Case Report

Malignant Transformation of Perianal Giant Condyloma Acuminatum

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Key Words
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Giant condyloma acuminatum or Buschke-Lowenstein tumor is characterized by its large size and is prone to infiltrating into underlying tissues although it is microscopically benign. It commonly affects the genitalia. Cases of perianal giant condyloma acuminatum are reported sporadically in the English literature. In Taiwan, only one case of perianal giant condyloma acuminatum was found in literature. We report a rare case of perianal giant condyloma acuminatum in a 56-year-old, non-homosexual, married man. There was a 10-cm × 6-cm × 4-cm fungating circum-anal mass extending into his left buttock. He initially received simple excision and electrofulgaration in Sep 2004. Pathology did not reveal evidence of malignancy. However, one year later, he received wide local excision for recurrent lesion. Pathology demonstrated malignant transformation with verrucous carcinoma. Three months later, wound healed by secondary intention. After follow-up for fifteen months, no anorectal condyloma has been found with examination under anesthesia. The patient had no anal stenosis or incontinence.
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In 1896, Buschke first described a giant condyloma acuminatum (GCA) on the penile foreskin. Buschke and Lowenstein further elaborated on this clinical entity in 1925.[1, 2] GCA, synonymous with Buschke-Lowenstein tumor, is a variant of condyloma acuminatum, which appeared cytologically benign but behaved in a malignant manner with the risk of transformation to invasive squamous cell carcinoma (SCC).[3] GCA is characterized by its aggressiveness to underlying tissues; resistance to simple excision, local electrofulgaration or therapeutic agents; and high recurrence rate, despite the lesion having shown no histological criteria of malignancy.[4] The first case of GCA located in anorectal and perianal regions was reported by Dawson in 1965.[5] Chu and colleagues, analyzing 42 cases of GCA in anorectal and perianal regions, observed that the hallmark of the disease is the high rate of recurrence (66%), malignant transformation (56%), and no distant metastases.[6] In a review literature of Creasman,[7] malignant transformation was described in thirty percent of cases of anorectal GCA. Although rare, perianal GCA has been well documented. In a review article by Trombetta, fifty-two cases of perianal GCA were found prior to 2000.[8] The incidence of perianal GCA in Taiwan is not clear, but at least one case (without malignant change) was reported in literature prior to 2006.[9] GCA is frequently indistinguishable from benign lesions. Among published studies, there is a consensus that GCA probably represents a verrucous carcinoma (VC).[10-14] Malignant transformations of GCA are rarely seen, but have occasionally been reported in the

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Table 1. Reported cases of perianal GCA with malignant transformation, showing recurrence after initial therapy.

Year/Author	Age/Sex	Sexual predisposition	Site of disease	Tumor size (cm)	Initial therapy	Recurrence	Treatment for recurrence	Follow-up period	Pathology
1965/Dawson[34]	54/M	Unkonwn	Perianal	10 × 10	WLE	Yes	Two times of WLE, R/T, pelvic exenteration	Unknown	SCC within GCA
1972/Drut[35]	39/M	Unknown	Perianal	15	WLE	Yes	Three times of WLE, APR	2 years	SCC within GCA
1973/Sturm[20]	49/M	Unknown	Perianal	5 × 10	APR	Yes	Local 5-FU	1 year	SCC within GCA
1977/Elliott[12]	39/M	Unknown	Anorectum	Unknown	Simple excision	Yes	APR, C/T	18 months	Verrucous carcinoma
1977/Gingrass[10]	41/F	Unknown	Perianal	2	WLE	Yes	Nil	24 months	Verrucous carcinoma
1982/Bogomoletz[36]	68/F	Unknown	Perianal	8	C/T	Yes	Two times of WLE	6 months	SCC within GCA
1983/Creasman[7]	35/M	Unknown	Perianal	10 × 15	WLE	Yes	APR	2 years	SCC within GCA
1983/Butler[37]	40/M	Unknown	Perianal	8 × 8 × 20	C/T, R/T	Yes	APR	3 years	SCC within GCA
1984/Creasman[7]	61/F	Unknown	Perianal	6 × 6	WLE	Yes	APR	1 year	SCC within GCA
1985/Creasman[7]	28/M	Unknown	Perianal	14 × 14	WLE	Yes	APR, C/T, R/T	6 months	SCC within GCA
1993/Chu[15]	33/M	Heterosexual	Rectum	6 × 10	WLE, C/T	Yes	WLE, C/T	22 months	SCC within GCA
1995/Marsh[38]	50/M	Heterosexual	Anus	25 × 30	R/T, C/T	Yes	Surgery was not done because of pleural metastases	Unknown	SCC within GCA
1995/Bjorck[22]	34/M	Heterosexual	Perianal	10×15×15	Topical podophyllin, refused to have aggressive treatment	Yes	WLE, fulguration, C/T, R/T.	4 years	SCC within GCA
1997/ Kibrite A[39]	33/M	Heterosexual	Perianal with extension to anal canal		Fulguration, fistulotomy, abscess drainage	Yes, with extension to rectum	APR, R/T,C/T,	Died 3 months after APR. (Autopsy: a pelvic tumor and multiple carcinomatous lesions on intestinal mucosa)	SCC within GCA
2006/De Toma[40]	46/M	Heterosexual	Perianal	6 × 8	Simple excision, systemic interferon	Yes	R/T,WLE with muscle grafting reconstruction	3 years	Verrucous carcinoma
Present case	56/M	Heterosexual	Perianal	4 × 5 × 6	Simple excision, fulguration	Yes, with size 4 × 6 × 10cm	WLE	15 months	Verrucous carcinoma

