Peyronie Disease: Clinicopathologic Study of 71 Cases with Emphasis on Histopathologic Patterns and Prevalent Metaplastic Ossification

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Original contribution

Peyronie disease: a clinicopathologic study of 71 cases with emphasis on histopathologic patterns and prevalent metaplastic ossification

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Summary Peyronie disease (PD) is a benign, superficial fibromatosis involving the fascial structures of the penis, causing deformity, pain, and loss of function, for which there are few contemporary studies of the histopathology. We performed a multi-institutional review of 74 routine and consultation specimens submitted with clinical concern for PD. Of these, three non-PD lesions were identified and excluded (a myointimoma, a mammary-type myofibroblastoma, and fibrocalcific atherosclerosis). Of the 71 confirmed to be PD, the majority of patients were white (83%), with a median age of 55 years (range: 26–88). The dorsal aspect of the penis was the most common site involved (78%), followed by lateral (12%) and ventral (10%) aspects. The median degree of curvature was 70° (range: 20–360°). On review, three overall histologic patterns characterized the lesions resected: dense fibrotic plaque (61%), dense fibrotic plaque with focal or patchy metaplastic ossification (35%), and plaque composed predominantly of metaplastic ossification (4%). The fibrotic component was predominantly nodular.

* Competing interest The authors declare that there are no conflicts of interest.
** Note: A preliminary analysis of a subset of these cases was presented at the 2017 USCAP Annual Meeting.
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1. Introduction

Peyronie disease (PD) is a progressive fibromatosis of the penile tunica albuginea resulting in plaque formation and deformity. Clinically, these plaques often result in penile curvature, sexual dysfunction, and pain. The exact prevalence of PD has been difficult to measure, with population estimates ranging from 0.5% of men carrying the diagnosis up to 13% of men who when evaluated meet criteria for diagnosis or show symptoms [1]. One study even suggests the prevalence may be as high as 19% in men aged 35–75 years with penile curvature [2]. Overall, the disease is thought to be significantly more common in individuals with Caucasian ancestry, which may relate in part to its putative association with palmar or plantar fibromatosis [1].

Although the precise pathogenesis of PD remains uncertain, some evidence implicates genetic and traumatic factors in its development and progression. A study of 317 patients with PD found that 22% of the patients reported history of coital trauma compared with 9.5% of the controls [3]. The leading hypothesis attributes the pathogenesis to repetitive microvascular injury with fibrin deposition, which is inadequately eliminated, persistent in tissue, and stimulates fibrosis of the tunica albuginea [4,5]. The frequent association of coital trauma with development of PD plaques is consistent with this hypothesis [3,4,6].

Anecdotally, we have been consulted by surgical pathologist colleagues regarding individual specimens obtained during surgical treatment of penile lesions thought to represent PD. In particular, cases showing patterns not well depicted in contemporary publications and texts have raised diagnostic questions. We suspect that the combination of an aging population and new technologies such as the injectable agent, collagenase clostridium histolyticum, approved for PD treatment since 2013 in the United States, has increased the saliency of PD to clinicians and the public. To evaluate and provide guidance regarding the spectrum of changes expected in PD specimens, we have performed a retrospective clinicopathologic analysis of cases from multiple academic medical centers, with results as follows.

2. Materials and methods

With institutional review board approval from the participating institutions, searches were performed of the laboratory information systems of VCU Health System, University of Michigan Health System, the Medical University of South Carolina, and the Henry Ford Health System. Cases (routine and consultations) previously diagnosed or submitted for treatment of or with suspicion of PD or penile fibromatosis identified by retrospective searches were included for review. For inclusion criteria, all cases were rereviewed and only included if the clinical history and histologic features were consistent with PD, and other entities were excluded.

