Literature Review of Benign Müllerian Papilloma contrasted with Vaginal Rhabdomyosarcoma

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Abstract:

Study Objectives: Benign Müllerian papillomas of the genital tract are rare hence can be mistaken for vaginal rhabdomyosarcoma on initial clinical review. This review of the literature will consolidate the previous cases of Müllerian papilloma reported and look for clues to differentiate the 2 entities.

Design: Case report and literature review

Setting: Pediatric Adolescent Gynecology Clinic in Tertiary Center

Data Source: A search of English language publications from January 2014 until 1951 (the first case report) was performed using the search words "Müllerian papilloma" and "pre-pubertal bleeding". References from previous published reports were also obtained for completeness.

Main Outcome: Literature review of Benign Müllerian papilloma

Results: Since 1951, fifty-six cases of Müllerian papilloma were reported, including 4 cases at our own institution. Co-morbid conditions were found in 31.5% of cases (with 3 cases associated with mesenchymal tumors). The average length of time from onset of symptoms (primarily vaginal bleeding) to diagnosis was 6.7 months (range 1 day to 3 years) with only one case diagnosed incidentally. Median age of presentation was 5 years (range 1day-52 years). Most cases were localized and resected with ease. Histology reveals complex papillary lesions without cytological atypia.

Conclusion: Benign Müllerian papilloma is distinguished from the more significant diagnosis of vaginal rhabdomyosarcoma by initial length of vaginal bleeding at presentation, lack of vaginal wall extension, ease of resection and histopathology. This is compared with vaginal rhabdomyosarcoma, commonly exhibit localized or distant spread at presentation.

Keywords: Benign Müllerian papilloma, rhabdomyosarcoma, prepubescent

INTRODUCTION:

Pre-pubertal vaginal bleeding is most frequently caused by local non-hormonal causes such as trauma, a foreign body or severe vulvovaginitis (1). Rarely, causes such as rhabdomyosarcoma of the vagina can present as vaginal bleeding. Rhabdomyosarcoma is the most common soft tissue sarcoma in children accounting for 4-6% of all malignancies in this age group (0-19). The most common primary sites for rhabdomyosarcoma are the head, the genitourinary tract, and the extremities(2). Younger age at diagnosis (1-9) and non-bladder/non-prostate genitourinary tract subtype have more favorable prognoses (3). The mean age of diagnosis of vaginal rhabdomyosarcoma is 2 years with almost all occurring in children under the age of 5 (4) compared with cervical rhabdomyosarcoma which is more commonly diagnosed in adolescences (5). Benign Müllerian papillomas (BMP) are rare polypoid masses, which also present with pre-pubertal bleeding, and on first inspection at vaginoscopy, may have an appearance very similar to either vaginal or cervical rhabdomyosarcoma. Therefore, this review aims to characterize any distinguishing features that may aid in the differential diagnosis and thus guide appropriate intraoperative management prior to final histopathology assessment. We will present 4 case reports of BMP along with a review of fifty-two reports in the literature, which may shed further light on clinical presentation and pathogenesis of these rare tumors.

Case 1: A 5-year-old girl presented with a 2-year history of intermittent painless bright red vaginal bleeding of varying amounts. She had attended previous health providers who had initially diagnosed vulvovaginitis, however with ongoing symptoms she was

referred to a Pediatric Gynecology Centre. At the initial consultation, a full history and physical examination using the frog leg position were performed. There was no personal history of trauma, irritation, bleeding diathesis, and no family history of gynecologic cancer. Examination was unremarkable for irritation, or vulvar dermatoses such as lichen sclerosis, and there was no obvious vaginal bleeding. Breast and pubic hair were Tanner stage 1. A bleeding profile was undertaken in view of the unusual duration of bleeding and the activated partial thromboplastin time (aPTT) was slightly increased however a bleeding disorder was excluded. Hormonal testing revealed a normal pre-pubertal profile. Ultrasound showed no significant abnormalities with normal urinary bladder, prepubescent ovaries and uterus. Vaginoscopy revealed a 3cm polypoid friable but solid mass arising from the ectocervix with no obvious extension into the anterior or posterior vaginal walls (Figure 1). A biopsy was performed and 2 weeks later a debulking procedure removed the entire mass to the base of the lesion using forceps and electro-cautery. The pathology described BMP as a complex papillary lesion covered by cuboidal or low columnar surface epithelium without cytological atypia supported by mature fibrous cores.

Case 2: A 7-year-old girl presented with a history of intermittent painless vaginal bleeding. She had a past history of osteosarcoma of the jaw 3 years earlier, treated with surgery, chemotherapy and radiation and considered cured. Physical examination confirmed Tanner Stage 1 breast/pubic hair with no evidence of vulvovaginitis. Vaginoscopy revealed a small polypoid mass with no extension into the surrounding tissue, originating from the region of the cervical os. This was removed entirely at initial

excision/biopsy surgery. At her most recent follow up at age 31, she has had no recurrence.

