Original Article

Perianal Paget's Disease, Report of 20 Cases

Yen-Chen Shao[1,2]
Hung-Hsin Lin[1]
Chun-Chi Lin[1]
Yuan-Tzu Lan[1]
Shih-Chin Chang[1]
Huann-Sheng Wang[1]
Tzu-Chen Lin[1]
Wei-Shone Chen[1]
Jen-Kou Lin[1]
Jeng-Kai Jian[1]
Shung-Haur Yang[1]
[1]*Division of Colon & Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei,*
[2]*Division of Colon & Rectal Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan*

Key Words
Anorectal carcinoma;
Perianal Paget's disease;
Wide local excision;
Abdominoperineal resection

Abbreviations
PPD: Perianal Paget's disease;
PPDIM: Perianal disease with internal malignancy;
EMPD: Extra-mammary Paget's disease;
APR: Abdominoperitoneal resection;
LAR: low anterior resection

Backgraound. Perianal Paget's disease (PPD) is a rare disease and usually delayed in diagnosis. Association with anorectal carcinoma is often observed. The purpose of this study was to review the diagnosis, management, and outcomes of patients with perianal Paget's disease at our hospital.

Method. Database of Pathology and Colorectal surgery at Taipei Veterans General Hospital were queried for all cases of perianal Paget's disease at Taipei Veterans General Hospital between 2000 and 2014. Clinical pathologic factors were investigated for association with recurrence and survival. Twenty patients with perianal Paget's disease were included in the study (12 male), median age at diagnosis, 76 years [range, 52-88 years]; and 13 with synchronous internal malignancy, 7 without.

Results. The most common symptoms were perianal bleeding and painful sensation. The 5-year overall survival of perianal Paget's disease with synchronous internal malignancy was 66.1 %. In nine patients with curative surgery, eight were disease-free during follow-up.

Conclusion. High incidence of concomitant internal malignance is noted. A relative high local recurrent rate for pure perianal Paget's disease receiving wide excision is present. Malignant transformation should be alerted at finding recurrence. If not malignance, repeated wide excision for local recurrence may be feasible. Radical surgery for perianal Paget's disease with internal malignancy (PPDIM) had acceptable oncological control, for local and distant.

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Paget's disease (PD) was defined as intraepithelial adenocarcinoma.[1] In 1874, Sir James Paget described this specific pathologic finding involving the areolar tissue of the nipple in a report on ductal breast cancer patients.[2] Paget's cells are characterized with signet ring cells with vacuolated, mucin-filled cytoplasm.[3] (Fig. 1.) Extra-mammary Paget's disease (EMPD) has been reported mainly at anus, perineum, thigh, groin, axilla, vulva, and scrotum.[4] Perianal Paget's disease (PPD) is one focus of concern, because of its high relevance with rectal cancer. PPD was first described by Darier and Coulillard in 1893.[5]

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Correspondence to: Dr. Shung-Haur Yang, Division of Colon & Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital, No. 201, Sec. 2, Shi-Pai Rd., Beitou Dist., Taipei 112, Taiwan. Tel: 886-2-2875-7054 ext. 107; Fax: 886-2-2875-7639; E-mail: yangsh@vghtpe.gov.tw

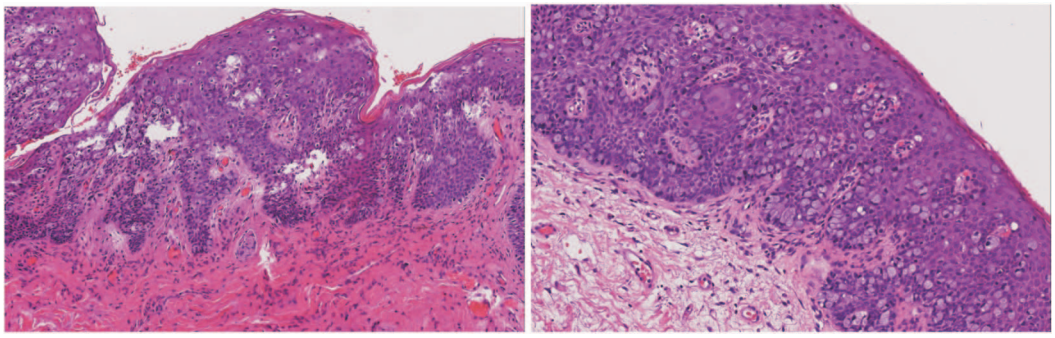

Fig. 1. A photomicrograph of hematoxylin and eosin appearance of perianal Paget's disease showing scattered clean cells in the basal layer. These cells are large and contain abundant mucin-filled cytoplasm. (Left. H & E 10X; Right. H & E 200X)

Associated internal malignancy of PD might origin from gastrointestinal tract, genitourinary system, and remote skin areas.[6] Its rare incidence made it very difficult to develop the treatment strategy. The aim of this report is to summarize our experience of PPD during a period of 15 years at our hospital.