Clinical parameters were collected, including original diagnosis, patient demographics, clinical history, plaque location, history of trauma or surgery, history of plantar/palmar fibromatosis, and prior diagnosis of erectile dysfunction. Gross and histopathologic parameters evaluated and tabulated included maximal thickness of plaque, the presence of ossification, thickness of metaplastic bone, and the presence, composition, and distribution of inflammatory cells. Fibrosis was evaluated and scored as predominantly lamellar/hyalinized, predominantly nodular, or mixed. The presence of metaplastic ossification was categorized as absent, focal, plaque-like, and extensive. In addition, the maximal thickness of the bone was recorded. After an initial histologic examination, three overall patterns were seen, and on rereview, each case was classified by pattern. These three patterns, defined based on proportions of fibrosis and metaplastic bone, were termed as follows: Pattern 1 consisted of fibrosis only; Pattern 2 showed fibrosis with foci of ossification; and Pattern 3 consisted predominantly of metaplastic bone. Immunostaining was performed under standard CLIA-compliant conditions on a Benchmark Ultra (Roche Diagnostics, Indianapolis, IN, USA). Markers studied included smooth muscle actin (SMA) clone 1A4 mouse monoclonal; CD34 clone QBend/10 mouse monoclonal, pancytokeratin AE1/AE3/PCK26; and β-catenin clone 14, mouse monoclonal, all supplied by Roche Diagnostics, Indianapolis, IN, USA (prediluted).

3. Results

3.1. Clinical characteristics

Database searches and histologic review of cases with a clinical or pathologic diagnosis suspecting PD or penile
fibromatosis identified a total of 74 cases, as summarized in Table 1. Three cases originally clinically thought to represent PD were excluded from analysis (and described in the following section). For the remaining 71 cases confirmed as PD, age at surgery ranged from 26 to 88 years (median: 55 years). The diagnosis was more common in individuals with race documented as white (n = 46; 64%) than black (n = 8; 14%) or American Indian (n = 1; 2%); race was not documented in 16 cases. The degree of curvature (erect) was documented for 43 cases and ranged from 20° to 360° (median: 70°). Of the 49 patients for whom the penile plaque site was documented, 38 were on the dorsal or dorsolateral aspect of the penis (78%) (Fig. 1A), whereas the remaining plaques involved the ventral (n = 5; 10%) or lateral (n = 6; 12%) aspect. Documentation included known history of local trauma (23%) and history of palmar or plantar superficial fibromatosis (28%) in subsets of patients. History of or comorbid erectile dysfunction was reported in 72% patients.

3.2. Gross and microscopic features

PD plaques were typically described macroscopically as elongated fragments of pink-tan to gray, rubbery tissue with a variably palpable bony or calcified component (Fig. 1B–C). Some cases were extensively sclerotic with diffuse ossification and requirement of decalcification for processing. Gross measurements were available for 58 cases and ranged from 0.7 cm to 5.0 cm in greatest dimension (median: 2.1 cm).

Histologically, the most consistent finding was extensive fibrosis of the tunica albuginea characterized by increased, dense collagen deposition and variable numbers of small spindled fibroblasts, forming a thickened (in the transverse plane) plaque. The pattern of collagen deposition in the fibrosis seen in this lesion varied from predominantly smooth, lamellar, and hyalinized (n = 33; 46%) to predominantly nodular (n = 13; 18%) (Fig. 2), with a significant number (n = 23; 32%) showing mixed arrangements of fibrosis. Microscopic measurement of maximal plaque thickness (perpendicular to the skin) varied from 0.1 cm to 1.8 cm (median: 0.4 cm).

