Well-Differentiated Villoglandular Adenocarcinoma of the Uterine Cervix: A Report of 15 Cases Including Two with Lymph Node Metastasis

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Abstract

Well-differentiated villoglandular adenocarcinoma is a recently described subtype of cervical adenocarcinoma. The tumor of this type is reported to have distinct clinicopathologic features and excellent prognosis. However, lymph node metastases of this tumor have been described in few reports. Fifteen cases of well-differentiated villoglandular adenocarcinoma treated at Maharaj Nakorn Chiang Mai Hospital were retrospectively reviewed for both clinical and histopathological features. All patients underwent radical hysterectomy with pelvic lymphadenectomy. In the cases with lymph node metastasis, adjuvant radiation therapy was also given. The patients ranged in age from 22 to 53 years (mean, 39.3). Fourteen patients were FIGO stage IB and one was stage IIA. All patients had exophytic friable cervical masses. Tumor size known in 14 cases ranged from 1.5 to 4 cm (mean, 2.3). Eleven tumors (73.3%) were confined to the inner third of the cervical stroma with 9 of these (60%) showing only superficial invasion (depth $\leq$ 3 mm). The tumors invaded deeply to the middle third in 3 cases (20.0%), and to the outer third in one (6.7%). Lymphatic invasion was observed in 3 cases, two of them had pelvic lymph node metastasis. Both patients had tumors involving deeper than the inner third of the cervical wall. The follow-up duration ranged from 21 to 144 months (mean, 67.5). Four of thirteen cases without nodal metastasis were lost to follow-up 36 to 59 months after surgery. All patients showed no evidence of disease at the last visit. Presence of lymphatic invasion and deep stromal involvement appeared to be the risk factors for lymph node metastasis of well-differentiated villoglandular adenocarcinoma.

Key word : Villoglandular Adenocarcinoma, Uterine Cervix, Lymph Node Metastasis

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Well-differentiated villoglandular adenocarcinoma is a subtype of adenocarcinoma of the uterine cervix recently described by Young and Scully in 1989[1]. To our knowledge, approximately sixty cases of well-differentiated villoglandular adenocarcinoma have been reported in the English literature[1-4]. Although the tumors showed an excellent prognosis without recurrence or extrauterine spread in the early studies, few cases of nodal metastasis have been described in the later reports[3,5-7]. The purpose of this study was to describe the clinico-pathological features of well-differentiated villoglandular adenocarcinoma treated in our hospital and to compare our findings with previous reports of this entity.

MATERIAL AND METHOD

The gynecologic tumor registry of the Department of Obstetrics and Gynecology of Maharaj Nakorn Chiang Mai Hospital was searched for cervical cancer cases coded as adenocarcinoma, adenosquamous carcinoma, anaplastic carcinoma, neuroendocrine carcinoma, and undifferentiated carcinoma treated by surgery between 1983 and 1994. Among a total of 106 cases the microscopic slides, pathology reports, and clinical records of which we were able to review, 74 patients had pure cervical adenocarcinoma. Of the 74 cases, twelve cases of well-differentiated villoglandular adenocarcinoma were identified. Three additional patients included two referred cases and a recent case collected by one of the authors (S.S.). All 15 cases formed the basis for this study. Three of these cases had been previously reported[5]. In our institution, patients with early stage cervical cancer (FIGO stage IB and IIA) are routinely treated by radical hysterectomy with pelvic lymphadenectomy which was the surgical treatment for all fifteen patients. Adjuvant radiation therapy was given to the patients who had pelvic nodal metastasis. The clinical data and follow-up information of each patient were obtained from the medical records.

Histopathological review included confirmation of the histologic subtype of the cervical tumors according to the previously described features[1,2], assessment of depth of invasion, epithelial differentiation, and the presence of either lymph-vascular invasion or pelvic lymph node metastasis. Stromal invasion was categorized as superficial if depth of invasion was 3 mm or less. For tumors with invasion deeper than 3 mm, depth of invasion was classified according to the one-third fraction of the involved cervical stroma as the inner, the middle, or the outer third. The adjacent tissue was also examined for an associated squamous intraepithelial lesion (SIL) and adenocarcinoma in situ (AIS). The number of microscopic slides of cervical tissue available for review varied from 1 to 21 (mean, 7.9) per case.

