GYNECOLOGY

Characterization of the T-cell response to polypropylene mesh in women with complications

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BACKGROUND: Polypropylene mesh is used widely for surgical treatment of pelvic organ prolapse and stress urinary incontinence. Although these surgeries demonstrate favorable functional and anatomic outcomes, their use has been limited by complications, the 2 most common being exposure and pain. Growing evidence suggests that T lymphocytes play a critical role in the regulation of the host response to biomaterials.

OBJECTIVE: The purpose of this study was to define and characterize the T-cell response and to correlate the response to collagen deposition in fibrotic capsules in mesh tissue complexes that are removed for the complications of pain vs exposure.

STUDY DESIGN: Patients who were scheduled to undergo a surgical excision of mesh for pain or exposure at Magee-Women's Hospital were offered enrollment. Forty-two mesh-vagina tissue complexes were removed for the primary complaint of exposure (n=24) vs pain (n=18). Twenty-one patients agreed to have an additional vaginal biopsy away from the site of mesh that served as control tissue. T cells were examined via immunofluorescent labeling for cell surface markers CD4+ (T_h), CD8+ (cytotoxic) and foxp3 (T-regulatory cell). Frozen sections were stained with hematoxylin-eosin for gross morphologic condition and picrosirius red for collagen fiber analysis. Interrupted sodium-dodecyl sulfate gel electrophoresis was used to quantify the content of collagens type I and III, and the collagen III/I ratio. Transforming growth factor–β and connective tissue growth factor, which are implicated in the development of fibrosis, were measured via enzyme-linked immunosorbent assays. Data were analyzed with the Student's *t* tests, mixed effects linear regression, and Spearman's correlation coefficients.

RESULTS: Demographic data were not different between groups, except for body mass index, which was 31.7 kg/m^2 for the exposure group and 28.2 kg/m^2 for pain (P=.04). Tissue complexes demonstrated a marked, but highly localized, foreign body response. We consistently observed a teardrop-shaped fibroma that encapsulated mesh fibers in both pain and exposure groups, with the T cells localized within the tip of this configuration away from the mesh-tissue interface. All 3 T-cell populations were significantly increased relative to control: CD4$^+$ T helper (P<.001), foxp3$^+$ T regulatory (P<.001), and CD8$^+$ cytotoxic T cell (P=.034) in the exposure group. In the pain group, only T-helper (P<.001) and T-regulatory cells (P<.001) were increased, with cytotoxic T cells (P=.520) not different from control. Picrosirius red staining showed a greater area of green (thin) fibers in the exposure group (P=.025) and red (thick) fibers in the pain group (P<.001). The ratio of area green/(yellow + orange + red) that represented thin vs thick fibers was significantly greater in the exposure group (P=.005). Analysis of collagen showed that collagen type I was increased by 35% in samples with mesh complications (exposure and pain) when compared with control samples (P=.043). Strong correlations between the profibrosis cytokine transforming growth factor–β and collagen type I and III were found in patients with pain ($r \geq 0.833$; P=.01) but not exposure (P>.7).

CONCLUSION: T cells appear to play a critical role in the long-term host response to mesh and may be a central pathway that leads to complications. The complexity of this response warrants further investigation and has the potential to broaden our understanding of mesh biology and clinical outcomes.

Key words: collagen, fibrosis, polypropylene mesh, T cell

Polypropylene mesh is used widely for surgical treatment of pelvic organ prolapse and stress urinary incontinence. Although these surgeries demonstrate favorable functional and anatomic outcomes, their use has been limited by complications,[1–6] which are most commonly mesh exposure through the vaginal epithelium and pain.[7] The mechanism of the host-tissue response as it relates to these complications has not been well-delineated.