Metaplastic ossification was present, at least focally in 28 cases (39%). Ossification was equally focal/microscopic (n = 13; 46%) or forming a plaque-like metaplastic bone (n = 15; 54%). Only one case contained significant dystrophic stromal calcification without metaplastic ossification (n = 1; 1%). Three cases showing plaque-like ossification (4% overall) showed extensive solid bone comprising the vast majority of the PD specimens. Maximal thickness of the metaplastic bone varied from 0.1 cm to 0.8 cm (median: 0.2 cm); plaques harboring metaplastic bone were significantly thicker overall (P = 0.001, U-test). In the majority of cases, inflammation was sparse to absent (n = 50; 70%). When present, inflammation was composed of mildly (23%) to moderately (7%) dense lymphoplasmacytic infiltrates located predominantly within zones of fibrosis. The inflammation was typically perivascular in distribution. Immunohistochemistry for markers associated with fibroblastic/myofibroblastic cells was performed on recut sections of a subset of cases (n = 10). All lesions were negative for pancytokeratin AE1/AE3, and all lesions showed a wild-type β-catenin staining pattern (ie, no nuclear accumulation). Subsets of cases were positive in scattered cells for SMA (3/10), and most cases showed focal (5/10) or patchy (4/10) staining of cellular processes (Supplementary Fig. 1).

Integrating these histopathologic features, we found that while the pattern of fibrosis or degree of inflammation was variable, all cases fell into the three overall histologic patterns (Fig. 3). Pattern 1 cases consisted of fibrosis only (n = 43; 61%). Pattern 2 cases were characterized by plaques with fibrosis and foci of ossification, the latter comprising a minority of the specimens (n = 25; 35%). Pattern 3 cases were composed predominantly or nearly entirely of metaplastic bone (n = 3; 4%). A nonsignificant trend toward lower age was noted in cases with any ossification versus those without ossification (median: 52 years versus 58 years, P = 0.1, U-test) and toward less prevalent inflammation in cases with any ossification (P = 0.09, χ² for trend). The pathologic features of these cases are summarized in Table 2.

One final PD specimen of interest was excised after the patient had undergone one cycle of up to four cycles of collagenase injection. Against medical advice, the patient had engaged in sexual activity less than two weeks after treatment and suffered a small corporal disruption. This was managed conservatively initially, with a delayed excision and grafting 5 months later. Fig. 4 shows representative morphology, which was at low power similar to untreated cases but exhibited a more haphazard pattern of plumper fibroblasts with stromal myxoid change, in areas evocative of later stage nodular fasciitis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical features of Peyronie disease cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature (n with data)</td>
<td>Category</td>
</tr>
<tr>
<td>Age (n = 71)</td>
<td>Median, x̅</td>
</tr>
<tr>
<td>Range</td>
<td>26–88 years</td>
</tr>
<tr>
<td>Race (n = 55)</td>
<td>White</td>
</tr>
<tr>
<td>Black</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Plaque site (n = 49)</td>
<td>Dorsal/dorsolateral</td>
</tr>
<tr>
<td>Lateral</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Ventral</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Erect curvature (n = 43)</td>
<td>Median, x̅</td>
</tr>
<tr>
<td>Range</td>
<td>20°–360°</td>
</tr>
<tr>
<td>History of trauma (n = 52)</td>
<td>12 (23%)</td>
</tr>
<tr>
<td>Personal or family history of fibromatosis (n = 57)</td>
<td>16 (28%)</td>
</tr>
<tr>
<td>History of or comorbid erectile dysfunction (n = 33)</td>
<td>24 (72%)</td>
</tr>
</tbody>
</table>
3.3. Non-PD entities encountered

The review identified three cases submitted with clinical concern for PD that were actually other lesions (Fig. 5). One was a myointimoma, a glans-based lesion arising in a 28-year-old man submitted in consultation for suspicion of PD. The second was a hyalinized myofibroblastoma at the penile base, and the third was corpus spongiosum tissue of the glans, involved by interstitial fibrosis and atherosclerosis with dystrophic calcification presenting as an indurated lesion with flaccid deformity.

4. Discussion

PD, a relatively common condition, affects predominantly older Caucasian men. The clinical features are characteristic and usually strongly suggestive of diagnosis to urologists. Detailed pathologic examination of tissue from excisional specimens may provide confirmatory support for the diagnosis, exclude clinical mimics, and offer insights into pathogenesis, although recent studies of the histopathology are lacking. Overall, we suspect that interest in this area will increase, given the aging population and increased use and availability of pharmaceuticals targeted toward maintenance of sexual function in aging men, including testosterone replacement and phosphodiesterase type 5 inhibitors. As even textbook authors have noted [7], there are few contemporary studies evaluating the histomorphologic features of PD in any detail.