Case 3: A 9-year-old girl presented with a three-week history of bright red painless vaginal bleeding on a background history of constipation. Her physical examination was unremarkable. Because of the multiple recurrences of bleeding despite treatment for constipation she underwent a vaginoscopy, which showed a frond-like polypoid mass originating from the cervix with the final pathology confirming BMP.

Case 4: A 10-year-old girl with a history of insulin dependent diabetes presented with a one-year history of intermittent painless vaginal bleeding. She was pre-pubertal on examination and investigation. A vaginoscopy showed a very small polypoid lesion originating from the cervix. An excisional biopsy to remove the lesion was undertaken using hysteroscopic forceps.

In summary, all patients presented with intermittent painless bright red prepubescent vaginal bleeding with Tanner Stage 1 breast/pubic hair and no evidence of vulvovaginitis with polypoid masses on vaginoscopy. Vaginoscopy was used to visualize the source of bleeding and the polypoid mass was subsequently removed ensuring the entire lesion was removed from the base of the stalk. The diagnosis of BMP was confirmed in all cases by 2 independent pathologists both specializing in gynecology pathology (CWC and JP). Cytogenetics of the lesion confirmed no clonal abnormalities in case 1 (Figure 3). All 4 patients have been followed up postoperatively with no more episodes of vaginal

bleeding. Case 1, 3 and 4 have had 1-2 years of follow-up. Case 2 has had yearly Papanicolaou testing in adulthood with no visible evidence of recurrence, and has had one hysteroscopy for abnormal uterine bleeding at age 26 (with benign proliferative endometrium on pathology).

METHODS:

A MEDLINE search was conducted of all articles published using the search terms "Müllerian papilloma" and "prepubertal vaginal bleeding" until January 2014. Standard reference tracing was also performed for completeness. Nineteen articles fitting the search criteria were initially obtained using MEDLINE and a further seven were found using reference tracing. All articles were read and non-English articles were excluded. The term "Müllerian papilloma" was first employed in 1981(6) and prior to that the terminology was found to be inconsistent. All the articles included were case reports, mostly of 1 or 2 cases with 1 case series including both pre-pubertal and adult cases of BMP that included 14 cases (7).

RESULTS:

Benign Müllerian papilloma (BMP) is a rare tumor of the female genital tract first reported in 1951(8). Since that first case, there have been 55 further reports from 23 different articles (including our case series of 4, summarized in this review) in the literature involving the cervix, vagina or both. These are summarized in Table 1(6, 9-29). The majority of cases (32/56, 57.1%) occurred in pre-pubertal girls with a median age of presentation being 5 years (range 1 day – 52 years). Similar to our cases, most subjects

presented with a history of painless intermittent bright red vaginal bleeding except for one report where the BMP was found incidentally(21). In the literature, vaginal bleeding was often first managed as vaginitis with review of vulvar hygiene and then only with subsequent diagnostic vaginoscopy if there was no resolution. On vaginoscopy, the presentation of BMP can parallel more sinister diagnoses such as rhabdomyosarcoma, endodermal sinus tumor, clear cell adenocarcinoma and papillary carcinomas because of its polypoid appearance. Diagnosis relies on histopathology. Definitive management requires excision of the tumor. The biopsy procedure and the excision may be done as a two-step procedure, which is the standard of care unless the excision is unavoidable with a biopsy (as the treatment for a rhabdomyosarcoma may require a conservative wide local excision with the possible addition of either one or both of chemotherapy and radiotherapy (30, 31)). Frequently by the time a rhadomyosarcoma presents with vaginal bleeding, there is already distant metastasis (in 28.4%) or direct/regional infiltration to adjacent organs (in 16.2%) (32).

Currently, 5 cases of recurrent BMP have been reported in the English literature (7, 9, 12, 16, 21, 27) with 1 of these 5 patients experiencing multiple recurrences and eventually being diagnosed with a malignant transformation (9, 12). That case involved a woman with an intellectual disability and severe cerebral palsy who, at the age of 42 years, underwent partial excision of the mass, with pathology showing borderline changes in the BMP of the vagina with a normal cervix. Three years later she was diagnosed with clear cell carcinoma of the upper one third of the anterior vagina, which was managed conservatively (without surgery) due to the patient's other medical conditions. The

associated use of diethylstilbestrol (DES) in this patient in utero could not be determined and would be useful to know due to its established association with vaginal adenosis and vaginal clear cell carcinoma (33). Three of the 5 patients with recurrences documented in the literature, had recurrences on more than 1 occasion (7, 9, 16, 21, 27). Given the rarity and limited number of recurrences and only 1 documented case of both borderline and subsequently malignant transformation, radical surgery on initial presentation in childhood should be avoided.

