

II. 原 著

II. 3 The management of vulvar Paget's disease in 376 Caucasian and 283 Japanese patients —Analysis of patient age and interval between symptoms and treatment —

Kobe City Medical Center General Hospital, Kobe, Japan

Department of Obstetrics and Gynecology

Tatsuji Hoshino, Asuka Hirao, Ruriko Oyama, Noriko Ohtake,
Sachiko Kitamura, Mami Suga, Kazunao Miyamoto, Aki Takaoka,
Yuko Imamura, Yoko Yamada, Masato Kita

Department of Dermatology

Noriko Ogoh, Yuka Higashida, Toru Nagano

Department of Plastic Surgery

Tomio Tsukie

Department of Clinical Pathology

Yukihiro Imai

Abstract

[Introduction] Vulvar Paget's disease is difficult to diagnose early because this is rare and often occurs in elderly women. A randomized controlled trial, meta-analysis and evidence-based medicine are not suitable methods of improving the prognosis. Since early diagnosis and treatment is necessary to improve prognosis, we extracted the causes of late diagnosis and the proposals to improve prognosis.

[Methods] Literature review was performed through Japana Centra Revuo Medicina and PubMed. Ten articles including our study on 283 Japanese and seven articles on 363 Caucasian were collected and examined to determine patient age, interval between the initial symptom and the start of therapy, reason for delay in treatment and measures to prevent delay.

[Results] The mean age (yrs) was 69.2 and 67.8, and the interval (yrs) was 3.4 and 1.9, in Japanese and Caucasian, respectively. Most studies indicated the delay was related with patient age, slight initial symptoms of the disease, slow progression and resemblance to eczema, mycosis and dermatitis. They also indicated that awareness of the disease among patients and doctors should be increased in order to promote early diagnosis.

[Conclusion] The mean age did not significantly differ among Japanese and Caucasian women. The interval before treatment was longer for Japanese women than for Caucasian women.

[Key words] Vulvar Paget's disease, Delay to diagnosis, female, human

(Kobe City Hosp Bull 49 : 29–35, 2010)

Vulvar Paget's disease 発症患者の376例のコーカシア人と283例の日本人の 平均年齢と症状自覚から診断・治療までの期間について

神戸市立医療センター 中央市民病院 産婦人科

星野 達二 平尾 明日香 小山 瑠梨子
大竹 紀子 北村 幸子 須賀 真美
宮本 和尚 高岡 亜妃 今村 裕子
山田 曜子 北 正人

皮膚科

大郷 典子 東田 由香 長野 徹

形成外科

月江 富男

臨床病理科

今井 幸弘

要 旨

[緒言] Vulvar Paget's diseaseの早期の診断は難しい。100万人の女性1人当たり年間発生が1人という稀な疾患であり、60歳から70歳という高齢者に発症する。したがって、Randomized controlled trial (RCT)、Meta-analysis、Evidence-Based Medicine (EBM) といった方法はこの病気の予後改善に必ずしも有効ではない。しかし、Paget's diseaseは上皮内の腺癌であり、悪性の腫瘍である。早期診断と早期治療が予後改善には必要である。診断の遅れとなる原因と早期診断のための提言を文献より検討した。

[方法] 医学中央雑誌とPubMedを通じて文献的検討を行った。われわれの検討を含めて10編の論文から283例の日本人と7編の論文から363例のコーカシア人の症例を集め、患者の年齢、初発症状から診断治療までの期間、治療の遅れの原因、それを防ぐための手立てなどを検討した。

[結果] 日本人の平均年齢は69.2歳、コーカシア人の平均年齢は67.8歳であった。初発症状発現から治療開始までの平均期間は3.4年と1.9年であった。多くの著者は初発症状発現から治療開始までの遅れの原因として、疾患の初発症状が軽微なこと、見つけにくい場所にできること、進行がゆっくりとしていること、患者が高齢であること、羞恥心のため受診がおくれること、湿疹・真菌症・接触性皮膚炎と間違えられやすいこと、合併する湿疹・真菌症・接触性皮膚炎が治療により改善することがあること、カンジダや白癬を証明されることがあることをあげている。また、この疾病を患者や医療者が十分に把握することが早期診断に寄与すると指摘している。

[結論] 平均年齢は日本人とコーカシア人で著明な差を認めない。初発症状発現から治療開始までの期間は日本人の方がコーカシア人よりわずかに長い。

[キーワード] 外陰ペーজেット病, 診断の遅れ, 女性, ヒト

(神戸市立病院紀要 49:29-35, 2010)

Introduction

Vulvar Paget's disease is difficult to diagnose early because this is a rare disease with an incidence of 1 patient per one million females per year and often occurs in elderly women aged 60–70 years old. A randomized controlled trial, meta-analysis and evidence-based medicine are not suitable methods of improving the prognosis of this disease. Vulvar Paget's disease is an adenocarcinoma in situ and a malignant disease. Since early diagnosis and treatment is necessary to improve prognosis, we extracted the causes of late diagnosis and proposals to improve prognosis from the literature.