The treatment for PD has long been surgical, although not without attempts at identifying less invasive methods. Overall, oral medications have shown little benefit [8,9]; however, intraliesional injection therapy with collagenase clostridium histolyticum is the first and only U.S. Food and Drug Administration-approved agent for treatment of PD, indicated with a curvature greater than 30° and less than 90° without hourglass deformity or calcified plaques, in the setting of normal erectile function [10,11].

To our knowledge, the post-treatment specimen described herein (excised owing to a treatment complication) represents the first description of the histologic findings associated with collagenase treatment, including a less dense, disorganized pattern of fibrosis, stromal myxoid change, and somewhat larger, reactive-appearing stromal fibroblasts more prominent than the tiny, indistinct fibroblasts in untreated lesions. These observations remain to be evaluated as more such cases are encountered prospectively. Otherwise, the clinical features seen in our cohort

Fig. 1  Clinical features of Peyronie disease (PD). A, By duplex ultrasound, the inverted V-shaped focus of echogenicity with shadow effect indicated by the yellow arrowhead represents a calcified PD plaque. B, Representative gross excision specimen of a PD plaque, photographed from the ventral aspect. C, The plaque pictured in panel B was serially sectioned showing a white pink, fibrous cut surface; alternate sections were generally submitted for histologic review. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
appear consistent with other clinical cohorts of PD, including the median age (55 years) and relative prevalence of dorsal, lateral, and ventral plaques [8,12]. The prevalence of cases with documentation of any erectile dysfunction in the records reviewed was higher (72%) than that described in clinical series (~20–50%) [12], which may reflect documentation based on patients’ reporting rather than distinction from difficulties related to PD and bias toward more severe disease and comorbidities in a cohort selected by surgery. Our cohort’s prevalence of history of superficial fibromatoses (23%) is also similar to prior cohorts [13,14].

Classically, the histomorphology of PD has been divided into phases: an early inflammatory phase with perivascular inflammation, followed by a fibrotic phase characterized by excessive collagen deposition with increased fibroblasts

Fig. 2 Patterns of fibrotic collagen deposition in PD. The thickened and hyalinized PD plaque involving the tunica albuginea showed predominantly paucicellular hyalinized and lamellar fibrosis in nearly half of the cases (A), a disorganized predominantly nodular pattern of fibrosis in a minority of cases (B), and a mixture of lamellar (white arrowheads) and nodular (blue arrowheads) patterns in nearly a third of cases (C). PD, Peyronie disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3 PD plaque anatomy and patterns. In this figure, all three panels show representative PD plaque histology, orienting the outer aspect of the plaques upward. Thus, the area indicated by the dashed, curved line represents where the skin and superficial soft tissue overlie the plaque. In the three panels, the layer of the fibrous PD plaques is identified by white arrowheads, with any osseous component with the plaque layer designated with green arrowheads. The deepest layer of underlying smooth muscular corpora cavernosa is designated by blue arrowheads. On review, a majority (61%) of cases demonstrated only a dense fibrous plaque (A). A smaller subset of cases demonstrated metaplastic ossification, which was focal or patchy, representing a minority of the lesion (35%) (B), and a small subset (4%) showed lesions composed nearly entirely of metaplastic bone (C). PD, Peyronie disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
and a haphazard arrangement of collagen bands, followed by ectopic bone formation accompanying the plaque in a subset of cases [15–19]. Several aspects of our histologic observations are at least consistent with this proposed model and sequence. The relatively lower prevalence of significant perivascular inflammation observed overall is consistent with contemporary clinical practice recommendations against surgery until later stabilization of the disease and plaque. Second, the trend we observed against inflammation in cases with ossification is consistent with ossification being a late-stage feature. Third, our observation that maximal plaque thickness was statistically significantly greater in cases with the proposed later stage ossification also supports this sequence. Finally, the immunohistochemical findings observed support consideration of PD as a lesion composed of cells with fibroblastic/myofibroblastic differentiation, with our observation of focal/scattered SMA-positive cells and more prevalent patchy CD34. Keratin, as is often expressed in myofibroblastic proliferations in the genitourinary tract and other sites, was not expressed in the cells of PD plaques. Importantly, against any relationship to CTNNB mutation as in desmoid-type fibromatosis, no nuclear accumulation/positivity of β-catenin was observed in any of these cases.

