Review

Clinical Features and Treatment of Penile Schwannoma: A Systematic Review

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Abstract

Schwannomas, although common in the head and limbs, are an exceedingly rare tumor of the penis. We conducted a systematic review to include 33 patients with schwannoma of the penile shaft or glans penis. Most patients presented with a single painless nodule on the dorsal aspect of the penile shaft. These nodules were slow growing, with an average of 62 months from the onset to presentation. Several cases were accompanied by sexual dysfunction. Most histologic studies were consistent, with a benign schwannoma that showed a palisading Antoni A and Antoni B pattern without malignant changes in cell morphology. Of the 14 studies in which a history of genetic disease was investigated, only 2 reported a connection to neurofibromatosis. These tumors were treated with surgical excision, and 4 malignant cases received additional chemotherapy or radiotherapy. All the patients had achieved full remission by the final follow-up examination. Given the rarity of this tumor, the present review of available case studies serves to comprehensively describe the clinical presentation and treatment approaches to penile schwannoma.

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Introduction

Schwannomas are neoplasms composed of Schwann cells, which are responsible for maintaining the myelin sheath of peripheral neurons. A loss of function in the *NF2* gene, which codes for the protein merlin, often gives rise to these tumors.[1] Abnormalities in this gene are also a causative factor in neurofibromatosis, a disorder leading to single or multiple nerve cell tumors. An estimated 3% of schwannoma cases will be associated with neurofibromatosis; thus, a family history of neurofibromatosis is an important clinical factor in these conditions.[2] Cranial nerve schwannomas are a relatively common finding and are discovered in 3% to 4% of patients at autopsy. Peripheral schwannomas, although not uncommon, have a lower incidence of 0.6 per 100,000 people annually, with the vast majority of these tumors found on the flexor surfaces of limbs.[1] Primary tumors of the penis, however, are exceedingly rare, with penile schwannomas even rarer, still. An estimate of as few as 1640 cases of penile cancer were diagnosed in the United States in 2014.[3]

Although the histologic features and morphology of penile schwannomas has yet to be extensively studied, such features of general schwannomas are well known. Formerly termed "neurilemmomas," conventional schwannoma histologic findings will demonstrate Antoni A patterns of nuclear palisades surrounding Verocay bodies with alternating Antoni B patterns. In contrast, cellular schwannomas might show a nonspecific pattern, and plexiform schwannomas might have almost entirely Antoni A with little Antoni B structure.[4] The classic immunohistochemical marker for schwannomas is S100 protein, because they are of neural crest cell origin. This staining marker is useful not only for differentiating neural crest-derived cells from mesenchymal lineages, but also for differentiating between benign and malignant schwannomas. It has been reported that in some cases of malignant transformation, these cells may lose S100 positivity.[5] Benign schwannomas are usually minimally invasive and contained within a capsule. Given this, wide surgical excision has been the standard of care. Malignant transformation of these cells is uncommon, and the prognosis for patients with single lesions is usually excellent.[6]

Schwannomas have been shown to occur most commonly in the extremities and head and neck region, and cases affecting the penis are exceedingly rare. To date, < 35 instances of penile schwannoma have been reported in the published data, with all of them published in the "case report and literature review" form. Thus, the present report is a review of the published studies to comprehensively analyze the available patient data to more definitely explain the clinical presentation and treatment options for penile schwannoma.