All biomaterials, which include polypropylene mesh when implanted in vivo, elicit highly orchestrated cellular and tissue responses that include inflammation and healing of the surgical wound as well as a foreign body reaction to the biomaterial that results in its fibrous encapsulation effectively separating it from surrounding tissues.[8–10] In some patients, the capsule is comprised of a thin layer of collagen and myofibroblasts; in others, it is thought to become pathologic with excessive fibrous tissue deposition. This has been proposed to result in contraction of the mesh that causes it to pull on adjacent tissues and trigger pain.[11] Mesh exposure is thought to occur when stiffness mismatches between the mesh and the underlying tissue initiate a maladaptive remodeling response that is characterized by tissue degradation and atrophy.[11–13] Even though macrophages represent the mainstay of the foreign body response, studies of polypropylene meshes implanted into primates showed that CD3$^+$ T cells were nearly as prevalent as macrophages in the inflammatory infiltrate surrounding mesh fibers.[10]

Growing evidence points towards T lymphocytes playing a critical role in the regulation of the host response to biomaterials that include macrophage fusion and the extent of fibrosis through their interactions with macrophages and fibroblasts via cytokine

Cite this article as: Tennyson L, Rytel M, Palcsey S, et al. Characterization of the T-cell response to polypropylene mesh in women with complications. Am J Obstet Gynecol 2019;220:187.e1-8.

0002-9378/$36.00
© 2018 Published by Elsevier Inc.
https://doi.org/10.1016/j.ajog.2018.11.121

AJOG at a Glance

Why was this study conducted?

This study was conducted to define the T-cell response to implanted vaginal mesh that is implanted during urogynecologic surgery and later removed from women with complications and to correlate the T-cell response with collagen deposition in the fibrotic capsule surrounding mesh fibers.

Key findings

Compared with tissue from control subjects, T cells in tissue from women with complications remain elevated as part of the host response for years after implantation. Mesh-tissue complexes that were removed for exposure had more $CD8^+$ cytotoxic T cells than those removed for pain. T cells have a spatially distinct distribution from macrophages that indicate disparate roles for these 2 cell populations.

What does this add to what is known?

The literature that has examined the T-cell response in women with vaginal mesh complications is scant. Our findings suggest that T cells may play a critical role in the long-term host response and lay the groundwork for further investigation.

and chemokine signaling.[14–21] Characterization of the T-cell response to polypropylene prolapse mesh and the role of T cells in complications, however, remains unclear. The purpose of this study was 2-fold: (1) to define and characterize the fibrotic capsule in polypropylene mesh tissue complexes that were removed for the separate complications of pain vs mesh exposure and (2) to compare the T-cell response in patients with pain (a presumably fibrotic response vs exposure) that is a response purportedly that is associated with degradation.[11] To further characterize the host response, we examined 2 predominant cytokines that are involved in the mediation of the transition to pathologic fibrosis: transforming growth factor−β (TGF-β1) and connective tissue growth factor (CTGF).[9,22] We hypothesized that patients with pain would have increased fibrosis as measured by thicker collagen fibers in the fibrous capsule compared with patients with mesh exposure and increased CD4+ T cells because of their purported role in tissue fibrosis. In patients with exposure, we anticipated observing a less-developed capsule with thinner collagen fibers that are associated with increased cytotoxic T cells, which is indicative of tissue destruction.

Materials and Methods

Patient acquisition

Patients who underwent surgical excision of mesh as part of a larger study (Magee Mesh Biorepository Institutional Review Board #10090194) were offered enrollment. For inclusion in the current study, mesh had to be removed for the primary indication of exposure or pain. Mesh exposure was defined as at least 2 mm of mesh visible through the vaginal epithelium; pain was defined as mesh being removed for the primary complaint of pain (with palpation, ambulation, or intercourse) without evidence of exposure. Patients were excluded from the study if they had acute infection (fever, worsening pain, and purulent drainage in the area of mesh) or erosion into the bowel or bladder. Patients were also excluded if they were unable to provide informed consent, were undergoing chronic immunosuppressive therapy, or had an autoimmune disorder. After consent was obtained, baseline demographic data that were abstracted from the electronic medical record included age, race/ethnicity, body mass index, gravidity, parity, hormone use, menopausal status, and smoking status (Table 1). Menopausal status was defined as premenopausal (regular menstrual periods within the last 12 months) and postmenopausal (no menstrual periods within the last 12 months.) Hormone use was defined as current use of systemic estrogen with or without progesterone or vaginal estrogen for >3 months. Smoking was defined as current smoker (yes/no).