The most remarkable aspect of the findings histologically regards the metaplastic ossification seen, which is a remarkably prevalent finding, involving nearly 40% of the plaques in this study. This rate of ossification is somewhat higher than the 20–34% of cases with calcification reported by clinical imaging studies, as reviewed recently [20]. This is also somewhat higher than the proportion of cases bearing histologic ossification in the older reported cohorts by Smith [17] (16%) and Davis [21] (26%) or in a report in the German language by Schick et al. [22] (32%) and may reflect referral bias of more complex cases to our urology specialty centers. From the standpoint of expected histologic range, the degree of ossification in these specimens has never been evaluated qualitatively or quantitatively histopathologically, such that the prevalence of the overall morphologic patterns observed herein may be referenced by surgical pathologists going forward. Pattern 1 (plaque-like fibrosis only) represented the majority of cases; pattern 2 (plaque-like fibrosis with focal or patchy bone) involved more than a third of cases; and pattern 3 (lesion composed of predominantly bone) was present in less than 5% cases. Cartilaginous metaplasia, which has been described in the study by Anafarta et al [15], was not observed in any case.

That said, the relatively high prevalence of explicit ossification in these specimens has never been evaluated qualitatively or quantitatively histopathologically, such that the prevalence of the overall morphologic patterns observed herein may be referenced by surgical pathologists going forward. Pattern 1 (plaque-like fibrosis only) represented the majority of cases; pattern 2 (plaque-like fibrosis with focal or patchy areas of osseous metaplasia) involved more than a third of cases; and pattern 3 (lesion composed of predominantly bone) was present in less than 5% cases. Cartilaginous metaplasia, which has been described in the study by Anafarta et al [15], was not observed in any case.

Table 2  Pathologic features of Peyronie disease cases.

<table>
<thead>
<tr>
<th>Feature (n with data)</th>
<th>Category</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross size (n = 58)</td>
<td>Median, x</td>
<td>2.1 cm</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.7 cm</td>
</tr>
<tr>
<td>Maximal plaque thickness (n = 71)</td>
<td>Median, x</td>
<td>0.4 cm</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.1 cm</td>
</tr>
<tr>
<td>Maximal bone thickness (n = 71)</td>
<td>Median, x</td>
<td>0.2 cm</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.1 cm</td>
</tr>
<tr>
<td>Fibrosis types (n = 71)</td>
<td>Hyalinized/lamellar</td>
<td>33 (46%)</td>
</tr>
<tr>
<td></td>
<td>Nodular</td>
<td>13 (18%)</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>23 (32%)</td>
</tr>
<tr>
<td></td>
<td>(None, bone only)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Overall histologic patterns (n = 71)</td>
<td>Fibrosis only</td>
<td>43 (61%)</td>
</tr>
<tr>
<td>Pattern 2</td>
<td>Fibrosis with focal/patchy bone</td>
<td>25 (35%)</td>
</tr>
<tr>
<td>Pattern 3</td>
<td>Predominantly bone</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Inflammation (n = 71)</td>
<td>None, trace</td>
<td>50 (70%)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>16 (23%)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

