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CASE REPORT
Breast

Two Independent Capsules Surrounding a Single Textured Implant in Ehlers-Danlos Syndrome

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Summary: Textured breast implants are associated with prolonged inflammation leading to increased risk for complications such as the development of anaplastic large cell lymphoma. The underlying molecular mechanisms that drive increased inflammation toward textured implants (compared with smooth implants) remain poorly understood. Here, we present the first known case of a patient with Ehlers-Danlos syndrome (EDS) who developed two independent fibrotic capsules around a single textured silicone implant. The patient was found to have one internal capsule tightly adherent to the implant and a second external capsule that was attached to the surrounding tissue. We observed that the internal implant-adherent capsule was composed of a highly aligned and dense collagen network, completely atypical for EDS and indicative of a high mechanical stress environment. In contrast, the external nonadherent capsule, which primarily interacted with the smooth surface of the internal capsule, displayed disorganized collagen fibers with no discernible alignment, classic for EDS. Remarkably, we found that the internal capsule displayed high activation of monocyte chemoattractant protein-1, a mechanoresponsive inflammatory mediator that was not elevated in the disorganized external capsule. Taken together, these findings demonstrate that the tight adhesion between the textured implant surface and the internal capsule creates a high mechanical stress environment, which is responsible for the increased local inflammation observed in the internal capsule. This unique case demonstrates that mechanical stress is able to override genetic defects locally in collagen organization and directly connects the textured surface of implants to prolonged inflammation.
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The foreign body response to breast implants often leads to capsular contracture, which necessitates expensive and invasive revision surgeries.[1] In this regard, textured breast implants were developed in the hopes of improving implant positioning and reducing rates of capsular contracture.[2] However, subsequent research has shown that textured implants are associated with prolonged inflammation, leading to unintended consequences such as the development of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).[3,4] The underlying molecular mechanisms that drive increased inflammation toward textured implants (compared with smooth implants) remain poorly understood.

In patients with underlying connective tissue disorders such as Ehlers-Danlos syndrome (EDS), collagen deposition is altered in a variety of settings, including foreign body response. The disorganized aggregation of collagen fibrils found within the connective tissue of patients with EDS is a hallmark of these disorders.[5] Here, we present a case of a patient with classical EDS (type I) caused by collagen type V alpha (COL5A) mutations, who was found to have two completely independent implant capsules around a single textured breast implant. The patient was found to have one internal capsule tightly adherent to the implant and a second external capsule, which was attached to the surrounding tissue. Because the internal capsule interacted directly with the textured implant and

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the external capsule interacted with the smooth surface of the internal capsule, this unique case provided a valuable window into the factors underlying the prolonged inflammation observed around textured implants.

CASE PRESENTATION

A 59-year-old woman with EDS and a history of left breast implant-based reconstruction with Allergan 410 textured implant (partial submuscular augmentation without mesh or acellular dermal matrix) for cancer presented to our clinic with a severe Baker IV capsular contracture and pain. The patient was concerned regarding the potential risk for BIA-ALCL and sought to exchange her textured implant for a smooth one. Intraoperatively, the left breast implant was found to lie within two distinct capsules (Fig. 1A–C). The internal capsule was tightly adherent to the breast implant, whereas the external capsule was only adherent to the surrounding native subcutaneous tissue (Fig. 1). Interestingly, the internal capsule was present on all textured surfaces but spared the few smooth portions of the textured implant, including the identifying information tag and orientation knobs (Fig. 1B). Upon gross examination, there were no signs of infection in the capsules or the implant. In addition, no evidence for infection was observed in pathology. Complete internal capsulectomy and external capsulectomy were performed, followed by placement of a smooth round silicone 560-cm^3 implant. The patient was discharged and completed a 5-day course of Keflex and had a routine postoperative course.

We found that the internal capsule was tightly adherent to the implant and appeared to be constrained and under high levels of mechanical stress relative to the external capsule, which was attached to the surrounding tissue. Hematoxylin and eosin staining of the internal capsule revealed that it was surprisingly organized and entirely comprised aligned collagen fibers with increased cellularity (**see figure, Supplemental Digital Content 1A**, Hematoxylin and eosin of internal capsule showing unidirectionally aligned fibers with increased cellularity. Optical fields were analyzed from six tissue sections of our case. Scale bars = 100 μm. *P* less than 0.05, **http://links.lww.com/PRSGO/C134**).