Methods

Literature review was performed through Japana Centra Revuo Medicina and PubMed. Literature was restricted to review articles regarding human female vulvar Paget's disease. The literatures was also restricted to those in which patient ages, the interval between symptoms and treatment, the reason for delay between symptoms and treatment and suggestions to reduce the delay were described. Ten articles^{1)–10)} including our study on 283 Japanese women and seven articles^{11)–17)} on 363 Caucasian women were collected and examined to determine patient age, interval between the initial symptom and the start of therapy, reason for delay in treatment and measures to prevent delay.

Results (Table1~2)

Only female patients with vulvar Paget's disease in each article were reviewed. The mean patient age was 69.2 years (41–88yrs) in 283 Japanese women and 67.8 years (35–88yrs) in 363 Caucasian women. The interval between the initial symptom and treatment was 3.4years (10~17.0yrs) in Asian women and 1.9 years (0.1~16.0yrs) in Caucasian women. Many of the Japanese studies described reasons for the delay between the initial symptom and the start of therapy and measures to prevent delay (Table2). However, few Caucasian studies described reasons for the delay between the initial symptom and the start of therapy and measures to prevent delay. Only the report of Parker mentioned the reasons as follows : the delay may reflect the disease mainly afflicts older woman who may delay seeking medical attention or may indicate a lack of knowledge about this disease in the general medical community.

1. According to the reason for delay in treatment

① Disease-related factors

Many authors indicated that the initial symptom was slight, the exanthema was present in an area where it was difficult to detect, the progress of the disease is slow and the disease is rare as reasons for the delay in treatment.

② Patient-related factors

Many authors indicated that the patients were elderly, the patients were less concerned about disease because of advanced age, and the patient did not notice the symptom or did not consider it abnormal, the patient's consultation tended to be late because of embarrassment.

③ Doctor-related factor

Many authors indicated that the doctor may have misdiagnosed the exanthema as eczema, contact dermatitis, candidiasis or mycosis.

2. Measures suggested to prevent delay

Many authors indicated that an educational approach to both doctors and the public is necessary for this disease. Ishihara emphasized that a doctor should suspect the disease when there is no improvement for a prolonged period of time.

Comments

Japanese textbook (Iikura and Yaegashi)¹⁸⁾ describes vulvar Paget's disease as follows : Patients are mostly postmenopausal women and younger patients are rare. The exanthema resembles eczema, contact dermatitis, candidal vulvovaginitis. Skin biopsy and rapid diagnosis is recommended in difficult cases of eczema-like exanthema.

English textbooks (Blaustein, Novak)^{19),20)} describe the vulvar Paget's disease as follows : Pruritus was present for a median duration of 2 years before the diagnosis. Almost all patients are postmenopausal women, with a median age of 70 years. Because of its clinical resemblance to dermatitis, these patients may be treated with various topical medications for some time before an accurate diagnosis is established by biopsy.

In this review, the mean patient age did not significantly differ among Japanese and Caucasian women. The interval before treatment was longer for Japanese women than for Caucasian women, there is some possibility that red exanthema was more easily distinguished on white skin than on pigmented skin. The initial symptoms in Paget's disease are erythema and pruritus. The symptoms are not severe, the exanthemas are not easy to detect because of patient's age and site of exanthema, and the patients may be reluctant to consult doctors due to a sense of shame or embarrassment.

Since the exanthemas may resemble contact dermatitis, eczema, or mycosis, the doctor may provide medical treatment for these conditions. However, to achieve early diagnosis and treatment, it is important for the initial doctor, especially gynecologists, to suspect Paget's disease in these cases and perform a biopsy or strongly recommend the consultation with a dermatologist since an exanthema involving the vulva causes patients to consult a gynecologist first in many cases, it is necessary for gynecologists to study color photographs and recognize exanthemas due to vulvar Paget's disease. Gynecologists must recognize this disease as a malignancy and provide rapid diagnosis in order to begin treatment without delay. Moreover, since there are some patients who rely on self-medication or folk medicine rather than consulting a doctor, education about the existence of vulvar Paget's disease must also be provided to the general public (Hoshino, Ohgo, Fujii et al)¹⁰⁾.

