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CARCINOMA IN SITU OF THE VULVA

Long term prognosis

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Abstract

Seventy-four patients with carcinoma in situ (CIS) of the vulva were followed over a 10-year period. The mean age was 52.8 years (range 21 to 90 years). Pruritus was the most common symptom. Forty per cent of the women were asymptomatic. Twenty-three per cent had a history of carcinoma in situ of the uterine cervix. Single lesions of CIS were found in the perineal area in 22 per cent, in the labia major and minor in 23 per cent, and in the clitoris in 7 per cent. Forty-two per cent of the patients had CIS in two or more of those areas. Seven of 74 patients (10%) had previously been irradiated for pelvic malignant tumours. Three women developed invasive squamous cell carcinoma of the vulva, two of them were previously irradiated. All 74 patients were treated surgically in different ways. Out of 38 women with histologically free margins of surgery, 6 had recurrence of dysplasia or CIS.

Key words: Genitourinary system, neoplasms; vulva, carcinoma in situ, surgery, prognosis.

Precancerous lesions of the vulva appear under the names of Bowen's disease, erythroplasia of Queyrat, Paget's disease and carcinoma in situ (CIS). This study is restricted to the in situ carcinomas of the squamous epithelium and excludes Paget's disease.

The histopathologic criteria of CIS of the vulva are disorientation and a loss of epithelial architecture that extends throughout the full thickness of the epithelium. Giant cells, multinucleated cells, abnormalities of nuclear or cytoplasmic ratio, dyskeratosis, corps ronds formation, abnormal mitoses, mitotic figures above the basal layer, an increased density of cell population may all be seen in varying degrees (8).

The etiology of CIS of the vulva is essentially unknown. Herpes virus induced antigens have been found in women with CIS of the vulva (11) and also human papilloma virus has been linked to this condition (5).

The present study is an attempt to elucidate the background variables, the clinical features and the long-term fate of CIS of the vulva referred to the Department of Gynaecologic Oncology, Radiumhemmet, during the period 1973 to 1982.

Material and Methods

Seventy-four cases of CIS of the vulva were referred to our department in 1973 to 1982, inclusive. The surgical treatment took place at the Departments of Obstetrics and Gynaecology in Karolinska sjukhuset and Södersjukhuset, Stockholm.

The follow-up of women with premalignant or malignant neoplasia of the vulva was performed at a joint vulvar clinic for the Stockholm region, with collaboration between gynaecologic oncologists from Radiumhemmet and gynaecologists from other departments. The diagnosis of all lesions was based on biopsies. Toluidine blue-stain was frequently used to delineate the lesion and to give guidance for the biopsy. All histopathologic diagnoses were reevaluated by one pathologist (J.W.). The clinical records and the pathology reports formed the basis for the study. Signs and symptoms, distributions of the lesions as well as the presence of previous, concomitant or subsequent malignant neoplasia were recorded. Familial occurrence of malignant tumours was also studied.

Age distribution at time of diagnosis of the 74 patients is shown in Table 1. Thirty-five women (47%) were 50 years

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of age or younger. The mean age was 52.8 years and the range 21 to 90 years.

The symptoms were recorded in 70 of the 74 patients. The main symptoms were pruritus in 22 patients and a diffuse irritation in 20 patients. Twenty-eight patients (40%) had no symptoms related to the vulvar lesion. The lesions in these patients were discovered during a routine gynaecologic examination.

The anatomic distribution of CIS in the 74 patients is illustrated in Table 2. The perferential site was the lower border of introitus down to the perineal skin. In 42 per cent of the cases, CIS was wide-spread and included two or more areas.

Data on familial occurrence of malignant disease was known in 58 out of 74 cases. A history of cancer in the family was found in 39 cases, i.e. 67.2 per cent. Twenty-eight women had one or more first-degree relatives with cancer. Gynaecologic cancer among relatives was found in 10 women (17.2%).

Twenty-nine of the 74 patients (39.2%) had an additional malignant disease either before, concomitant with or after the CIS of the vulva (Table 3).

Seven women had received radiation treatment because of other malignant diseases in the pelvic area. No direct irradiation had been given towards the vulva region. However, this region might have received a minor radiation dose, estimated at about 5 per cent of the administered reference dose to the treated pelvic malignancy.

Three women were currently subjected to immunosuppressive treatment or had previously received such treatment. One of them, suffering from rheumatoid arthritis, had been treated with daily doses of cortisone; another, with a transplanted kidney, had received daily doses of cortisone and in addition azathioprine for long periods. The third patient, with Hodgkin's disease, had for extended periods been treated with cortisone and cytostatics.

Treatment and further course. The operations included biopsies, minor resections, partial vulvectomy and, in a few cases, total vulvectomy. Among the 74 women, a total of 281 resections were performed which means, on an average, 3.8 per patient. One patient was operated upon 14 times because of recurrent and/or persistent disease. In a few cases, the patients were pretreated with interferon or with cytostatics locally without any obvious effect.

In 38 of the 74 women one or more resections were carried out until a histologically free margin was obtained. Six out of these 38 patients had recurrence of dysplasia or CIS and 2 of them progressed to invasive squamous cell carcinoma. Of 20 cases with histologically un-proven or doubtful free margin in the surgical specimen, 11 cases recurred as dysplasia or CIS. In 16 patients it could not be evaluated if the margins of the specimens were free from CIS or not. In this group 7 recurrences occurred including one case with invasive squamous cell carcinoma. The interval between the primary resections and the recurrence of CIS and/or dysplasia ranged from 2 months to 2 years and 9 months. The interval between the recurrence of CIS and the development of invasive squamous cell carcinoma ranged from one year and 5 months to 3 years and 3 months.