RESULTS

The patients' ages ranged from 22-53 years (mean, 39.3). Fourteen patients presented with either abnormal vaginal bleeding or vaginal discharge or both. The other patient presented with an abnormal cervical smear that led to a subsequent biopsy. Three patients had a history of taking either oral or injectable contraceptives or both, while eight denied any history of hormonal treatment. Information on contraception was not available in four patients. Of fifteen cases, 14 were initially FIGO stage IB and only one was stage IIA (Table 1). On clinical examination, all cases had exophytic friable cervical tumors ranging from 1.5-4 cm in size (mean, 2.3). The size of lesion was not recorded in one case.

Histologically, all tumors had exophytic branching papillary structures (Fig. 1). The papillae were typically long and slender with the lack of complex epithelial budding (Fig. 2). Thick or broad papillae with fibromatous stroma were observed in occasional cases. In most tumors, the papilllae were lined with stratified columnar epithelium which was predominantly of mucinous (endocervical-like) type. The amount of the cytoplasm was, however, variable. Goblet cells were focally present in a few tumors. In three cases (cases 5, 11, and 13), predomination of mucin-depleting endometrioid epithelium was observed. The epithelial cells exhibited mild to moderate nuclear atypia. Mitotic figures and apoptotic bodies were occasionally seen. The deep portion of tumors was mostly well demarcated and composed of elongated branching glands separated by fibromatous or desmoplastic stroma (Fig. 3). Mild to moderate inflammatory response in the papillary or the deep stroma was common. Focal irregularity of the advancing margin was seen when the tumors were deeply invasive of the stroma. Lymphatic invasion was observed in three cases.

In case 12, the tumor arose discontinuously from both anterior and posterior cervical lips. A separate focus of an early invasive adenocarcinoma of poor differentiation (by architectural grade), with

Table 1. Clinical and pathological features of the patients with well-differentiated villoglandular adenocarcinoma.

Case No.	Age	Tumor Stage	Size (cm)	Depth of invasion	Lymphatic invasion	Lymph node metastasis	Clinical outcome	Duration (months)
1	36	IB	2	S	-	-	ANED	144
2	27	IB	3	S	-	-	ANED	128
3	35	IB	2	S	-	-	ANED*	59
4	22	IB	NA	S	-	-	ANED*	56
5	35	IB	3	Middle 1/3	-	-	ANED	76
6	53	IIA	2	S	-	-	ANED	80
7	39	IB	2	S	present	-	ANED	81
8	48	IB	2	Inner 1/3	-	-	ANED	64
9	35	IB	2	Inner 1/3	-	-	ANED*	48
10	49	IB	2	S	-	-	ANED	62
11	34	IB	2	Outer 1/3	present	present (3/15)	ANED	56
12	49	IB	3	S	-	-	ANED*	36
13	45	IB	4	Middle 1/3	present	present (3/21)	ANED	46
14	46	IB	2	Middle 1/3	-	-	ANED	55
15	37	IB	1.5	S	-	-	ANED	21

S : superficial invasion (depth ≤ 3 mm), ANED : alive with no evidence of disease, NA : data not available, * : patients lost to follow.

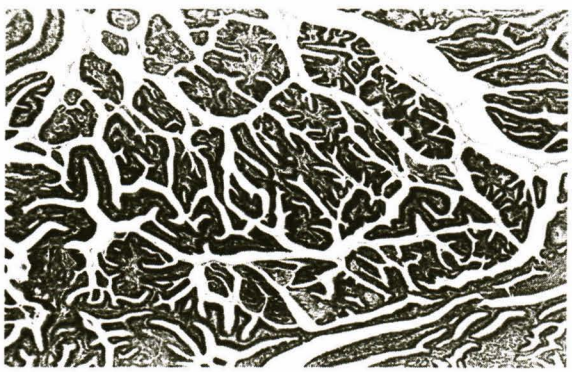

Fig. 1. The exophytic part of the tumor is composed of branching papillae with thin fibrovascular cores. Epithelial budding is lacking. (Hematoxylin and eosin (H&E), original magnification, x 40).

invasive depth of 2.3 mm and lateral dimension of 3.1 mm, was present in case 3. AIS was observed in six cases. High-grade SIL was associated with AIS in three of these cases.

Eleven tumors (73.3%) were confined to the inner third of the cervical wall with nine cases (60.0%) showing only superficial invasion (depth ≤ 3 mm). Three cases (20.0%) had tumors invading to the middle third. In the remaining patient (6.7%), the tumor invaded to the outer third of the cervical stroma. In cases 11 and 13, metastatic tumor in the pelvic lymph nodes was detected. Both cases were associated with lymphatic invasion in the primary tumors. The tumor in case 11 involved the outer third of the cervical wall. The other tumor (case 13) invaded the middle third of the cervical stroma with involvement of the entire ectocervical surface (tumor size 4 cm). Metastatic tumors in the lymph nodes showed papillary pattern similar to the cervical tumors. In case 11, cystic component with intracystic papillary growth was also observed and accompanied by marked fibrotic stromal reaction (Fig. 4).