Acknowledgement

The study reported in this paper was supported in part by Grant 2010 and 2011 "Kasahara Memorial Foundation for Medical Research" from Kobe City Medical Center General Hospital.

Literature

- 1) Ikeda S, Tajima K, Ishibashi Y, et al. Extramammary Paget's disease. *Clinical Dermatology*. 1970 ; 24 : 15-32. (In Japanese with no English summary)
- 2) Inaba Y, Ishikawa T, Kamide R. Prognosis of extramammary Paget's disease. *Clinical Dermatology*. 1990 ; 44 : 1143-1147. (In Japanese with no English summary)
- 3) Shigeta T, Kobayashi M, Yorifuji K, et al. Treatment for genital Paget's disease. *Western Japanese Dermatology*. 1992 ; 54 : 1136-1140. (In Japanese with an English summary)
- 4) Ohara K, Onishi Y, Kawabata Y. Diagnosis and treatment of extramammary Paget's disease. *Skin Cancer*. 1993 ; 8 (Special Issue) : 39-59. (In Japanese with an English summary)
- 5) Ishihara K. National survey results of Paget's disease. *Skin Cancer*. 1994 ; 9 : 37-43. (In Japanese with no English summary)
- 6) Ueda E, Morishima Y, Nagata M, et al. Stastical Survey of 30 patients with Paget's disease since 1982 to 1991 at the department of dermatology, Kyoto prefectural University of medicine. *Western Japanese Dermatology*. 1996 ; 58 : 116-120. (In Japanese with an English summary)
- 7) Tsuruoka S, Tsuyuki S. A stastical summary of 25 patients with extramammary Paget's disease. *Skin Cancer*. 1996 ; 11 (2) : 248-253. (In Japanese with an English summary)
- 8) Asano K, Fukami Y, Tamura T, et al. A stastical survey of patients with extramammary Paget's disease seen at Department of dermatology, Asahikawa Medical College. *Skin Cancer*. 1998 ; 13:12-17. (In Japanese with an English summary)
- 9) Kikuchi H, Tsumori S, Kurokawa M, et al. Stastical survey of 58 patients with extramammary Paget's disease at the Department of Dermatology, Miyazaki University of Medicine. *Western Japanese Dermatology*. 2005 ; 67 : 387-391. (In Japanese with an English summary)
- 10) Hoshino T, Ohgo N, Imai Y, et al. Macroscopic view of vulvar Paget's disease, delay in patient consultation and establishment of a diagnosis. *Journal of Hyogo medical association*. 2010 ; 52 : 25-32. (In Japanese with an English summary)
- 11) James H, Graham JH, Elson B, Helwig EB. Extramammary Paget's disease. Cutaneous premalignant lesions. *Advances in Biology of Skin*. United States Public Health Service. 1966 ; 305-314.
- 12) Breen JL, Smith CI, Gregori CA. Extramammary Paget's disease. *Clinical Obstetrics and Gynecology*. 1978 ; 27 : 1107-1115.
- 13) Feuer GA, Shevchuk M, Calanog A. Vulvar Paget's disease : The need to exclude an Invasive lesion. *Gynecologic Oncology*. 1990 ; 38 : 81-89.
- 14) Molinie V, Paniel BJ, Leibowitch NL, et al. Paget's disease of the vulva. *Ann. Dermatol. Venereol*. 1993 ; 120 : 522-527. (In French with an English summary)
- 15) Fanning J, Lambert HCL, Hale TM, et al. Paget's disease of the vulva : Prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. *Am J Obstet Gynecol*. 1999 ; 180 : 24-27.
- 16) Parker JR, Bevers DB, Deavers M, et al. Paget's disease of the Vulva : Pathology, Pattern of Involvement, and Prognosis. *Gynecologic Oncology*. 2000 ; 77 : 183-189.
- 17) Maclean AB, Makwana M, Ellis PE, et al. The manage-

- ment of Paget's disease of the vulva. *Journal of Obstetrics and Gynecology*. 2004 ; 24 : 124-128.
- 18) Niikura H, Yaegashi N. Tumors in the external genitalia. *Nihon Sanka Fujinka Gakkai Zasshi*. 2009 ; 61 : N77-85. (In Japanese)
- 19) Wilkinson EJ. Paget disease. In : Kurman RJ, ed. *Blaustein's pathology of the female genital tract*, Fifth edition. New York : Springer, 2002 : 123-126.
- 20) Addis IB, Hatch KD, Berek JS. Paget's disease of the Vulva. In : Berek JS, ed. *Berek & Novak's Gynecology*, Fourteenth edition. Philadelphia : Lippincott Williams & Wilkins, 2007 : 592-596.