On the day of surgery, the excised mesh-tissue complex was placed in a sterile specimen container and immediately placed on ice and prepared for analysis. Patients were given the option of undergoing an additional full-thickness vaginal biopsy from an uninvolved area (no mesh) on the anterior or posterior wall to serve as control tissue. The control specimens also were placed immediately on ice and sent for analysis.

Tissue extract acquisition and histologic preparation

After being deep frozen, a portion of tissue was extracted in high salt extraction buffer for biochemical assays.[11] Additional pieces were embedded into OCT compound (Tissue-Tek; Sakura Finetek USA Inc, Torrance, CA), flash frozen in liquid nitrogen, sectioned (7 μm), and stored at −80°C.

Immunofluorescent labeling of T cells

Tissue sections were quadruple-labeled for CD4+ (T_h 1; Santa Cruz Biotechnology, Dallas, TX), CD8+ (cytotoxic; Abcam, Cambridge, MA), foxp3 (regulatory T cell [T_{reg}]; Abcam), and nuclear marker 4', 6-diamidino-2-phenylindole, as described,[11] and imaged with a Nikon ECLIPSE 90i upright microscope (Nikon Instruments Inc, Melville, NY). Six images that had been magnified by 200 were acquired over 2 locations within the tissue, as described earlier. For each image, 2 trained technicians who were blinded to the complication group counted the number of total cells and the number of cells that expressed CD4, CD8, and foxp3 to define the T_h, cytotoxic T-cell, and T_{reg} cell population, respectively.

Cytokine determination

Protein concentrations were quantified with the use of DC protein assay (Bio-Rad Laboratories, Hercules, CA). Quantification of cytokines TGF-β and

TABLE 1
Descriptive statistics of study population

Variables	Mesh exposure (n=24)	Pain (n=18)	*P* value
Age, y[a]	52.92±12.38	49.00±11.88	.31
Body mass index, kg/m^2[a]	31.74±5.90	28.22±4.39	.040
Parity, n[b]	2 (2, 3)	2 (2, 3)	.30
Time implanted, mo[a]	53.63±37.70	48.39±37.16	.39
Menopausal status, n (%)[c]			.75
Premenopausal	8 (33)	7 (39)	
Postmenopausal	16 (67)	11 (61)	
Smoking, n (%)[c]			.58
Nonsmoker	8 (33)	9 (50)	
Smoker	7 (29)	4 (22)	
Former smoker	9 (38)	5 (28)	
Race/ethnicity, n (%)[c]			—
White	24 (100)	18 (100)	
Hormone usage, n (%)[c]			.53
Yes	10 (42)	10 (56)	
No	14 (58)	8 (44)	

[a] Values are given as mean±standard deviation; probability value from Student's *t* test; [b] Values given as median (25 percentile, 75 percentile); probability value from Mann-Whitney *U* test; [c] Probability value from Fisher's exact test.

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CTGF was performed with the use of commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, and MyBioSource, San Diego, CA, respectively). All samples were run in duplicate or triplicate with 40-μg total protein per sample per assay. A patient sample that had been characterized previously for analyte amounts served as an internal control.

Fibrotic capsule quantification

Frozen sections were stained with Masson's trichrome and hematoxylin and eosin for gross tissue morphologic evidence and picrosirius red for collagen fiber thickness.[10–12,23,24] The picrosirius red images were taken with a Nikon ECLIPSE 90i upright microscope with the use of a polarized light setting. Six images were acquired over 2 locations of mesh-tissue interface (original magnification, ×200; 3 images were taken in each location) where the fibrotic capsule could be located easily. Nikon elements software (Nikon Instruments Inc) was used to apply custom threshold color filters to quantify areas of red, orange, yellow, and green in close proximity to mesh fibers, which is consistent with thickness of collagen fibers: red indicates thicker, and green indicates thinner fibers. The same color thresholds were used for all samples. The ratio of green/(yellow+orange+red) was calculated to present the ratio of thin/thick fibers.