SCC=squamous cell carcinoma; GCA= giant condyloma acuminatum; WLE=wide local excision; APR=abdominoperineal resection;R/T=radiotherapy; C/T=chemotherapy.

literature (Table 1).

Case Report

A 56-year-old man had a giant cauliflower-like condyloma of the perianal region. This lesion had been increasing slowly for more than ten years. He initially had simple excision and electrofulgaration in September 2004, when the size of the lesion was about 4-cm × 5-cm × 6-cm. Pathology revealed features of GCA. It showed papillomatous epidermal hyperplasia, cytopathic alterations and cytoplasmic vacuolization (koilocytotosis) involving the more superficial epidermal layers. The basement membrane zone was compressed and displaced and no significant squamous atypia was seen in any section.

The patient did not follow-up for one year for personal reasons, but returned for a check-up because of recurrent giant condyloma in the perianal region.

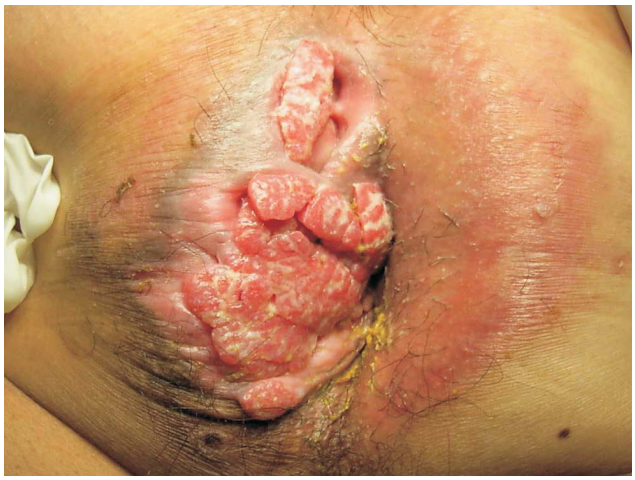

Fig. 1. Massive 10-cm × 6-cm × 4-cm exophytic, warty, gray-white, soft tumor of perianal region before treatment.

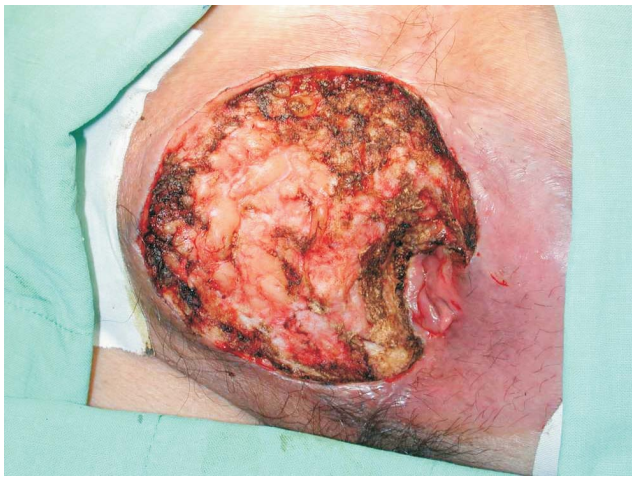

Fig. 2. Open wound immediately after wide local excision.