Trichrome staining demonstrated that this internal capsule was composed of thick fibrous tissue with increased collagen deposition (**see figure, Supplemental Digital Content 1B**, Trichrome stain, demonstrating increased collagen deposition in the internal capsule compared with the external capsule. Optical fields were analyzed from six tissue sections of our case. Scale bars = 100 μm. *P* less than 0.05, **http://links.lww.com/PRSGO/C134**). Herovici stain, differentiating between mature (red) and immature (blue) collagens, demonstrated predominantly mature collagen in the internal capsule (**see figure, Supplemental Digital Content 1C**, Herovici stain, demonstrating increased deposition of mature, red collagen staining in the internal capsule. Optical fields were analyzed from six tissue sections of our case. Scale bars = 100 μm. *P* less than 0.05, **http://links.lww.com/PRSGO/C134**), and picrosirius red staining confirmed a highly aligned and tightly packed collagen fiber arrangement (**see figure, Supplemental Digital Content 1D**, Picrosirius red staining, demonstrating the internal capsule with highly aligned and tightly packed collagen fibers, whereas the external capsule shows a disorganized network, consistent with the typical histological presentation of EDS. Optical fields were analyzed from six tissue sections of our case. Scale bars = 100 μm. *P* less than 0.05, **http://links.lww.com/PRSGO/C134**). The presentation of highly organized parallel collagen fibers is consistent with previous

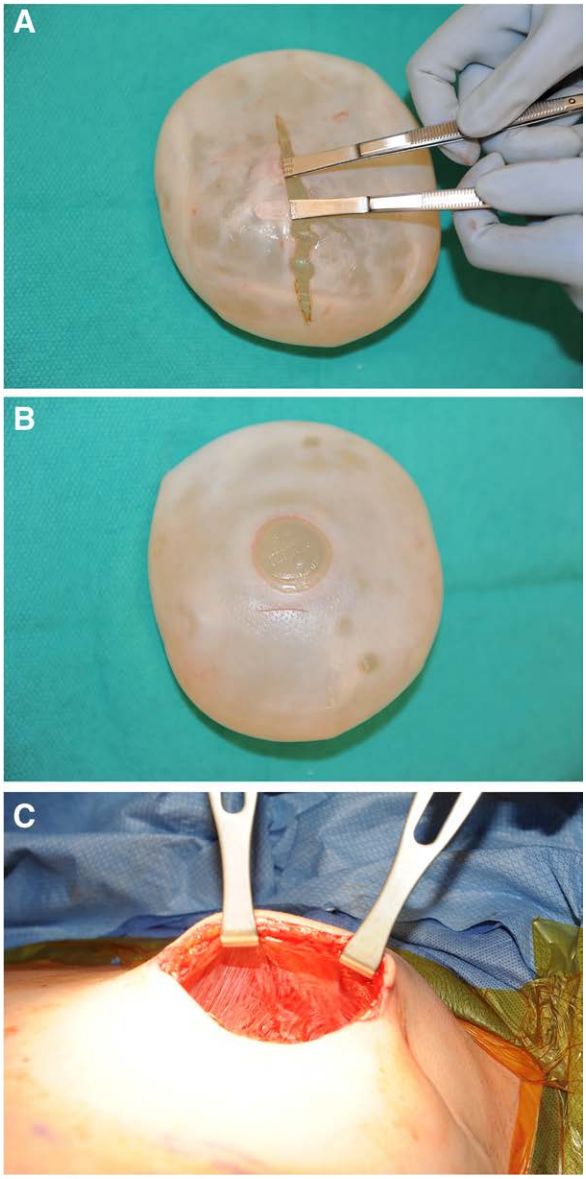

Fig. 1. Intraoperative photographs of double capsule formation around a textured breast implant in a patient with Ehlers-Danlos syndrome. (A) Internal capsule adherent to textured implant surface after opening the capsule on the back table. This capsule has been incised vertically and forceps inserted to demonstrate the tight adherence. (B) The internal capsule covered all textured surfaces but spared the smooth central area on the deep surface of the implant and the three orientation knobs. (C) View of the external capsule, adherent to native subcutaneous tissue, through the wound (superior).

histological evaluations of double capsules.[6–9] However, this presentation is completely atypical of a patient with EDS, which is a disorder known for disorganized, wavy, and weak collagen architecture.[5,10]

To confirm that the adherence of the internal capsule tissue to the implant resulted in elevated mechanical stress, we stained for αSMA, which identifies myofibroblasts that are commonly found in areas of contracture.[11] We observed a significant increase in myofibroblasts in the internal capsule [**see figure, Supplemental Digital Content 1E**, Immunofluorescence staining of the internal capsule shows a higher activation of alpha-smooth muscle actin (αSMA) positive (green) myofibroblasts compared with external capsule. Optical fields were analyzed from six tissue sections of our case. Scale bars = 100 μm. *P* less than 0.05, **http://links.lww.com/PRSGO/C134**]. In as much as elevated mechanical stress is associated with inflammatory signaling,[12] we subsequently performed immunofluorescence staining for monocyte chemoattractant protein-1 (MCP1), an important inflammatory signaling molecule, and observed significantly higher expression in the internal capsule [**see figure, Supplemental Digital Content 1F**, Immunofluorescence staining shows increased expression of cytokine MCP1 (red) in the internal capsule, indicating a highly inflammatory environment. Optical fields were analyzed from six tissue sections of our case. Scale bars = 100 μm. *P* less than 0.05, **http://links.lww.com/PRSGO/C134**].