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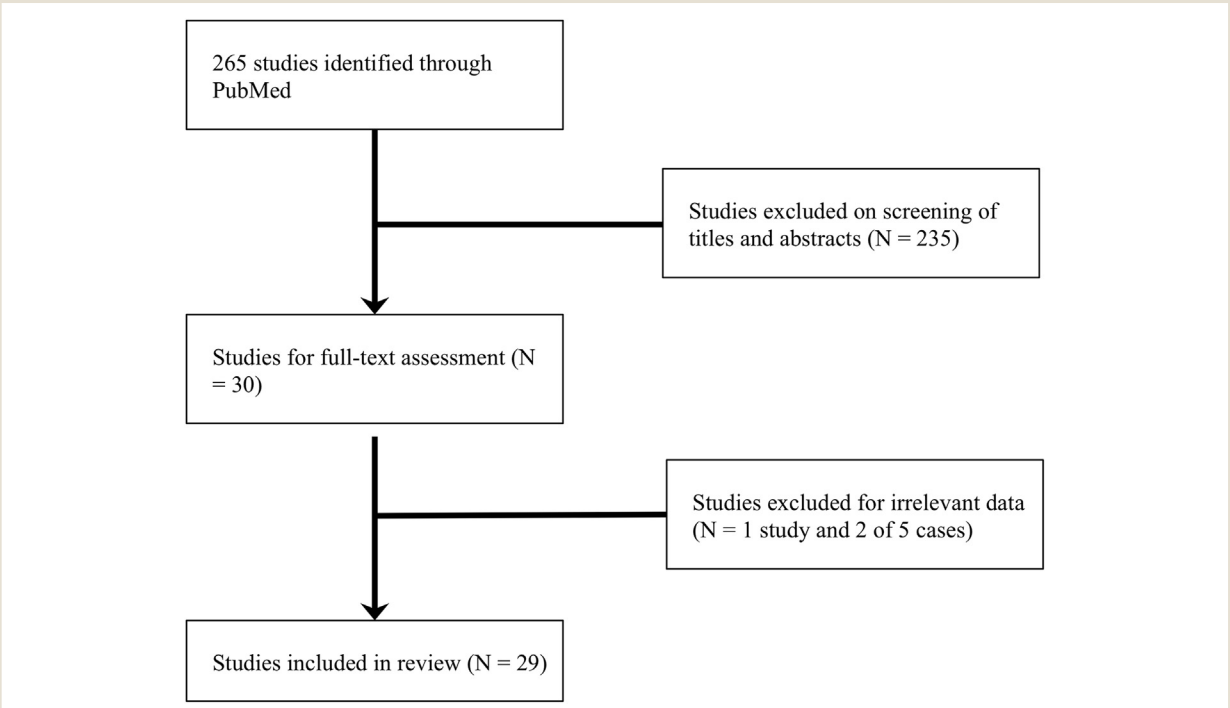
Figure 1 Systematic Search of PubMed Returned 265 Studies. After a Review of the Titles, Abstracts, and Full-Text, 29 Studies Were Included in the Present Review



Materials and Methods

The National Library of Medicine's PubMed database was systematically searched to August 2015. The following search terms were used: "penile" and "penis" combined with "schwannoma," "neurilemmoma," "nerve sheath tumor," "Schwann cell tumor," and "neurofibrosarcoma." The titles and abstracts were screened for possible inclusion, and, subsequently, the full text of the potentially relevant studies were retrieved for review. The studies were excluded if not written in English, not of primary human subjects, or not of malignancies of the penis (ie, schwannomas affecting the scrotal and pelvic regions were excluded).

Results

An initial search of PubMed returned 265 studies (Figure 1). After screening the titles and abstracts for relevance, the full text of 30 reports were retrieved for review. On full text review, 1 report and 3 of 5 cases in a second report were excluded because they discussed schwannomas not affecting the penis. Ultimately, 29 studies were included in the present review, consisting of 33 cases total.[7-35] All included studies were case reports (25 studies) or case series (4 studies). The greatest number of cases was reported in the United States (8 studies), followed by China and India (5 studies each). A summary of the study characteristics are reported in Table 1.

Clinical Presentation

The mean patient age was 39.2 years (range, 14 months to 78 years). The clinical presentation of the 30 included cases (with sufficient information reported) is summarized in Table 2. Most of the lesions presented on the dorsal aspect (n = 18; 60.0%) of the penis and the penile body or shaft (n = 13; 43.3%). Patients presented with a single nodule (n = 20; 66.7%) or multiple nodules (n = 10; 33.3%), with a high of 5 nodules in 1 case. The lesions were generally painless, with only 5 patients reported to have experienced pain or discomfort. Sexual dysfunction was a common complaint, including erectile dysfunction in 3 (10.0%), abnormal penis curvature in 2 (6.7%), pain with ejaculation in 2 (6.7%), impotence in 1 (3.3%), pain with intercourse in 1 (3.3%), and a history of Peyronie's disease in 2 (6.7%). A delayed visit to a medical professional was common, with a mean of 62.0 months (range, 0.25-300 months) after the onset of symptoms. The most common symptom that prompted patients to seek medical care was sexual dysfunction.