DISCUSSION:

Given the concern regarding the alternative diagnosis of rhabdomyosarcoma in the context of vaginal bleeding and a polypoid lesion on vaginoscopy, the main distinguishing features of BMP may include, a relatively long duration of prepubertal bleeding prior to presentation, lack of systemic or abdominal physical examination findings, frond-like structure on vaginoscopy originating from either the vaginal wall or cervix with lack of extension into the vaginal walls (rather than the grape-like vesicular appearance of vaginal or cervical rhabdomyosarcoma), ease of resection and characteristic histopathology showing complex arborizing papillae with fibrovascular cores, and lined by bland cuboidal or low columnar epithelium with no cytological atypia or mitotic activity. Our literature review demonstrates that the mean time to diagnosis for BMP from initial onset of symptoms was 6.7 months (range 1 day to 36 months). In comparison, genital rhabdomyosarcoma has a more fulminant course, with 16.2% presenting with local/regional metastasis at the time of clinical presentation with mucosanginous discharge (32, 34-36) (Table 2).

It is important to note that the majority of cases of BMP reported in the literature particularly in the young, have been associated with another medical presentation ranging from physiological conditions or benign complaints (chronic abdominal pain, pregnancy) to more concerning pathology (history of osteosarcoma). Therefore, in some of these patients, BMP may have been discovered incidentally during management of other conditions, or may have been diagnosed earlier due to co-existing medical care. Furthermore, only cases that cause vaginal bleeding will be investigated by vaginoscopy/hysteroscopy, thus, it is entirely possible that asymptomatic cases are not detected, or may even spontaneously resolve, as suggested by Norris *et al.* in 1966(7).

BMP are thought to develop from maternal hormones that induce intrauterine development of the tumors according to Norris *et al*.(7). However the presence of mesenchymal tumors/conditions [osteosarcoma (current report), Proteus syndrome(22), Wilms tumor (15)] reported in our review is interesting and may shed light on a separate pathophysiology. Vaginal bleeding in a prepubertal girl with a history of mesenchymal tumor may raise further suspicion regarding the presence of a BMP. We await further reports, which will enable exploration of such a potential association.

Less than 10% (5/56) of reported cases of BMP presenting with abnormal uterine bleeding eventually have recurred, with only 1 borderline lesion and subsequent malignant transformation occurring in the same patient (0.9%), Given the paucity of cases reported in the literature, and the low possibility of recurrence the question of long term follow up remains a challenge, particularly in the pediatric population. When these

young women reach the age for cervical screening according to respective country guidelines, it may be useful to include the clinical history of previous BMP diagnosis both to assist the pathologist in review of the slides or to flag the potential for cytopathologist review rather than automated review or HPV DNA testing alone (37). This has been recommended for cases associated with recurrences (21). In 1 case report published in 2007, BMP was confirmed on routine cytological smear as well as on the Thin Prep™ PreservCy™ slide (cytyc Corp., Boxborough, Massachusetts, MA)(13). The one previous report of transformation to clear cell carcinoma raises the question of whether human papillomavirus (HPV), may be a potential etiological agent. Clear cell carcinoma of the cervix has been associated with HPV positivity (38), and has also been reported in very young patients who have never been sexually active (39). However in a report by Hollowell *et al.*, BMP did not demonstrate positivity for either low or high risk Human Papilloma Virus (HPV) genotypes (13). HPV testing of the biopsy specimen is not recommended in the pediatric population, as it does not change management in that age group.

In conclusion, BMP is a very rare benign tumor of the vagina and cervix, which may present with vaginal bleeding and initially raise concern regarding rhabdomyosarcoma. BMP may be recurrent with only one case of malignant transformation in an older woman reported, therefore invasive surveillance in children is not recommended. Surveillance during routine cytological screening in older asymptomatic women is recommended. BMP in children has been reported in association with mesenchymal tumors, which may shed new light on pathophysiology of these tumors.

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Figure Legend:

Figure 1A: Vaginoscopy photograph with 10x magnification of a polypoid cluster of friable tissue protruding from the cervical os with normal prepubescent vaginal hypoestrogenic mucosa and no extension to the anterior or posterior aspects of the vaginal walls.

Figure 1B Demonstration of the vascularity of the pedicle within the mass.

Figure 2: Complex papillary lesion covered by cuboidal or low columnar surface epithelium without cytological atypia supported by mature fibrous cores with a variably dense mixed inflammatory infiltrate including focally prominent mast cells. Haematoxyllin &Eosin staining. The original magnification of the image was 1.6x (picture courtesy of DM).

Table 1: Review of Published English Language Müllerian Papilloma Literature (1951-2013)

N/A – Not Available

Table 2: Comparison of Müllerian Papilloma and Rhabdomyosarcoma. Genital Rhabdomyosarcoma presents on average at an earlier age, can present with metastatic disease and is more likely to be located on the anterior wall of the vagina compared with MP (23).