In contrast, the external capsule comprised loosely dispersed collagen fibers of varying diameters with an irregular fiber outline and no observable alignment, which is classic for type I EDS (**see figure, Supplemental Digital Content 1A–D**, **http://links.lww.com/PRSGO/C134**). Further, increased immature collagen along the edges of the external capsule indicated an ongoing process. Finally, immunofluorescence staining for myofibroblast marker αSMA and inflammatory cytokine MCP1 were both markedly decreased.

DISCUSSION

Although double capsules have been reported in some patients before,[9,14–16] this is the first known case of a patient with EDS with two independent implant capsules surrounding a single textured silicone implant. It seems likely that the two capsules resulted from the shearing of a single capsule at some point in the past, probably due to the COL5A genetic defect present in this patient's type I EDS. We found that the internal capsule was adherent to the underlying textured surface and mechanically constrained

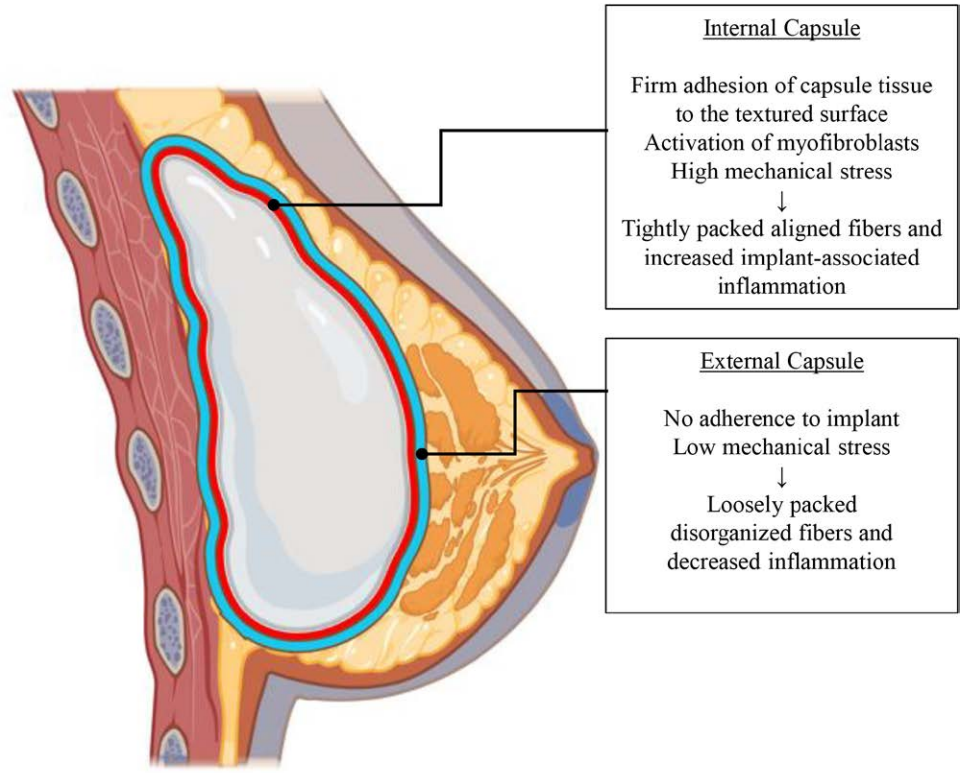

Fig. 2. Local mechanical stress overrides the underlying genetic defect in collagen synthesis and organization characteristic of EDS. The presence of a textured breast implant creates adhesion and subsequently a high mechanical stress environment leading to myofibroblast activation and deposition of collagen in a highly organized pattern. In contrast, the external nonadherent capsule, under low mechanical stress, forms in a manner more consistent with EDS. The mechanical activation of inflammatory signaling protein MCP1 in the adherent/internal capsule provides a direct mechanism for breast implant–associated inflammation, which plays a significant role in the pathogenesis of BIA-ALCL.

by the implant. The significant increase in the number of myofibroblasts in the internal capsule confirmed the presence of a high mechanical stress environment. In contrast, the external capsule primarily interacted with the smooth surface of this internal capsule. This provided the opportunity for the implant and the implant-adherent internal capsule to move within the external capsule. The external capsule demonstrated significantly lower numbers of myofibroblasts, confirming the presence of a lower mechanical stress environment. This resulted in a stark difference in collagen architecture between the two capsules. The internal capsule had highly aligned collagen fibers, similar to those described in pacemaker leads, which are subject to high mechanical forces.[17] In contrast, the external nonadherent capsule displayed a loose collagen phenotype classic for type I EDS.[5,10] Remarkably, we found that the internal capsule displayed high activation of MCP-1, a mechanoresponsive inflammatory mediator that was not elevated in the disorganized external capsule. Taken together, these findings demonstrate that the tight adhesion between the textured implant surface and the internal capsule creates a high mechanical stress environment, which is responsible for the increased local inflammation observed in the internal capsule (Fig. 2).