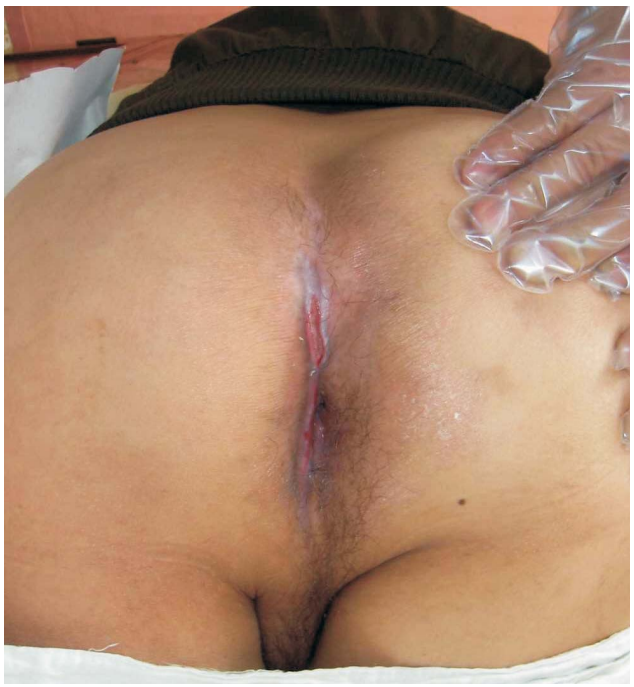

Fig. 3. Perianal area, secondary healing three months postoperatively.

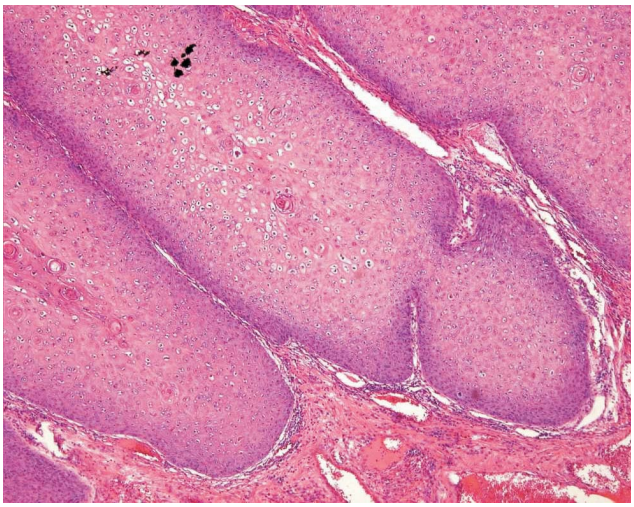

Fig. 4. Marked appearance of acanthosis, hyperkeratosis, and papillomatosis. Bulbous masses of well-differentiated squamous cells infiltrating into underlying connective tissue, with minimal nuclear atypia (hematoxylin and eosin; × 40).

Physical examination revealed a 10-cm × 6-cm × 4-cm fungating circum-anal mass extending into his left buttock (Fig.1). He had slight pain on digital rectal examination. The anal canal was normal. No enlarged inguinal lymph nodes were palpated bilaterally. The patient was married and denied having any homosexual activity. The patient had no detectable immunological defects and had no symptoms of acquired immunodeficiency syndrome. Chest x-ray film revealed no suspected lesions. Gallium-67 tumor survey revealed no abnormality in the whole body. Routine admission laboratory results were within normal limits.

Biopsy demonstrated VC. The tumor was distal to the anal verge, and the anal sphincters were not affected. Under general anesthesia, wide local excision was performed, with a 1.5-cm margin of normal tissue. Blood loss was minimal. The wound was left open for secondary healing (Fig. 2). Complete healing took about three months and no wound infection was observed (Fig. 3).