Collagen and collagen type III/I ratio

Interrupted sodium-dodecyl sulfate gel electrophoresis (SDS-PAGE) was used to quantify the contents of mature collagen type I and type III and their ratios.[25] Briefly, the salt-insoluble tissue pellets after protein extraction were digested with pepsin and freeze dried. Samples were diluted in 2% SDS at 2 mg/mL and isolated on 6% gels by interrupted SDS-PAGE. Purified collagen type I and III (Abcam, Cambridge, MA) were also run on the gels as internal controls, and protein standards (prestained SDS-PAGE Standards High Range; Bio-Rad) were used to indicate molecular weight. Semiquantification of collagen bands was performed by densitometric scanning of protein bands corresponding to α1(I) and α1(III) chains on an imaging densitometer (Bio-Rad Laboratories). The values were normalized to purified collagen type I α1(I) to minimize interexperimental errors. The relative collagen subtype III/I ratio was determined as α1(III) 2/α1(I)×3.

Statistics and sample size calculation

Sample size calculation was based on the demonstration of a difference in T-cell populations as compared with control populations. Because of the limited amount of sample, T-cell assays were prioritized, and sample sizes were reduced on remaining assays, based on sample availability (ie, some samples were exhausted precluding our ability to perform all assays on them). Power analysis showed that 14 women would have 80% power to detect at least a 20% difference in number of T cells between mesh explant and control tissues based on a paired Student's *t* test evaluated at the 2-sided .05 significance level. Statistical analysis was performed with STATA software (version 14.2; StataCorp, College Station, TX); statistical tests were evaluated at the 2-sided .05 significance level. Differences in demographics between participants with mesh exposure or pain were evaluated with the use of Student's *t*, Mann-Whitney *U*, and Fisher's exact tests, where appropriate. Comparison of thick vs thin fibers after picrosirius red staining was made with the use of Student's *t* tests. Spearman's correlation coefficient (*r*) was used to evaluate the relationship of T-cell populations, cytokines, fiber thickness, and collagen ratios with each other and with demographics and time since mesh implantation. Linear regression was used to assess the relationship between T-cell populations and time since implantation. Mixed effects linear models were used to evaluate differences in T-cell populations, cytokines, and collagen subtypes measured in control, exposure, and pain tissue samples.

TABLE 2
Excised mesh brand and type categorized by mesh complications

Mesh device	Removal because of exposure (n=24)	Removal because of pain (n=18)
AMS Monarc TOT (AMS, Minnetonka, MN)	4	3
AMS Miniarc	2	
Bard Ajust Single Incision Sling (Bard, Murray Hill, NJ)		2
Bard Pelvilace		1
Boston Scientific Obtryx TOT (Boston Scientific, Malborough, MA)	1	
Boston Scientific Solyx Single Incision Sling	2	1
Boston Scientific Prefyx	1	
Boston Scientific Lynx TVT		1
Caldera Desara Sling System (Caldera, Agoura Hills, CA)	1	
Coloplast Restorelle Y mesh (Coloplast, Minneapolis, MN)		1
Gynecare TVT Secur (Ethicon, Somerville, NJ)	2	2
Gynecare TVT (Ethicon)	2	1
Gynecare TVT Exact (Ethicon)	1	
Gynecare TVT Abbrevo (Ethicon)	1	
TOT (hand cut prolene mesh)		1
TOT unspecified	4	4
TVT unspecified	1	1
Original medical records not available	2	

Of the 42 patients enrolled in this study, mesh brand information was not able to be determined for 1 of the patients in the exposure group.

TOT, trans-obturator tape; *TVT*, tension-free vaginal tape.

