment for MCAS might help identify inappropriate candidates for other implantation surgeries, too (e.g., abdominal or pelvic mesh of at least certain constructions). The investigation would seem to be warranted, too, as to whether preoperative diagnosis and treatment of MCAS might mitigate postimplantation illness when implantations are medically necessary rather than just matters of cosmesis.

CONCLUSION

Although our studied cohorts were small and we could not definitively assess for MCAS in this retrospective work, our results nevertheless suggest not only that an association between BII and (possibly antecedent) MCAS is likely, but also that in many BII patients, BII fundamentally may be an implant-triggered worsening of MCAS, a prevalent but underrecognized disease which often manifests worsening of inflammatory and allergic-type symptoms in response to novel environmental and foreign material antigenic exposures. Further research is needed not only to definitively assess for MCAS in BII patients and to independently confirm our findings, but also to evaluate whether preimplantation assessment for MCAS can help patients and surgeons alike better identify inappropriate candidates for breast implantation and potentially even other implantation surgeries.

REFERENCES

1. Website. U.S Food & Drug Administration. Available at: https://www.fda.gov/medical-devices/implants-and-prosthetics/breast-implants. Accessed February 21, 2024.
2. Coroneos CJ, Selber JC, Offodile AC, et al. US FDA breast implant postapproval studies: long-term outcomes in 99,993 patients. *Ann Surg*. 2019;269:30–36.

3. Website. Healing Breast Implant Illness. 2024. Available at: https://www.healingbreastimplantillness.com/.
4. Wee CE, Younis J, Isbester K, et al. Understanding breast implant illness, before and after explantation: a patient-reported outcomes study. *Ann Plast Surg*. 2020;85(S1 Suppl 1):S82–S86.
5. Misere RML, Colaris MJL, Tervaert JWC, et al. The prevalence of self-reported health complaints and health-related quality of life in women with breast implants. *Aesthet Surg J*. 2021;41:661–668.
6. Afrin LB, Ackerley MB, Bluestein LS, et al. Diagnosis of mast cell activation syndrome: a global "consensus-2". *Diagnosis (Berl)*. 2021;8:137–152.
7. Molderings GJ, Haenisch B, Bogdanow M, et al. Familial occurrence of systemic mast cell activation disease. *PLoS One*. 2013;8:e76241.
8. Maitland A, Brock I, Reed W. Immune dysfunction, both mast cell activation disorders and primary immune deficiency, is common among patients with hypermobile spectrum disorder (HSD) or hypermobile type Ehlers Danlos Syndrome (hEDS). Proceedings of the EDS ECHO Summit. 2020.
9. Schofield JR, Afrin LB. Recognition and management of medication excipient reactivity in patients with mast cell activation syndrome. *Am J Med Sci*. 2019;357:507–511.
10. Miller CS, Palmer RF, Kattari D, et al. What initiates chemical intolerance? Findings from a large population-based survey of U.S adults. *Environ Sci Eur*. 2023;35:1–19.
11. Afrin LB. Mast cell activation disease and the modern epidemic of chronic inflammatory disease. *Transl Res*. 2016;174:33–59.
12. Katzin WE, Centeno JA, Feng LJ, et al. Pathology of lymph nodes from patients with breast implants: a histologic and spectroscopic evaluation. *Am J Surg Pathol*. 2005;29:506–511.
13. Miller CS, Palmer RF, Dempsey TT, et al. Mast cell activation may explain many cases of chemical intolerance. *Environ Sci Eur*. 2021;33:1–15.
14. Molderings GJ, Zienkiewicz T, Homann J, et al. Risk of solid cancer in patients with mast cell activation syndrome: results from Germany and USA. *F1000Res*. 2017;6:1889.
15. Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. *Blood*. 2010;116:5812–5817.
16. Henning C, Wang J, Swift R, et al. Removal of a silicone gel breast implant in a multiple myeloma patient improved disease status: a case report. *Case Rep Oncol*. 2020;13:1103–1108.
17. Talkington J, Nickell SP. Borrelia burgdorferi spirochetes induce mast cell activation and cytokine release. *Infect Immun*. 1999;67:1107–1115.
18. Arber DA, Tamayo R, Weiss LM. Paraffin section detection of the c-kit gene product (CD117) in human tissues: value in the diagnosis of mast cell disorders. *Hum Pathol*. 1998;29:498–504.
19. Samoszuk M, Kanakubo E, Chan JK. Degranulating mast cells in fibrotic regions of human tumors and evidence that mast cell heparin interferes with the growth of tumor cells through a mechanism involving fibroblasts. *BMC Cancer*. 2005;5:121.
20. Samreen N, Glazebrook KN, Bhatt A, et al. Imaging findings of mammary and systemic silicone deposition secondary to breast implants. *Br J Radiol*. 2018;91:20180098.
21. Molderings GJ, Kolck UW, Scheurlen C, et al. Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. *Scand J Gastroenterol*. 2007;42:1045–1053.
22. Molderings GJ, Meis K, Kolck UW, et al. Comparative analysis of mutation of tyrosine kinase kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics*. 2010;62:721–727.
23. Molderings GJ, Afrin LB. A survey of the currently known mast cell mediators with potential relevance for therapy of mast cell-induced symptoms. *Naunyn Schmiedebergs Arch Pharmacol*. 2023;396:2881–2891.
24. Walsh LJ, Murphy GF. Role of adhesion molecules in cutaneous inflammation and neoplasia. *J Cutan Pathol*. 1992;19:161–171.
25. Kappel RM, Boer LL, Dijkman H. Gel bleed and rupture of silicone breast implants investigated by light-, electron microscopy and energy dispersive X-ray analysis of internal organs and nervous tissue. *Clin Med Rev Case Rep*. 2016;3:1–9.
26. Vliagoftis H, Dimitriadou V, Boucher W, et al. Estradiol augments while tamoxifen inhibits rat mast cell secretion. *Int Arch Allergy Immunol*. 1992;98:398–409.
27. Afrin LB, Self S, Menk J, et al. Characterization of mast cell activation syndrome. *Am J Med Sci*. 2017;353:207–215.