Material and Methods

PPD cases were retrieved from the database of Pathology and Colorectal surgery at Taipei Veterans General Hospital, during the period between 2000 and 2014. After exclusion of PD originating from the scrotum, perineum, and perivulvar, twenty cases of PPD were included. Clinicopathological parameters were included for analysis, including demographic factors, treatments (surgery or radiotherapy), and oncological outcomes. Overall survival (OS) was calculated using the Kaplan-Meier method, and the difference was measured by the log-rank test. Continuous variables were compared with the independent T test. p value of < 0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS software version 16.

Results

Patient and tumor characteristics

Twenty patients (12 males) were included into our study. The mean age and median age at diagnosis were 74.9 years and 76 years, respectively, with a range of 52 to 88 years. Median follow-up from the time of diagnosis was 35.0 months, with a range of 2.9 to 144.3 months.

Thirteen cases (65%) had synchronous internal malignancy (PPDIM), and seven cases without. The median age of PPDIM was 73 years, and pure PPD was 77 years. (Table 1) PPDIM include 13 cases of anorectal carcinoma. One of them was with suspect cholangiocarcinoma compressing common bile duct. The most common symptom was perianal bleeding (8 cases), followed by painful sensation (5 cases), skin

Table 1. Baseline characteristics of patients with perianal Paget's disease

Variable	Pure PPD (n = 7)	PPDIM (n = 13)
Age, median (range)	77 (60-87)	73 (52-88)
Gender		
Female	3	5
Male	4	8
Symptoms		
Bleeding	6	2
Pain	4	1
Skin erosion	3	1
Itchy	3	0
Mass	2	0
Skin rash	0	1
Internal malignancy		
Anorectal carcinoma		12
Anorectal carcinoma with unknown liver tumor compressing CBD*		1

PPD = perianal Paget's disease; PPDIM = perianal Paget's disease with internal malignancy. * CBD = common bile duct.

erosion (4 cases), itching sensation (3 cases), palpable mass (2 cases), and skin rash (1 case). Table 2 shows the TNM stage of patients with PPDIM.

Management

Table 3 shows the treatments applied. Pure PPD were all treated with wide excision initially, except one case refusing any treatment. Three cases developed local recurrences. One of them turned out to be adenocarcinoma, so salvage abdominoperitoneal resection (APR) was performed. The other cases received repeated wide excision. In the group of PPDIM, 8 cases received directly APR, 1 case curative low anterior resection (LAR), 2 cases wide excision, and 2 cases wide excision plus radiotherapy. In nine patients with radical surgery, eight were disease free during follow-up, and one had distant metastasis (multiple lung and bone metastasis). 4 cases received local wide excision. One died in 3 months due to obstructive jaundice; one had local recurrence after a follow up of 3.73 months, but he refused further management and then lost follow up; one received wide excision and local radiotherapy, disease recurrence with bowel obstruction was observed after follow up of 9.87 months, he received diverting colostomy; the other patient received wide excision, radiotherapy, and chemotherapy because of inguinal lymph nodes metastasis was noted initially, he died due to liver and bone metastasis after 13.37 months.

Table 2. TNM stage of PPDIM

Stage	Case number
T	
is	2
1	2
2	6
3	3
N	
0	10
1a	1
1b	1
2	0
3*	1
M	
0	12
X[#]	1

PPDIM = perianal Paget's disease with internal malignancy.
* A patient with bilateral inguinal lymph nodes metastasis.
[#] A patient with synchronous suspect cholangiocarcinoma of distal common bile duct.

Table 3. Treatments for perianal Paget's disease

	Pure PPD	PPDIM
Nil	1	0
Wide excision	5	2
Wide excision with radiotherapy	1	2
Wide excision with low anterior resection	0	1
APR	0	8

PPD = perianal Paget's disease; PPDIM = perianal Paget's disease with internal; APR= abdominoperitoneal resection.

Outcome

After excluding one case refusing treatments, three out of six pure PPD had local recurrence. The 5-year overall survival of PPDIM was 66.1%. (Fig. 2) Eight radical surgeries are all disease free during follow-up, one had lung and bone metastasis.

Discussion

PD represents a skin neoplasm, which may be primary or secondary. The origin of Paget's cell has been a debated issue in the literature. Primary EMPD was thought to be an epidermotropic neoplasm arising from

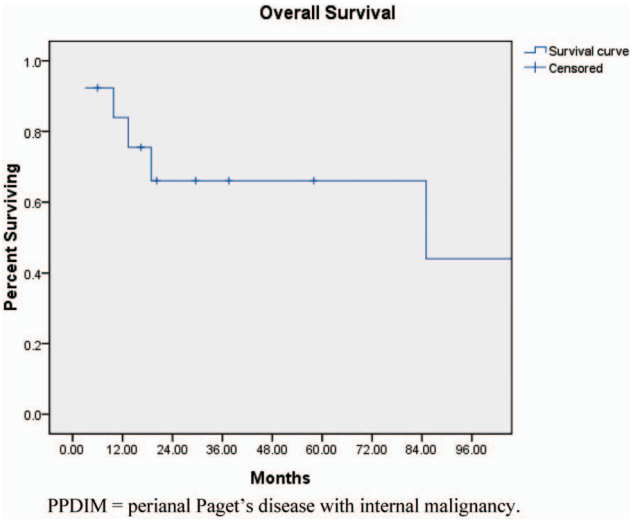

Fig. 2. Overall survival of patients with PPDIM.

the apocrine glands.[4] Secondary PD represents a downward spreading of anorectal adenocarcinoma.[3] In our study, we found more than half patients (13/20) had a concomitant anorectal carcinoma. It is not surprising that Paget's disease is often associated with anorectal malignancy. Suenaga et al. reported a case the continuity between the perianal lesion and the anal canal carcinoma in the epidermis. They diagnosed the lesion as a Pagetoid spread of anal canacl carcinoma.[7] However, there is no clear differential to distinguish primary from secondary PPD.