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Results

Demographic data

Mesh-vagina tissue complexes were excised from 42 women: 24 complexes were excised for exposure, and 18 complexes were excised for pain. Twenty-one patients agreed to have an additional biopsy from the vagina away from the site of mesh implantation and served as no-mesh controls. There were no differences in patient age, parity, menopausal status, race/ethnicity, smoking history, hormone use, and time of mesh implantation (Table 1; $P>.05$). Body mass index was greater in the mesh exposure group compared with the pain group (31.7 vs 28.2; $P=.04$). The meshes that were excised are shown in Table 2. Length of time of mesh implantation varied from 1−144 months.

Immunofluorescent labeling

Mesh-tissue complexes demonstrated a marked, but highly localized, foreign body response.[11] We consistently observed a teardrop-shaped cellular response that included the mesh capsule around each mesh fiber in both pain and exposure groups. Within the teardrop, the T-cell population and macrophages were spatially distributed at distinct sites. Although the T cells were localized to the "cap" of the teardrop away from the mesh-tissue interface, the macrophages were limited to the area immediately surrounding mesh fibers at the base of the teardrop (Figure 1).

All 3 T-cell populations were elevated in the exposure group as compared with control tissues: $CD4^+$ T_h ($P<.001$), $foxp3^+$ T_{reg} ($P<.001$), and $CD8^+$ cytotoxic T cell ($P=.034$). In the pain group, however, only T_h ($P<.001$) and T_{reg} cells ($P<.001$) were increased with cytotoxic T cells ($P=.52$) not different from control (Figure 2). A direct comparison of the pain and exposure groups showed more $CD8^+$ cytotoxic T cells in the exposure group ($P=.032$). Interestingly, a comparison of control tissue that did not contain mesh in women with pain vs exposure showed that women with pain had a higher number of T_{regs} (4.02 ± 3.95 vs $1.48+1.27$; $P=.042$). In all mesh explants, CD4+ T_h cells decreased with time after implantation ($\beta=-0.44$; $P=.025$) where β is the mean change in the count of CD4+ T_h cells per month. In other words, for each month of implantation, T_h cells decreased by 0.44, whereas the quantity of T_{regs} and cytotoxic T cells remained the same ($P>.9$).

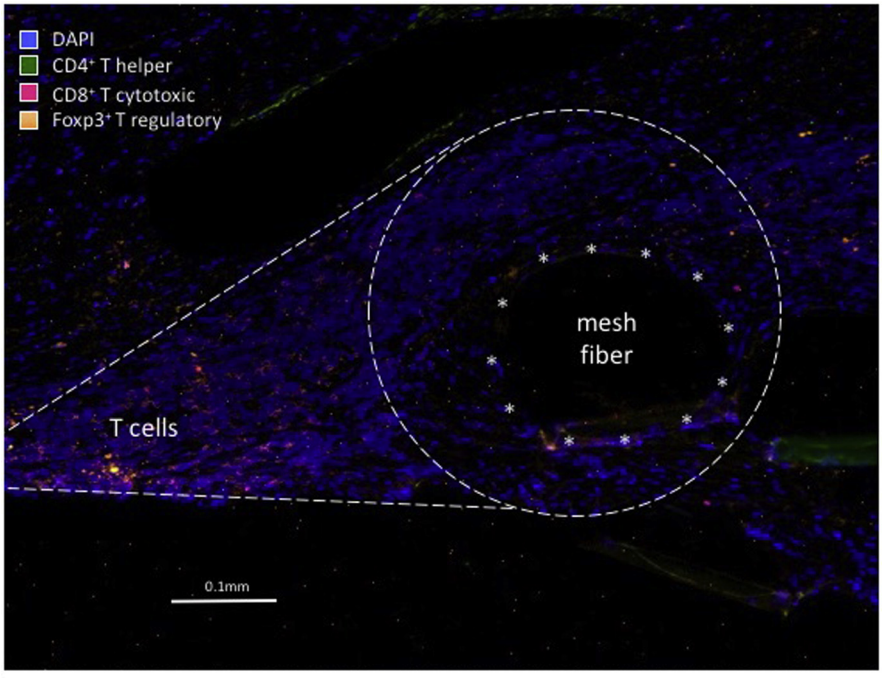
Biochemical endpoints

TGF-β decreased with increasing age ($P=.001$). TGF-β was higher in mesh-vagina explants compared with control tissue but was not significantly different between exposure and pain groups ($P<.001$ and $=.37$, respectively). Although CTGF was higher in mesh-vagina explants compared with control tissue ($P<.001$) and not significantly different between pain and exposure ($P=.11$), it was moderately to highly correlated with all T-cell subtypes (T_h, $r=0.639$ [$P<.001$]; cytotoxic T, $r=0.651$ [$P<.001$]; T_{reg}, $r=0.644$ [$P<.001$]).