The follow-up duration ranged from 21 to 144 months (mean, 67.5). Four cases (cases 3, 4, 9, and 12) were lost to follow after 36 to 59 months post-operatively. All patients were alive and well with no evidence of the disease at the last visit (Table 1). Both patients with initial nodal metastasis showed neither recurrence nor metastatic lesion 46 and 56 months after surgery.

DISCUSSION

Well-differentiated villoglandular adenocarcinoma was first described on the basis of the following main clinico-pathological features including distinctive villoglandular morphologic pattern, young age group of the patients, superficially invasive nature in most cases, and excellent prognosis

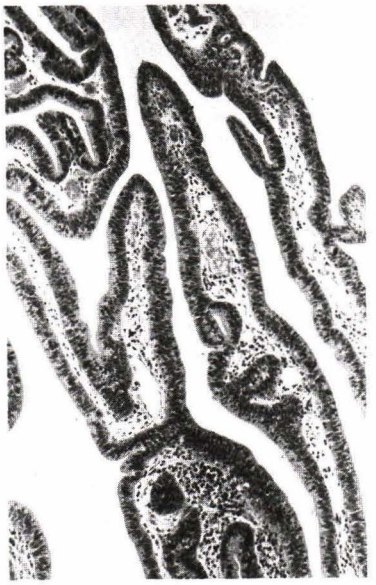

Fig. 2. **The surface portion shows elongated and slender villous fronds lined by stratified mucinous epithelium with minimal nuclear atypia. Inflammatory infiltrate in the papillary stroma is noted. (H&E, original magnification, x 100).**

Fig. 3. **The invasive component consists of irregularly shaped and branching glands separated by desmoplastic stroma. (H&E, original magnification, x 100).**

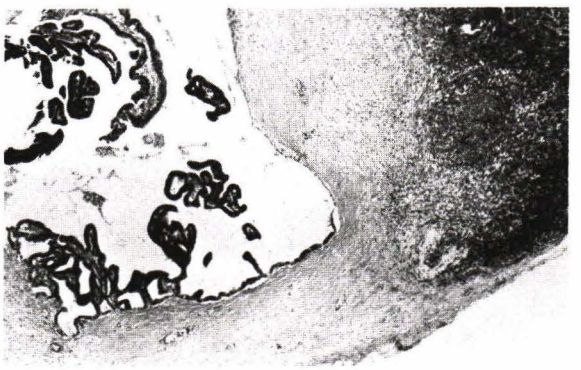

Fig. 4. **Metastatic tumor in the pelvic lymph node (case 11). Lymphoid tissue is replaced by a cystic lesion containing papillary adenocarcinoma. Prominent fibrotic stromal response is observed. (H&E, original magnification, x 40).**

(1). The subsequent large series reported by Jones et al(2) also confirmed these characteristic features. It was, thus, suggested that tumors of this type may be managed more conservatively than the usual cervical adenocarcinoma(1,2). Recently, a few cases of lymph node metastasis have been reported(3,5-7), reflecting the aggressive potential of this tumor.

Young and Scully(1) originally described the younger average age (33 years) of the patients with well-differentiated villoglandular adenocarcinoma than that of classical adenocarcinoma. However, the mean age of the patients in the reported series ranged from 33 to 52 years(1-4) with an overall average age of approximately 38 years. In our hospital, the previous studies of cervical cancer treated by radical hysterectomy with pelvic lymphadenectomy showed a median patients' age of 39 years (range 21-70) for 626 cases of all histologic types(8) and a mean age of 40 years (range 22-55) for 74 cases of pure adenocarcinoma(9). The average age of the patients with well-differentiated villoglandular adenocarcinoma in our study (39.3 years) was, thus, not apparently different from that of other histologic types including adenocarcinoma of similar tumor stage.

The majority of previously reported cases of well-differentiated villoglandular adenocarcinoma had superficially invasive tumors. In six of eight uteri (75%) reported by Young and Scully(1), the tumors were confined to the inner third of the cervical wall and were deeply invasive in the remaining two (25%). Jones et al(2) described that eighteen

Table 2. Clinico-pathological information of the cases of well-differentiated villoglandular adenocarcinoma with lymph node metastasis.