Two of the patients with CIS of the vulva who progressed to invasive squamous cell carcinoma, had previously received X-ray treatment because of a squamous cell carcinoma of the uterine cervix. The interval between the irradiation and the diagnosis of CIS was 2 and 20 years respectively. One patient with CIS of the vulva progressing to invasive squamous cell carcinoma, suffered from diabetes mellitus, polymyalgia rheumatica and hypertension and had been operated upon because of a goitre. She had been substituted with Levaxin and insulin for several years and had been given cortisone less than one year. All three women who developed invasive squamous cell car-

Table 1

Distribution of age of 74 patients with CIS of the vulva

Age	No. of cases	
	1973–1977	1978–1982
≤19	0	0
20–29	1	3
30–39	7	6
40–49	8	10
50–59	7	0
60–69	12	9
≥70	7	4
Total	42	32

Table 2

Distribution of CIS in the vulva. I: The clitoris and adjacent parts of introitus, labia major and labia minor; II: main part of introitus, labia major and minor on the left side; IV: on the right side, and; III: the posterior parts of introitus, labia major and minor and the perianal area.

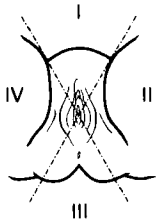
	Area	Individuals	
		No	Per cent
	I	5	6.8
	II	8	10.8
	III	16	21.6
	IV	9	12.2
Areas combined (≥2 areas)		31	41.8
Areas not recorded		5	6.8

Table 3

Previous, concomitant or subsequent malignant tumours in 29 of 74 patients with CIS of the vulva

Neoplasia	No.
Invasive squamous cell carcinoma of the uterine cervix	4
CIS of the uterine cervix	17
Carcinoma of the ovary	1 a)
Carcinoma of the breast	2
Renal adeno carcinoma	1
Hodgkin's disease	1
Basal cell carcinoma	1
CIS of the rectum	1 a)
Squamous cell carcinoma metastases with unknown primary tumour	1 b)

a) Concomitantly with CIS of the vulva, b) after CIS of the vulva. All other malignancies occurred before CIS of the vulva. (Addendum: After the observation time of this series of vulvar CIS, an additional case of extragenital carcinoma, a small cell carcinoma of the lung, has been diagnosed in a 68-year-old woman.)

cinoma in the vulva were over 63 years of age at the time of the in situ cancer diagnosis. None of the women with immunosuppressive treatment progressed to invasive carcinoma. In the whole material one patient died of invasive carcinoma of the vulva, one of Hodgkin's disease, three of other cancers, and three of cardiovascular disease during the period of observation.

Discussion

It has been suggested that there is an increase in the incidence of CIS of the vulva (4, 6, 8, 19). Recent reports indicate (1, 3, 4, 8–10, 12, 17, 18) that the disease is found more frequently in younger women than one might expect. It is, however, not possible to infer from published data that there is a real incidence increase of CIS of the vulva, not even in young women. Lack of proper registration within whole geographic areas of these lesions makes any discussion about changing incidence rates invalid. Nor can our study support the hypothesis of changing natural history and age distribution. Better diagnostic methods, better health care facilities, and access to specialized clinics where early lesions are detected, can probably explain most of the observed changes in the panorama of this disease.

The mean age in our investigation was 52.8 years which corresponds to previous data (14). In contrast, the mean age for CIS of the uterine cervix reported in many screening programmes is much lower, e.g. 35.5 years in Sweden (15). The linkage, if any, between CIS in the cervix and in the vulva still remains to be clarified.

The preferential site of CIS of the vulva at the lower border of introitus and in the perineal or anal skin is in accordance with earlier observations (9, 16). It is also obvious from the present investigation that CIS of the vulva often has a large extension.

Apparently CIS of the vulva often occurs without any alarming symptoms. Accordingly, the diagnosis of CIS depends on the physician's careful inspection of the vulva during routine gynaecologic examination.

Approximately half of the patients had a first-degree relative with cancer, a number which is slightly higher than that given by LYNCH (13). The association of multiple primary carcinoma and CIS has been described in many reports (1–4, 6, 7, 19). In our series, 40 per cent of the patients with CIS of the vulva had a previous, present or subsequent genital or extragenital malignant neoplasia. As reported previously (1), CIS of the uterine cervix was the most frequent precedent malignancy. This coincidence probably speaks in favour of a common cause of the two diseases. Three of our patients developed later on invasive squamous cell carcinoma of the vulva. Two of them had previously received radiation treatment because of squamous cell carcinoma of the cervix uteri. Whether or not these two cases of cancer were radiation induced or represented multicentric disease in the lower genital canal is an intriguing question.

Immunosuppressive treatment or immunodeficiency diseases have been reported to enhance the development of invasive cancer from CIS (3). To date, none of the women with immunosuppressive treatment in the present series has progressed to invasive carcinoma.

The value of extensive surgery in CIS of the vulva has been questioned. The extent of surgery with respect to histologically free margins seems, in our study, to be of importance for disease free survival and will encourage us, as far as possible, to eradicate the lesions. However, with the apparently low risk of progression to invasive carcinoma, mutilating operations should be avoided. We are currently testing laser beam treatment combined with biopsies or limited resections.

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