Fig. 4  A post-treatment PD plaque. One PD plaque specimen had been previously treated with collagenase clostridium histolyticum, suffering a small corporal rupture, which was excised and grafted 5 months later. At low power (A), a thickened fibrotic plaque was still apparent, although at higher power (B), greater interstitial myxoid change, disorganization, and increased cellularity was noted. PD, Peyronie disease.
Dystrophic calcifications (noted in only one case) is remarkable and highlights something of an unintentional misnomer that is often repeated in the surgical literature. Dystrophic calcification, which by definition occurs in the setting of necrosis or degenerative changes, has been frequently applied as a label to PD plaques, referencing a 1988 study detecting dystrophic penile calcifications in PD by plain X-ray films [23]. Such plaques are also visible by ultrasound (Fig. 1) [20,24], computed tomography, and magnetic resonance imaging [25]. We emphasize that our observations, in the largest cohort ever studied and spanning multiple decades, document that the plaque calcification is in actuality predominantly metaplastic ossification. This observation is also consistent with smaller, older series, which similarly documented metaplastic ossification rather than stromal dystrophic calcification [17,21,22]. Although this distinction may appear technical, we would argue that it may be of relevance to future innovations in management. As current collagenase treatments are considered relatively contraindicated in patients with calcified plaques owing to high rates of treatment failure [24,26], realization that such plaques nearly always represent bona fide bone will be necessary to develop nonsurgical future therapeutic strategies.

Finally, a subset of cases uncovered during this review represented other recognizable entities submitted with suspicion of PD. One such case was a myointimoma, a rare myointimal neoplasm usually arising within the corpus spongiosum of the glans penis [27–29]. Myointimomas present as small, nodular lesions on the glans penis of children and young adults and are treated by simple excision [28,30]. We suspect that this myointimoma may have engendered a differential diagnosis with PD, in part owing to the slightly older age of the affected patient (28 years). The lesions show a serpiginous to nodular growth pattern and extend along vascular channels; these neoplasms are composed of cells with tapered nuclei and elongated cytoplasmic processes within a fibrous and myxoid stroma. Differentiating these from PD plaques is typically straightforward with awareness of the entity, its distinctive histoanatomic location, the angiocentric pattern, and myoid cellularity, as opposed to the paucicellular fibrosis of PD (correlated with appropriate clinical presentation and context). In addition, the diffuse SMA positivity characteristic of myointimomas contrasts the negative to focal/scattered staining of this marker seen in PD.

Another interesting case that was clinically suspected to represent a PD plaque and sent for expert consultation was a mammary-type myofibroblastoma, showing variable epithelioid morphology and dense hyalinization, from around the base of the penis. Mammary-type myofibroblastomas have been frequently reported in genitourinary sites [31,32] and may show overlapping histologic features with spindle cell/pleomorphic lipoma, with which they share CD34 positivity and loss of RB1 expression. Most notably, mammary-type myofibroblastomas demonstrate a...
proliferation of spindled to epithelioid cells within a hyalinized collagenous background with a variably abundant adipocytic component [32,33]. Certainly, the adipocytic component is not present in PD, but extensive hyalinization and a pauciadiPOSE pattern could mimic a PD plaque. In such cases, close attention to the pattern of fibrosis, the presence of metaphasic bone, and the clinical history can help differentiate these from PD plaques. The one final non-PD lesion was fibrocalcific atherosclerosis excised from the glans of a 60-year-old black man with extensive history of vascular disease, renal failure, and diabetes mellitus. It was described as indurated, focally ulcerated, and impacted flaccid penile curvature, raising a clinical, nonhistologic differential with PD.

5. Concluding remarks

In summary, we have described the clinicopathological range of PD, spanning more than 70 cases. Certainly, the pathogenesis of this disease continues to be actively investigated, and clinical interventions for this disease continue to evolve. We hope that greater awareness that the calcification of these specimens represents true ossification might inform development of future investigational therapies. Yet the three overall patterns seen here, and their prevalence described in this diverse cohort, provide needed context for evaluation of the infrequent specimens encountered in surgical pathology practice, as well as a foundation for comparison with potential future specimens excised after treatment failures or complications.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2020.07.013.

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