Pathology studies confirmed a diagnosis of VC arising within the GCA, showing negative surgical margins. Marked acanthosis, hyperkeratosis, and papillomatosis were seen. Some bulbous masses of well-differentiated squamous cells showed infiltration into the underlying connective tissue with minimal nuclear atypia (Fig. 4). No chemotherapy or radiotherapy was scheduled. Neither tumor recurrence nor metastases occurred up to fifteen months after surgery. No anorectal condyloma was found with examination under anesthesia. The patient had no anal stenosis or incontinence.

Discussion

Pathologically, GCA and ordinary condylomas have many similar characteristics, which mainly include clear vacuolization of prickle cells in the superficial layer of the epidermis (koilocytosis) suggesting human papillomavirus infection, infrequent mitosis, and considerable superficial hyperkeratosis with underlying epidermis thickening (acanthosis). GCA can be differentiated from ordinary condylomas by the characteristic “pushing” rather than “infiltrating” effect that tends to compress and displace the underlying tissue.[15] Tumor size did not correlate with histologic diagnosis.[8] Hull provided a description of pathological properties of GCA: the presence of multiple fistulas, intact basement membrane, lack of vascular and neural invasion, thickened squamous epithelium with prominent papillomatosis, lack of anaplasia, and fistulous tract frequently lined with neopalstic epithelium.[16] VC, a variant of SCC, has low malignant potential. In contrast to ordinary condylomas and GCA where the basement membrane is intact without invasion into the underlying stroma, VC penetrates the underlying tissues.[7, 15] VC is different from SCC in that scattered dyskeratotic and/or slightly atypical squamous cells occur but a major degree of cytologic atypia or malignancy is not present.[17] As a result, it is hypothesized that GCA represents a spectrum between simple condylomas and SCC. Bogomoletz concluded that simple condylomas, GCA, and VC may represent a contiguous but not obligatory precancerous spectrum.[18] Chu and colleagues described the average time of malignant transformation from benign GCA to histologic malignancy as being approximately five years.[6] In our patient, the initial pathology study (after simple excision and electrofulgaration) confirmed GCA without malignant component. However, only one year later, pathology study (after wide local excision) demonstrated the recurrent GCA to have undergone malignant transformation of VC. This suggests that only simple excision is inadequate and may lead to an ominous sequence.

Historically, GCA treatments comprise topical agents, simple excision, wide local excision, abdominoperineal resection, chemotherapy and radiotherapy. However, topical agents have been well documented to be ineffective in treating perianal GCA.[3, 19] Although no clearly-defined guidelines have been established for the management of GCA, most authors recommend complete surgical resection.[5,10,20] Gingrass and Bubrick recommended wide local excision with histologically clear margins. When the anal sphincter is invaded, abdominoperineal resection should be the surgery of choice.[10, 12] Other surgeons also made a plea for early radical surgical excision for permanent cure due to clinical and pathologic features of this locally malignant condition.[6, 8, 12, 21] Creasman[7] sug-

gested early control of local disease with radical excision. If the margins are free of tumor, no further treatment is warranted but vigilant follow-up is necessary.

Multimodality treatment for perianal GCA may prevent extensively destructive extirpation. Bjorck and colleagues reported a case successfully treated with a combination of surgery, radiotherapy, and chemotherapy.[22] Butler and colleagues also reported a case in which otherwise un-resectable GCA with invasive carcinoma was rendered operable with chemoradiotherapy.[23] In 2005, Chao[24] described a case of GCA with malignant transformation, where local control was achieved with chemoradiotherapy. In 2006, Tytherleigh MG[25] also observed that chemoradiotherapy resulted in significant down-staging of the tumor allowing radical surgery feasible. Furthermore, Sobrado and colleagues[26] reported a case successfully treated by telecobalt therapy only; they concluded that radiation could be used as salvage or neoadjuvant therapy for locally advanced lesions with good outcomes. However, because radiotherapy for oral VC was reported to be associated with malignant change, opponents considered radiotherapy contraindicated in the management for perianal GCA.[27-29]

The treatment of choice for perianal GCA is still controversial; there is no evidence to support widely-destructive surgery or chemo- and/or radiotherapy. Although the majority of surgeons prefer abdominoperineal resection, but for patient's life quality, relatively less destructive surgery is the best choice.[30] In our patient, the initial simple excision and electrofulgaration by the first surgeon (inexperienced) was inadequate, which caused recurrent perianal GCA one year later. Another surgeon performed wide local excision with margins free of tumor. Since no anal sphincters were invaded by tumor, abdominoperineal resection was not considered for our patient. Because there was no evidence of systemic or residual disease (pathology,chest x-ray, whole body gallium tumor scan and physical exam of bilateral groin areas), no further adjuvant therapy was suggested accordingly. At follow-up fifteen months later, no recurrence was noted by random biopsies.