References	No. of case(s)	Age (years)	Tumor stage	Size (cm)	Stromal invasion >1/3	Lymph-vascular invasion	Treatment	Follow-up outcome	Duration (months)
Young et al[7]	2	ND	ND	ND	present	ND	ND	ND	ND
Kaku et al[3]	2	54	IIB	ND	present	present	RH&RT	DOD	46
		33	IB	ND	present	present	RH&RT	ANED	10
Garcia et al[6]	1	ND*	IB	3	ND#	ND	RH&RT	ANED	4
Present study	2	34	IB	2	present	present	RH&RT	ANED	56
		45	IB	4	present	present	RH&RT	ANED	46

ND : not described, DOD : dead of disease, ANED : alive with no evidence of disease,
RH&RT : radical hysterectomy with pelvic lymphadenectomy followed by radiation therapy,
* : pregnant patient, # : depth of invasion 0.7 cm.

of 19 invasive tumors (94.7%) were confined to the inner third of the cervical wall and only one (5.3%) invaded deeply into the outer third. Kaku et al[3] reported a series of seven cases, three of which (42.9%) had tumors invading into the middle or the outer third of the cervical wall. In eleven cases (73.3%) of our study, the tumors were confined to the inner third of the cervical wall, whereas only four cases (26.7%) were deeply invasive to the middle or the outer third. The difference in the frequency of deeply invasive tumors among the reported series may be partly affected by the difference in proportion of asymptomatic patients with early tumor detection. In 24 cases reported by Jones et al[2], the manner in which the cervical lesion was discovered was known in 8 patients, all of them had abnormal cervical smear prior to cervical biopsy. Only one of ten cases in the study by Young and Scully[1] presented with an abnormal cervical smear. All patients reported by Kaku et al[3] were symptomatic, mostly with abnormal uterine bleeding. Two of their patients were stage IIB. In our study, only one patient was asymptomatic. It may be possible that the number of cases with deeply invasive tumors in the reported series is inversely proportional to the number of tumors with early detection.

In the two large series of well-differentiated villoglandular adenocarcinoma, no evidence of extrauterine spread and recurrence was reported [1,2]. Recently, two unpublished cases of well-differentiated villoglandular adenocarcinoma with lymph node metastasis were mentioned by Young et al[7]. Both tumors were deeply invasive and exhibited more cytologic atypia than the usual villoglandular adenocarcinoma. Subsequently, a few cases of nodal involvement by tumors of this type have been described including one in our series[3, 5,6]. Information on cases with nodal metastasis including ours is summarized in Table 2. Lymph-vascular space invasion and cervical stromal invasion deeper than the inner third appeared to be the risk factors associated with metastasis. Both of our patients with nodal metastasis received adjuvant radiation therapy and were alive and well 46 and 56 months after surgery. Only one published case of well-differentiated villoglandular adenocarcinoma was reported to have an adverse clinical outcome [3]. The patient had a stage IIB tumor with pelvic nodal metastasis. Vaginal recurrence developed 30 months after surgery and she died of disease at 46 months.

Young and Scully[1] estimated the frequency of well-differentiated villoglandular adenocarcinoma to be considerably less than 10-15 per cent of cervical adenocarcinoma. We are aware of a single series of early stage invasive adenocarcinoma, by Costa et al[10], in which well-differentiated villoglandular adenocarcinoma was a separately classified subtype. In that series, four cases of villoglandular adenocarcinoma were observed among 39 pure adenocarcinoma. Excluding 6 serous and 5 clear cell adenocarcinomas and one adenoid cystic carcinoma in their study (these subtypes were very rare in our hospital) and considering only adenocarcinomas of mucinous or endometrioid differentiation, the relative frequency of well-differentiated villoglandular adenocarcinoma would be 14.8 per cent (4 of 27 cases) of the group. The figure

was only slightly less than our findings (16.4% or 12 of 73 cases of adenocarcinoma of mucinous or endometrioid type)[9].

Based on the suggestion by Young and Scully[1] and Jones et al[2], conservative treatment (conization) could be justified in selected cases of well-differentiated villoglandular adenocarcinoma, if preservation of fertility is desired. Conization, as a sufficient treatment, should be restricted to cases where the tumor shows only focal or superficial invasion (depth ≤ 3 mm) with clear surgical margins in the absence of lymph-vascular space invasion. Then, the patient should be monitored with great care and hysterectomy should be performed after completion of the family. Due to the possible risk of pelvic lymph node metastasis, radical hysterectomy with pelvic lymphadenectomy would be the surgical treatment of choice in cases with stage IB tumors.