Workup

The blood and urine chemistry values were rarely reported. In the 5 patients for whom blood analyses and/or urinalyses were performed, all test results returned within normal limits. The histopathologic findings, summarized in Table 3, were described in 25 cases, of which 6 were graded as malignant. Generally, the histologic findings of penile schwannoma included spindle-shaped or elongated cells (n = 17; 68.0%), often palisading (n = 5; 20.0%) in an Antoni A pattern (n = 17; 68.0%). An Antoni B pattern was observed in 12 cases (48.0%). Many of the lesions were well delineated and/or encapsulated (n = 4; 16%). Signs of aggressive malignancy were rarely seen, although a few cases were reported to have a high number of mitoses (n = 1; 4.0%), necrosis (n = 1;

Table 1 Study Characteristics and Patient Demographics

Characteristic	Studies (Cases) (n)
Country	
China[13,27,33,35]	4 (5)
Germany[20,32]	2 (2)
India[11,15,17,21,28]	5 (5)
Ireland[26]	1 (1)
Japan[16,30,31]	3 (3)
Korea[14]	1 (1)
Spain[7]	1 (2)
Taiwan[8,19,34]	3 (4)
UK[10,12]	2 (2)
USA[9,18,22,23,24,25,29]	7 (8)
Total	29 (33)
Study design	
Case report	25 (25)
Case series[7,9,13,34]	4 (2 each)
Demographics	
Total patients (n)	33
Age (year)	
Mean	39.2
Range	1.2-78

Table 2 Clinical Presentation of Penile Schwannoma (n = 30)

Variable	n (%)
Nodules	
Single	20 (66.7)
Multiple	10 (33.3)
Maximum	5
Pain/discomfort	5 (16.7)
Sexual dysfunction	
Erectile dysfunction	3 (10.0)
Abnormal penile curvature	2 (6.7)
Pain with ejaculation	2 (6.7)
Peyronie's disease	2 (6.7)
Impotence	1 (3.3)
Pain with intercourse	1 (3.3)
Follow-up duration (mo) (n = 26)	
Mean	62.0
Range	0.25-300
Location	
Dorsal	18 (60.0)
Ventral	3 (10.0)
Body/shaft	13 (43.3)
Glans	10 (33.3)
Root	6 (20.0)

4.0%), hemorrhage (n = 1; 4.0%), or pleomorphic appearance (n = 2; 8.0%). Additionally, 1 case was described as having microcystic changes. The use of immunostaining during the evaluation was reported for 19 cases. All cases stained positively for S100. Fewer cases stained positively for vimentin (n = 4; 21.1%) and epithelial membrane antigen (n = 1; 5.3%). No cases stained positively for actin, desmin, smooth muscle actin, or neuron-specific enolase. In 12 cases, neurofibromatosis was ruled out clinically and/or a family history was not present. Only in 2 cases was the possibility of neurofibromatosis reported because of the clinical diagnosis and family history, respectively.

Some form of imaging was performed in 14 cases, with ultrasound the most common modality used (n = 12). Of the 5 cases, the lesion was found to be hypoechogenic in 4. Hypervascularity, determined by Doppler imaging, was reported in 4 cases, and 2 were reported to be avascular or not hypervascular. Five cases had well-defined margins and/or were well-encapsulated, and one had irregular margins. Computed tomography use was reported in 7 cases and was primarily used to rule out metastasis (n = 5).

Outcome

At a mean follow-up period of 20.6 months (range, 1-108 months), 18 of 22 patients had achieved complete remission without recurrence (sufficient data were provided only for 22 cases). Of the 6 malignant cases, 3 developed recurrent and/or metastatic tumors that required more extensive treatment but resulted in eventual remission. Only 1 of the 16 patients with benign lesions developed a recurrence.

All benign tumors were treated with surgical excision. In 2 cases, partial penectomy was performed, with 1 patient undergoing concurrent prostatectomy. One patient showed the growth of 3 new nodules 4 months after the initial surgery, which was successfully treated with additional resection.[23] With this single exception, all

Table 3 Histologic Characteristics of Penile Schwannoma

Characteristic	n (%)
Histologic finding (n = 25)	
Spindle/elongated cells	17 (68.0)
Antoni A pattern or Verocay bodies	17 (68.0)
Palisading	5 (20.0)
Antoni B	12 (48.0)
Well-delineated and/or encapsulated	4 (16.0)
Mitosis	1 (4.0)
Necrosis	1 (4.0)
Hemorrhagic	1 (4.0)
Pleomorphic	2 (8.0)
Immunostaining (n = 19)[a]	
Positive S100; S100 diffuse staining	19 (100)
Diffuse staining	6 (31.6)
Positive vimentin	4 (21.1)
Positive MUC1/EMA	1 (5.3)
Negative actin	3 (15.8)
Negative desmin	4 (21.1)
Negative SMA	3 (15.8)
Negative NSE	1 (5.3)

Abbreviations: EMA = epithelial membrane antigen; MUC1 = mucin 1; NSE = neuron-specific enolase; SMA = smooth muscle actin.
[a]Not all stains performed in the 19 cases providing immunostain data.

cases of benign schwannomas had no recurrence after surgical treatment.