Table 1. The interval between the initial symptom and treatment and patient age

Authors	Number of Patients	The interval (years) between the initial symptom and treatment, mean (range)	The patient's age, mean (range)
IkedaSetal ¹⁾	5	6.1 (2.5-10)	60.4 (51-67)
InabaYetal ²⁾	10	4.1 (0.3-13)	65 (41-86)
ShigetaTetal ³⁾	10	5.4 (1-17)	71.8 (55-86)
OharaKetal ⁴⁾	34	3.5 (0.3-15)	66 (44-80)
IshiharaK ⁵⁾	162	no description	no description
UedaEetal ⁶⁾	7	1.8 (0.5-4)	72.3 (58-84)
TsuruokaSetal ⁷⁾	6	2.8 (1-8)	66.3 (44-88)
AsanoKetal ⁸⁾	6	2.9 (0.4-10)	72.2 (62-85)
KikuchiHetal ⁹⁾	26	2.6 (0-15)	72.4 (46-88)
HoshinoTetal ¹⁰⁾	17	3 (0.5-9)	73 (59-87)
Subtotal (Japanese)	283	3.38	69.2
JamesHetal ¹¹⁾	43	2 (no description)	no description (35-82)
BreenJLetal ¹²⁾	13	1 (01-3)	58.4 (46-74)
FeuerGAetal ¹³⁾	19	1.2 (0.3-5)	65.2 (44-81)
MolinieVetal ¹⁴⁾	36	2.5 (0.3-6)	67 (45-91)
FanningJetal ¹⁵⁾	100	2 (0.5-16)	70 (35-100)
ParkerJRetal ¹⁶⁾	76	1.9 (no description)	67.5 (no description)
MacleanABetal ¹⁷⁾	76		68 (47-93)
Subtotal (Caucasian)	363	1.93	67.8
Total (all)	646	2.36	68.2

Table 2. The reason for delay in treatment and measures to prevent delay in Japanese literature

Authors	The reason for delay in treatment	Suggested measures to prevent delay
Ikeda S et al ¹⁾	(no description)	(no description)
Inaba Y et al ²⁾	(no description)	(no description)
Shigeta T et al ³⁾	The initial symptom was slight. The patient did not notice or did not consider it abnormal.	(no description)
Ohara K et al ⁴⁾	The initial symptom was slight. The exanthema was present in an area that was difficult to examine. The patient overlooked a exanthema because the symptom was slight and location was difficult to examine. The patient's consultation tended to be late because of embarrassment. The doctor tended to misdiagnose the lesion as eczema or mycosis.	The public awareness about skin cancer is low. The educational activity to the public may lead the patients to recognize skin cancer.
Ishihara K ⁵⁾	The doctor may mistake the exanthema for eczema or mycosis.	The doctor should suspect the disease in case of no signs of improvement over a long period of time.
Ueda E et al ⁶⁾	The patients were elderly.	(no description)
Tsuruoka S et al ⁷⁾	The initial symptom was slight. The exanthema was present in an area that was difficult to examine. The patient did not consult a doctor because of embarrassment. The patients less concern about disease because of advanced age. The doctors may misdiagnose the exanthema as eczema or mycosis.	Raising awareness to both doctors and the public is necessary for this disease.
Asano K et al ⁸⁾	Disease progressing is slow. The patient may not consult a doctor because of embarrassment. The doctor may misdiagnose the exanthema as eczema, candidiasis or mycosis.	Raising awareness to both doctors and the public is necessary for this disease.
Kikuchi H et al ⁹⁾	The exanthema has slight symptoms in the early stage. The exanthema was located in the area that is difficult to examine. The doctor may misdiagnose the exanthema as eczema or mycosis.	(no description)
Hoshino T et al ¹⁰⁾	This is a rare disease. The patients are elderly.	The doctor should suspect the disease. An educational approach to the public is necessary for this disease.