Picrosirius red staining

Characterization of the fibrous capsule via picrosirius red demonstrated a greater area of green (thin) fibers in the exposure group ($P=.025$) and red (thick) fibers in the pain group ($P<.001$). The ratio of green/(yellow+orange+red) was greater in the exposure group ($P=.005$) as compared with the pain group and indicated thinner fibers. There was a moderate positive correlation between length of mesh implantation and the area of orange (thick) fibers ($r=.487$; $P=.03$), the area of yellow (thick) fibers ($r=.460$; $P=.041$), and total capsule collagen and length of implantation ($r=.497$; $P=.026$), which supports collagen deposition and maturation of the fibrous capsule over time.

FIGURE 1
Immunofluorescent micrograph



Immunofluorescent micrograph shows the typical T-cell response to a mesh fiber in women with mesh complications. Unlike what is typically seen with the foreign body response in which macrophages immediately surround the mesh fiber (*asterisks*), T cells are observed at a distinct location away from the fiber. (Original magnification, ×200.)

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We did not find a correlation between fiber type (green, yellow, orange, red) and a specific population of T cells. We did find a positive correlation between the number of cells within the capsule and the ratio of (green/[orange+yellow+red]) that supported thinner fibers within the capsule with an increased cellular response (r=.524; P=.037).

Collagen and collagen ratios

Analysis of collagen subtypes showed that collagen type I increased by 35% in samples with mesh complications (exposure and pain) when compared with controls (P=.043), although collagen type III was not significantly different (P=.478). In defining the relationship between TGF-β and collagen, we observed strong correlations of TGF-β with collagen I, collagen III, and the collagen III/I ratio in patients with pain (I: r=0.833 [P=.01]; III r=0.833 [P=.01]; III/I ratio: r=0.857 [P=.007]) but not exposure (P>.65).

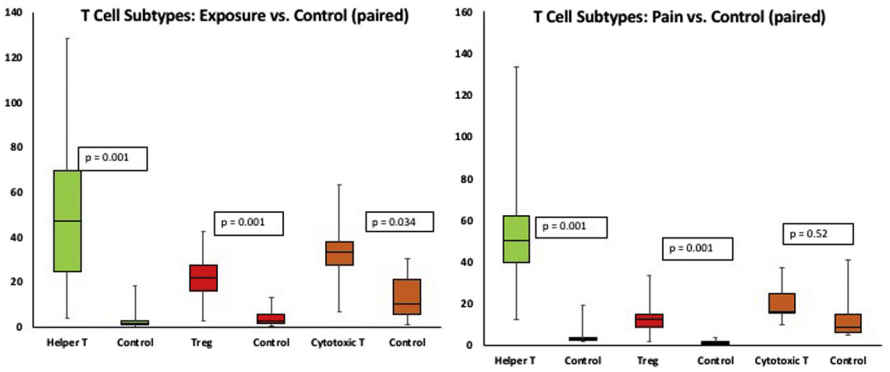
Comments

In mesh-tissue complexes removed for the complications of pain vs exposure, a highly specific host response is observed that is characterized by a fibrous capsule with a dense cellular infiltrate that includes macrophages and T cells at spatially distinct sites that indicate disparate roles for these 2 cell populations. The most important findings in this study were that T cells, typically a transient population associated with the adaptive immune response remain elevated in tissues of women with complications relative to control tissue not containing mesh, years after mesh implantation. No clear distinction was found in the T-cell populations in tissue mesh complexes from women with pain vs exposure, except that $CD8^+$ cytotoxic T cells were higher in women with exposure. The finding of more T_{reg} cells in the control tissue of women with mesh removed for pain deserves further investigation, and we are currently studying differences in T-cell immunity in patients with and without mesh complications. The fibrous capsule in women with pain had thicker, more densely packed collagen fibers with a greater increase of collagen type I than women with exposure. In both the pain and exposure groups, the profibrotic cytokine CTGF was moderately to highly correlated with the 3 different populations of T cells.