The presentation of highly organized collagen fibers in the internal capsule is completely atypical of a patient with EDS, which is a disorder known for disorganized, wavy, and weak collagen architecture.[5,10] Despite the presence of EDS, the internal capsule in this patient displayed highly organized and parallel collagen fibers, which is typical for a textured breast implant under a high mechanical stress environment and is consistent with previous reports on other double capsules.[6–9] Thus, this unique case demonstrates that mechanical stress is able to locally override genetic defects in collagen organization and directly connects the textured surface of implants to prolonged inflammation. These findings may have important implications for implant-related adverse events, such as BIA-ALCL and the yet ill-defined syndrome known as breast implant illness, which may represent the sequela of a prolonged inflammatory state induced by the textured surface of breast implants.[18]

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REFERENCES

1. Major MR, Wong VW, Nelson ER, et al. The foreign body response: at the interface of surgery and bioengineering. *Plast Reconstr Surg.* 2015;135:1489–1498.
2. Webb LH, Aime VL, Do A, et al. Textured breast implants: a closer look at the surface debris under the microscope. *Plast Surg (Oakv).* 2017;25:179–183.
3. Collett DJ, Rakhorst H, Lennox P, et al. Current risk estimate of breast implant-associated anaplastic large cell lymphoma in textured breast implants. *Plast Reconstr Surg.* 2019;143:30S–40S.
4. Swanson E. The textured breast implant crisis: a call for action. *Ann Plast Surg.* 2019;82:593–594.
5. Hausser I, Anton-Lamprecht I. Differential ultrastructural aberrations of collagen fibrils in Ehlers-Danlos syndrome types I-IV as a means of diagnostics and classification. *Hum Genet.* 1994;93:394–407.
6. Giot JP, Paek LS, Nizard N, et al. The double capsules in macrotextured breast implants. *Biomaterials.* 2015;67:65–72.
7. Glicksman CA, Danino MA, Efanov JI, et al. A step forward toward the understanding of the long-term pathogenesis of double capsule formation in macrotextured implants: a prospective histological analysis. *Aesthet Surg J.* 2019;39:1191–1199.
8. Efanov JI, Giot JP, Fernandez J, et al. Breast-implant texturing associated with delamination of capsular layers: a histological analysis of the double capsule phenomenon. *Ann Chir Plast Esthet.* 2017;62:196–201.
9. Hall-Findlay EJ. Breast implant complication review: double capsules and late seromas. *Plast Reconstr Surg.* 2011;127:56–66.
10. Bicca Ede B, Almeida FB, Pinto GM, et al. Classical Ehlers-Danlos syndrome: clinical, histological and ultrastructural aspects. *An Bras Dermatol.* 2011;86(4 Suppl 1):S164–S167.
11. Rao K B, Malathi N, Narashiman S, et al. Evaluation of myofibroblasts by expression of alpha smooth muscle actin: a marker in fibrosis, dysplasia and carcinoma. *J Clin Diagn Res.* 2014;8:ZC14–ZC17.
12. Wong VW, Rustad KC, Akaishi S, et al. Focal adhesion kinase links mechanical force to skin fibrosis via inflammatory signaling. *Nat Med.* 2011;18:148–152.
13. Sobey G. Ehlers-Danlos syndrome - a commonly misunderstood group of conditions. *Clin Med (Lond).* 2014;14:432–436.
14. Toscani M, Rizzo MI, Spinelli G, et al. Breast implant complication: calcifications in the double capsule. *Plast Reconstr Surg.* 2013;131:462e–464e.
15. Van Slyke AC, Roller JM, Alaghehbandan R, et al. Defining double capsules: a clinical and histological study. *Aesthet Surg J.* 2021;41:NP1437–NP1444.
16. Barnea Y, Kedar DJ. Management of double capsule. In Kim JYS (Ed.), *Managing Common and Uncommon Complications of Aesthetic Breast Surgery.* Cham, Switzerland: Springer; 2021:109–112.
17. Rennert RC, Rustad K, Levi K, et al. A histological and mechanical analysis of the cardiac lead-tissue interface: implications for lead extraction. *Acta Biomater.* 2014;10:2200–2208.
18. Magnusson MR, Cooter RD, Rakhorst H, et al. Breast implant illness: a way forward. *Plast Reconstr Surg.* 2019;143:74S–81S.