A MEDLINE (Ovid) search was performed for reports of perianal GCA with malignant transformation and twenty-nine cases were found prior to 2006 in the English literature. Among these twenty-nine cases, fifteen patients had recurrence after initial therapy. We compared the characteristics, different treatments and follow-up outcomes of these fifteen patients to those of our in Table 1.

Great concern bas been expressed about the big wound caused by excision of perianal GCA. Many methods have been described for treating skin defects after wide excision, including secondary healing, skin grafts, and S-plasty. After wide local excision, we kept our patient's wound open for secondary healing without skin grafting. Although our patient finally healed, it took a period of three months and scarred tissue remained. In a case reported by Chaidemenos and colleagues in 2006, excellent cosmetic results and shorter healing time of only four weeks were obtained with immediate mesh-skin grafting.[31] As a result, Chaidemenos suggested this treatment option as first line treatment for GCA. However, this requires more patient compliance to avoid fecal contamination. Since our patient had poor compliance, we didn't adopt skin grafting for fear of easy wound infection. In a study by Mestrovic[32] the use of mesh-skin grafts in treating skin defects after radical local excision of GCA was compared to other methods such as secondary wound healing. Mestrovic and colleagues concluded that the use of mesh-grafts in covering the wounds after radical excision of anorectal GCA compares favorably to secondary healing in terms of wound healing time, and gives good functional and cosmetic results. In subsequent cases, we would consider immediate skin grafting as the first choice of therapy for patients with good compliance.

Metcalf and colleagues investigated the incidence of dysplasia in patients with anal condyloma acuminatum and concluded that homosexual orientation, disease above the dentate line, and HIV seropositivity increase the risk of dysplasia in perianal condyloma.[33] However, our patient, despite not having the aforementioned three risk factors, was observed having malignant transformation. Metcalf also found the incidence of dysplasia in perianal condyloma is significant enough to warrant consideration of biopsy in all patients. Therefore, regardless of condyloma size, biopsies of the condylomata should be examined to exclude the presence of malignant

transformation and to confirm the clinical diagnosis for every patient.

In summary, our patient did not suffer recurrence, anal incontinence, or anal stenosis fifteen months postoperatively, although scarred tissue remained in the perianal area. This observation, combined with findings from previous literature, led us to conclude the following for patients with perianal GCA: First, simple excision and electrofulgaration alone do not provide adequate treatment. Second, aggressive wide local excision should be the choice of surgery. Finally, secondary wound healing is feasible for non-compliant patients for preventing wound contamination. Further multi-institutional controlled randomized studies are necessary to delineate the clearly-defined guidelines for the management of perianal GCA.

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病例報告

肛周區尖形濕疣惡性變化：一病例報告

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巨大尖形濕疣，或可稱之為 Buschke-Lowenstein 腫瘤，其特色是大的腫瘤外觀而且有浸犯到下層組織的傾向，雖然病理學上是良性的組織。此疾病通常發生在生殖器區。肛門周邊巨大尖形濕疣在英文醫學文獻上偶有報導。然而在台灣，到目前為止，只有一例的肛門周邊巨大尖形濕疣被報導。在此我們報導一位五十六歲已婚的非同性戀者被診斷有肛門周邊巨大尖形濕疣。疣狀腫瘤大小有十公分乘六公分乘四公分，在肛門周邊並且往左側臀部侵犯。初次於民國九十三年九月接受簡單切除及電灼燒治療。當時病理報告是巨大尖形濕疣無惡性成份。然而一年後因為復發腫瘤再次接受手術。手術方法是廣泛式切除。病理報告是巨大尖形濕疣含有惡性疣狀癌成份。傷口於三個月後以次級癒合機轉癒合。術後十五個月追蹤沒有發現任何尖形濕疣復發。也沒有肛門狹窄或失禁的情形發生。

關鍵詞 巨大尖形濕疣、Buschke-Lowenstein 腫瘤、疣狀癌、惡性變化。