In contrast, the malignant growths often required more extensive treatment, in addition to surgical excision. Of the 6 patients with malignant disease, radiotherapy was used in 3 and chemotherapy in 1. One patient with multiple metastases from a penile schwannoma underwent microsurgery and, separately, several gamma knife radiosurgeries for brain metastases, surgical removal of a gall bladder metastasis, and penectomy.[32] Another particularly refractory case received 2 unsuccessful courses doxorubicin and ifosfamide, followed by partial urethrectomy and partial penectomy.[15] The patient ultimately underwent complete penectomy with adjuvant 3-dimensional conformal radiation therapy (total dose, 5580 cGy). This case demonstrated a 35% growth in tumor size after chemotherapy. After the last therapy, however, no recurrence was observed. Finally, another malignant case received surgical removal, followed by postoperative radiotherapy (60 Gy in 30 fractions) and adjuvant chemotherapy with ifosfamide and Adriamycin. At 3 months of follow-up, no recurrence had been observed. Two additional malignant cases were treated with surgical excision.[9] Although one of these patients was reportedly alive and well at 2 years postoperatively, the other was lost to follow-up. Another case of a malignant penile schwannoma in a 3-year-old boy demonstrated no signs of recurrence at 5 years, 6 months after multiple tumor resections.[26]

Discussion

The overall clinical picture of penile schwannoma is fairly consistent. It generally presents as a painless mass most commonly on the dorsal shaft. Often, patients will delay seeking medical attention until sexual function has been affected. Blood and urine chemistry findings are generally unremarkable. Histopathologic examination will exhibit characteristics of a classic schwannoma: spindle-shaped cells often palisading, with a mixture of Antoni A pattern and Antoni B patterns. Generally, the lesion will be well-delineated and/or encapsulated. All cases will stain positively for S100, with most staining diffusely; findings suggestive of a benign lesion. Neoplasms can also stain positively for vimentin and/or epithelial membrane antigen. Ultrasonography will show a well-demarcated hypoechogenic mass. The vascularity of penile schwannomas varies. Computed tomography should be performed to rule out malignancy, although most schwannomas will be benign.

The patient's primary concern in the management of penile schwannoma is the preservation of sexual function. Interference with sexual function was found to be a major provoking factor for patients to seek medical attention, with the longest duration of disease before diagnosis at 25 years.[30] This pattern of presentation is very different from that of penile cancer. In a study of 243 patients with penile carcinoma, no patients reported sexual dysfunction as a presenting complaint.[36] Also, although surgical excision can have cosmetically excellent results, more extensive surgery is often required, including partial, or even, full penectomy in patients with advanced disease. Surgical resection has provided varied results. Full and rapid recovery can be seen in patients, with the return of nocturnal erections as early as 1 month and normal erections at 6 months.[22] However, adverse effects such as the loss of sexual desire and other dysfunction are possible outcomes.

Chemotherapy was administered in 1 case of a malignant peripheral nerve sheath tumor, consisting of 2 cycles of doxorubicin and ifosfamide.[29] The tumor was unresponsive to therapy, growing 35% by volume. Currently, chemotherapy regimens are ineffective for the treatment of penile schwannomas. Alternatively, van Eck et al[32] discussed a case in which gamma knife radiosurgery was used in the treatment of multiple brain metastases from penile schwannoma. The excellent response of these tumors is suggestive of the high sensitivity of this malignancy to single high-dose radiation. Additionally, gamma knife surgery can offer a minimally invasive treatment option for the primary tumor. Further investigation of this approach is warranted.

Conclusion

Penile schwannoma is a rare neoplasm with an excellent prognosis. The clinicopathologic characteristics are consistent with those of benign peripheral nerve sheath tumors, most commonly located on the dorsal aspect of the penis. Surgical removal is the primary treatment modality, with excellent survival rates. In malignant cases, combined therapeutic approaches, including radiotherapy and chemotherapy modalities, should be used. Preservation and restoration of sexual function, however, remains a challenge. Further investigation of minimally invasive alternatives to surgical treatment is highly desirable.

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