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มะเร็งปากมดลูกชนิด Well-differentiated villoglandular adenocarcinoma: รายงานผู้ป่วย 15 ราย

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Well-differentiated villoglandular adenocarcinoma เป็นชนิดย่อยของมะเร็งปากมดลูกในกลุ่ม adenocarcinoma ที่เริ่มมีรายงานเมื่อประมาณสิบปีมานี้ และเป็นมะเร็งชนิดที่พบน้อย จากรายงานในระยะเริ่มแรก มะเร็งชนิดนี้มีลักษณะทางพยาธิวิทยาและคลินิกที่ค่อนข้างเด่นชัดเฉพาะกลุ่ม และมีการพยากรณ์โรคดีมาก อย่างไรก็ตามในระยะหลังได้เริ่มมีรายงานที่พบมะเร็งกระจายไปต่อมน้ำเหลือง รายงานนี้ได้ศึกษาย้อนหลังผู้ป่วยมะเร็งปากมดลูกชนิด well-differentiated villoglandular adenocarcinoma ที่ได้รับการรักษาในโรงพยาบาลมหาราชนครเชียงใหม่ จำนวน 15 ราย โดยทบทวนทั้งลักษณะทางคลินิกและลักษณะทางพยาธิวิทยาของมะเร็ง ผู้ป่วยทุกรายได้รับการผ่าตัดแบบ radical hysterectomy with pelvic lymphadenectomy ผู้ป่วยที่มีมะเร็งกระจายไปต่อมน้ำเหลืองได้รับรังสีรักษาร่วมด้วย ผู้ป่วยมีอายุระหว่าง 22-53 ปี (ค่าเฉลี่ย 39.3) ผู้ป่วย 14 รายเป็นมะเร็งในระยะ IB (FIGO) อีกหนึ่งรายเป็นระยะ IIA ผู้ป่วยทุกรายมีมะเร็งเป็นก้อนเนื้อยุ่ยที่ปากมดลูก ใน 14 รายที่ทราบขนาด มะเร็งมีขนาดตั้งแต่ 1.5-4 ซม. (ค่าเฉลี่ย 2.3) ผู้ป่วย 11 ราย (73.3%) มีมะเร็งแทรกลงภายในหนึ่งในสามของผนังปากมดลูก ในจำนวนนี้ 9 ราย (60%) มีความลึกไม่เกิน 3 มม. ผู้ป่วย 3 ราย (20.0%) มีมะเร็งแทรกลึกไม่เกินสองในสามของผนังปากมดลูก และ 1 ราย (6.7%) มีมะเร็งแทรกลึกเกินสองในสามของผนังปากมดลูก ตรวจพบกลุ่มเซลล์มะเร็งแทรกเข้าสู่หลอดน้ำเหลืองในผู้ป่วย 3 ราย ซึ่ง 2 ใน 3 รายนี้พบมะเร็งกระจายไปต่อมน้ำเหลืองร่วมด้วย มะเร็งในผู้ป่วยทั้งสองรายแทรกลึกเกินกว่าหนึ่งในสามของผนังปากมดลูก สามารถติดตามผู้ป่วยภายหลังการผ่าตัดมดลูกได้เป็นระยะเวลาตั้งแต่ 21-144 เดือน (ค่าเฉลี่ย 67.5) แต่ไม่สามารถติดตามผู้ป่วย 4 รายในกลุ่มที่ไม่มีมะเร็งกระจายไปต่อมน้ำเหลืองได้ภายหลังการผ่าตัดเป็นเวลา 36-59 เดือน จากข้อมูลการติดตามครั้งสุดท้าย ผู้ป่วยทุกรายไม่มีการเป็นซ้ำหรือการแพร่กระจายของมะเร็งไปสู่อวัยวะอื่น ๆ ข้อมูลที่ได้จากการศึกษานี้และการทบทวนวารสารพบว่าปัจจัยเสี่ยงที่สัมพันธ์กับการกระจายไปต่อมน้ำเหลืองของมะเร็งชนิด well-differentiated villoglandular adenocarcinoma ได้แก่ การแทรกของเซลล์มะเร็งเข้าสู่หลอดน้ำเหลือง และการแทรกของมะเร็งลึกลงในผนังปากมดลูก

คำสำคัญ : มะเร็งปากมดลูก, villoglandular adenocarcinoma, การกระจายของมะเร็งไปต่อมน้ำเหลือง

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