We consistently observed a teardrop-shaped fibroma that encapsulated mesh fibers in both pain and exposure groups, with the T cells localized at the "cap" away from the mesh-tissue interface. The shape is observed frequently in both animal models and in women from whom mesh is excised for complications. It requires that a mesh fiber be cut on the cross section and therefore is not always observed. This distribution of T cells is different from the localization of macrophages, which is immediately abutting the mesh fibers.[11] The shape of the response may represent micromotion of a stiff material (mesh) against a softer material (vagina) that results in repetitive injury followed by an adaptive immune response with T_h cells and cytotoxic T cells that participate in the initial host response to the injury and T_{reg} cells involved in resolution of inflammation and repair. Alternatively, the T cells may be responding to cytokines and chemokines that are released by macrophages at the fiber surface, and the cell distribution represents a gradient of these signals.

In a previous study, we demonstrated a positive correlation between M2 (pro-remodeling) macrophages and the profibrotic cytokine interleukin-10 in women with pain.[11] Our findings in the present study of thicker or more mature collagen fibers with a higher proportion of collagen type I in the pain group supports a progressive fibrosis as a potential mechanism that contributes to pain. Likewise, we observed a positive correlation between thicker collagen fibers and length of mesh implantation that suggests maturation of capsule collagen over time. Finally, we showed a strong correlation between TGF-β and collagen type I in patients with pain but

FIGURE 2
Box and whisker plots



Box and whisker plots show T-helper, T-regulatory, and cytotoxic T cells were greater in (**left**) the exposure group compared with paired control tissue, whereas in the (**right**) the pain group only T-helper and T-regulatory cells were greater compared with paired control tissue.

T_{reg}, T-regulatory cell.

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not exposure. Together the data suggest that a mechanism of pain is increased mature collagen deposition that leads to increased stiffness of the tissue and decreased mobility that causes it to pull on adjacent structures an leads to pain.

TGF-β and CTGF were increased in the mesh-tissue complexes compared with controls even years after mesh implantation, which provides further evidence of an on-going chronic host response (Table 3). Although TGF-β is considered a central mediator of fibrosis, similar to interleukin-10, it also acts as an antiinflammatory cytokine that mediates the transition from a proinflammatory response to a pro-remodeling tissue healing response. However, TGF-β may trigger chronic fibrosis when acting in synergy with other profibrotic cytokines, such as CTGF.[20] Our finding that the amount of TGF-β correlated with the collagen deposition (both I and III) in patients with pain provides a supportive evidence for the critical role of TGF-β in chronic fibrosis.

Our finding that $CD8^+$ cytotoxic T cells are increased in women with exposure supports our hypothesis that exposure represents a degradative response. In a previous study,[11] matrix metallopeptidase 9 (MMP-9) was found to be increased in patients with exposure relative to those with pain and matched controls. Whether induced by tissue micro-injury or in response to cytokine/chemokine signals, the adaptive immune response that is triggered after mesh implantation brings T_h cells, $foxp3^+$ T_{reg} cells, and $CD8^+$ cytotoxic T cells into the region. Depending on the ongoing stimulus, our data suggest that T_h and T_{reg} favor a fibrotic response with collagen deposition. On the other hand, a higher cytotoxic T-cell $CD8^+$ population, as seen in women with exposure, appears to trigger degradation and eventually an exposure. Cytotoxic $CD8^+$ T cells, among others, have the ability to produce MMP-9 on stimulation,[26] which suggests that mesh exposure is a potentially T-cell–derived event with MMP-9 playing a pivotal role. It is our general impression that the response to mesh in most women is simply the default foreign body response that occurs after implantation of any device (eg, breast implant, insulin pump, pacemaker). What is not clear is the reason that some individuals experience an overzealous foreign body response to implanted materials. Evolving data suggest that small perturbations in the host response to mesh may change the balance from normal healing to profibrosis to degradation. Future studies will determine which specific host factors direct this response.