Literature review of Benign Müllerian papilloma

Table 1: Review of Published English Language Müllerian Papilloma Literature

Article	Age	Length of vaginal bleeding (months)	Co-morbidities	Location	Follow up (months)	Recurrence
McQuillan (Unpublished)	5 years	24	Prolonged Activated Partial Thromboplastin Time (APTT)	Cervix	16	
McQuillan (Unpublished)	7years	<3	Osteosarcoma	Cervix	300	
McQuillan (Unpublished)	9 years	1	Constipation	Cervix	12	
McQuillan (Unpublished)	10 years	12	Insulin Dependent Diabetes	Cervix	12	
Smrkolj 2012(22)	19years	NA	Proteus Syndrome	Cervix	60	
Kumar 2012 (14)	4 years	NA	None	Cervix	0	
Tumini 2010 (23)	9 years	NA	NA	Vagina	NA	
Reck-Burneo 2009 (20)	2 years	4	None	Anterior Vaginal Wall	36	
Hollowell 2007 (13)	15 months	3	None	Cervix	6	

Mierau 2005 (19) (includes report from Steelman 2001 (24))	4 years 9 days	36 9 days	None None	Posterior vaginal wall	4 48	
Lane 2005 (15)	18 months	9	Multiple renal cysts & Wilms Tumour)	Cervix	8	
Arbo 2004 (10)	2 years	6	None	NA	NA	
Abu 2003(9) (includes Dobbs 1998 (12))	4 years	NA	Cerebral Palsy	Vagina	46 years	10 recurrences including borderline malignant changes in 1998 and clear cell malignant changes in 2002
Cohen 2001 (11)	13 years	NA	Post tylenol use	Vagina	NA	
McCluggage 1999 (17)	24 years	NA	Pregnant	Vagina	NA	
Smith 1998 (21)	4 years	None	Chronic abdominal pain	Cervix	35	2 recurrences at 12 & 24 months
Schmedding 1997 (25)	2 years	1.5	NA	Cervix	6	
Luttges 1994 (16)	5years	NA	Whooping cough	Vagina		recurrence at 24 months
Ulbright 1981 (6)	5 years	NA	NA	Posterior vaginal wall	1	

Andrews 1981 (26)	NA	NA	NA	Cervix	NA	
Norris & Taylor (7) 1966	1 day 1 day 36, 30, 20, 52, 20, 51, 29, 41, 18, 17, 40, 31	1 day 1 day Median 2 to 3 months (longer if pregnant)	None 8 pregnant	Vagina Vagina Vagina	96 9 Patient 12 (age 31): 100	Patient 12: 2 recurrences at 4 & 6 months
Janovski & Kasdon 1963 (27)	5 years	12	NA	Cervix (then vagina)	20	recurrence at 4 months
Selzer & Nelson 1962 (28)	3 years 3 years	NA	NA	Cervix Cervix	8.5 2	
Novak 1954 (29)	14 months	<3	NA	Vagina	7	
James 1951 (8)	3 years	<3	NA	Cervix	120	

NA - not available

Table 2: Comparison of Müllerian Papilloma and Rhabdomyosarcoma.

	Müllerian Papilloma	**Rhabdomyosarcoma**
Median Age	5 years, (range 1 day to age 52)	3.7 years (range 0.16 to age 15) (31) but on average 2 years (2) for vaginal and slightly older for cervical rhabdomyosarcoma in the second decade of life (5).
Presentation	Vaginal bleeding (average duration 6.71 months, range 1 day to 3 years)	Vaginal bleeding (61%) with 44.6% having local, regional or distant spread (mainly lung and bone) and a further 28.4% unstaged (27)
Past Medical Conditions	19 with Associated Co-morbid condition (including 8 pregnancy and 3 mesenchymal tumors)	One case associated with trisomy 8 (28); other genetic conditions increase the risk of childhood rhabdomyosarcoma (30)
Location	Vagina (but both anterior and posterior walls) or less	Anterior Wall of the Vagina

	commonly cervix	
Physical examination	Tanner stage 1	Tanner stage 1
Vaginoscopy	Well demarcated friable polypoid cluster with no local infiltration	Gray or tan edematous friable polypoid cluster with possible local infiltration in the vagina or protruding from the cervix.
Resection	Easy with minimal blood loss	Risk of hemorrhage and worse prognosis with incomplete resection (29)
Microscopic Findings	Papillae covered by bland epithelium without cytological atypia or mitotic activity. No cambium layer. Fibrovascular stromal cores.	Densely cellular cambium layer underlying intact epithelium and the presence of associated spindled stromal cells showing rhabdomyoblastic differentiation.

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