Most reported series are of few cases because PPD is a very rare disease. In this study, we collected 20 PPD cases at Taipei Veterans General Hospital during a 15-year period. As in other series, most cases had nonspecific symptoms which were hard to distinguish from other benign anorectal disease. Delay in diagnosis was very common.[1,6]

Local wide excision is the prime treatment of pure PPD. Beck and Fazio [8] reported a relatively low recurrence rate by using intraoperative frozen sections of quadrant biopsy during wide local excision. In a review article by Kubota et al.,[9] local wide excision and abdominoperineal resection with or without irradiation are adopted treatments.

Although without comparative analysis in our study, PPDIM seems to have acceptable prognosis. Eight cases received APR and one with LAR was of curative intent. Only one had distant recurrence. Among the four PPDIM not receiving APR, one was due to advanced metastases; one with synchronous suspicious cholangiocarcinoma and died due to obstructive jaundice; two cases received local wide excision because patients refused APR. It is not sure that an aggressive surgery as APR is necessary for all PPDIM having rectal cancer, since sphincter preservation is a paramount in optimizing quality of life.[10] However, in terms of oncological result, APR works well. This is the main meaningful finding in this series. The possibility of neoadjuvant or adjuvant radiotherapy to avoid APR merits further investigation.

For cases of pure PPD, local wide excision still carries a relative higher chance of local recurrent rate. Three of six pure PPD had local recurrence. This might be due to the skip nature of local disease, resulting in a discontinuous spreading of Pagetoid cells beyond the visible margin. Among the 3 local recurrences, 2 were disease-free after repeat local wide excision after a follow up of 38.60 and 32.47 months, respectively; one was found to be adenocarcinoma at recurrence. Right side inguinal lymph nodes and lung metastasis was also present at recurrence. Salvage APR and right inguinal lymph nodes dissection later performed, however the lung metastasis progressed. This reminds us that malignant transformation or missed diagnosis initially, might be a cause of local recurrence. Re-evaluation and staging was mandatory at handling local recurrence.

This series still has the limitations as in other series: small case number and retrospective analysis. Therefore, we could not analyze if there is any difference of survival regarding the surgical options. Neither, can the analysis of the adjuvant radiotherapy therapy be done.

Conclusion

PPD is a rare disease and usually delayed in diagnosis due to non-specific symptoms. High incidence of concomitant internal malignance is noted. A relative high local recurrent rate for pure PPD receiving wide excision is present. Malignant transformation should be alerted at finding recurrence. If not malignance, repeated wide excision for local recurrence may be feasible. Radical surgery for PPDIM had acceptable oncological control, for local and distant.

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原　著

肛門 Paget's 氏症，20 例病例

邵彥誠 [1,2]　林宏鑫 [1]　林春吉 [1]　藍苑慈 [1]　張世慶 [1]　王煥昇 [1]
林資琛 [1]　陳維熊 [1]　林楨國 [1]　姜正愷 [1]　楊純豪 [1]

[1] 臺北榮民總醫院　外科部　大腸直腸外科
[2] 臺中榮民總醫院　外科部　大腸直腸外科

背景　肛門 Paget's 氏症是一罕見疾病。臨床上常見合併肛門直腸癌。本研究目的為回顧本院在此疾病的診斷、處置以及成效。

方法　從臺北榮民總醫院大腸直腸外科以及病理科資料庫中擷取了 2000 年至 2014 年於本院接受治療的肛門 Paget's 氏症患者。統計分析臨床表徵及病理等因子與復發及存活率之間的關係。

結果　共有 20 名 (12 名男性) 患者收錄至本研究中，平均年齡 76 歲；13 名個案合併有肛門直腸癌，7 名則無。最常見的症狀為流血及肛門疼痛。合併有肛門直腸癌的患者五年存活率為 66.1%。9 名接受根除性手術的患者中，有 8 名在追蹤過程中無疾病復發。

結論　高比例的患者合併有肛門直腸癌。接受局部廣泛性切除的單純肛門 Paget's 氏症患者，有相對較高的復發率。追蹤過程中需注意復發疾病惡性化。若無惡性化，多次局部廣泛性切除是可行的。對於合併有肛門直腸癌的患者，廣泛性手術有可接受的局部及遠端腫瘤控制。

關鍵詞　肛門直腸癌、肛門 Paget's、局部廣泛性切除、腹部會陰部切除。