A major limitation of the current study is that it was not possible to include a control group of mesh-tissue complexes that were obtained from women who underwent mesh implantation without a complication. As such, the current study does not assess the inflammatory response to prolapse mesh in women with a good outcome and focuses only on the inflammatory response in the setting of complications. We analyzed the host response to mesh in a primate model in a previous study and found that the host response to a mesh with a stable geometry (no pore collapse) and adequate pore size (>1 mm) to preclude bridging fibrosis is typical of the default foreign body response and is limited to the area immediately around the mesh fiber.[10] Our control biopsy specimens were comprised of vaginal tissue that was uninvolved with mesh yet were still obtained from women with a mesh complication. Thus, although this controls for individual variation in the immune response, it is possible that cell immunity is different in women with complications that are relative to those who do not experience a complication. Our strict criteria to include only patients with pain (absence of exposure) in the pain group and only exposure (absence of pain) in the exposure group limited our sample size because these complications often occur together. Because of the limited size of some of the excised meshes, we were not able to perform all of the assays on all of the samples. Thus, a lack of difference in some of the results, specifically collagen subtypes, may be due to an insufficient sample size. Finally, we used all methods possible to quantitate our data as objectively as possible, but the methods were still dependent on tissue staining and cell-labeling techniques and therefore remain semiquantitative.

In conclusion, T cells appear to play a critical role in the long-term host response to mesh and may be a central pathway that leads to mesh complications. The complexity of the T-cell response as it relates to normal and abnormal host response to mesh warrants further investigation and has the potential to broaden our understanding

TABLE 3
Comparisons of growth factors and collagen measurements in vaginal mesh-tissue complexes removed for mesh exposure or pain

Variable	Tissue type[a]			*P* values[b]		
	Control	Exposure	Pain	Exposure vs control	Pain vs control	Pain vs exposure
T-cell population	n=21	n=20	n=17			
$CD4^+$ T helper cell	3.81±5.30	52.75±36.69	58.47±56.02	<.001	<.001	.722
$Foxp3^+$ T-regulatory cell	3.17±3.49	21.87±17.18	14.62±9.18	<.001	<.001	.081
$CD8^+$ cytotoxic	18.84±27.83	37.38±24.75	23.33±15.04	.034	.520	.032
Growth factors, μg/mg	n=11	n=15	n=10			
Transforming growth factor-β	2.18±1.57	4.15±1.89	4.67±2.06	.008	.004	.540
Connective tissue growth factor	1.88±1.16	6.51±3.63	4.14±2.93	<.001	.008	.060
Collagen	n=12	n=16	n=11			
Thin/thick fibers	—	3.14±1.09[b]	1.72±0.91[c]	—	—	.005[d]
Collagen I[e]	0.91±0.41	1.15±0.48	1.33±0.64	.120	.057	.392
Collagen III[e]	0.27±0.18	0.28±0.17	0.39±0.32	.920	.256	.251
III/I ratio[e]	0.19±0.06	0.15±0.06	0.18±0.11	.081	.818	.303

[a] Values represent mean±standard deviation; [b] Probability values from mixed effects linear regression; [c] N=10; [d] From Student's *t* test; [e] Values normalized to internal controls.

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of mesh biologic effect and clinical outcomes. ■

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Received July 3, 2018; revised Oct. 27, 2018; accepted Nov. 1, 2018.

Supported by National Institutes of Health awards R01 HD061811 (P.M.).

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funding source had no involvement in the study design, collection of data, analysis of data, interpretation of data, writing of the report, or the decision to submit for publication.

The authors report no conflict of interest.

Presented at the American Urogynecologic Society (AUGS), Providence, RI, October 3—7, 2017.

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