THE PROBLEM OF THE SO-CALLED PRECANCEROUS LESIONS OF THE VULVA TEN YEARS OF PROSPECTIVE EXPERIENCE

Key words: Vulvar deseases.

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SUMMARY

One hundred and seventy six cases of vulvar dystrophies diagnosed and followed between 1968 and 1979 are presented.

Characteristics of one hundred and twenty five cases of lichen sclerosus are described. Three of them were associated with CIS and micro-invasive carcinoma of the vulva in the first diagnostic study.

Relevant data from twenty one cases of epithelial hyperplasia and twenty seven cases of mixed dystrophy are described. Three of the hyperplastic dystrophies and four of the mixed dystrophies have atypia (dysplasia).

In only one case of mixed dystrophy an early invasive carcinoma started « de novo » in a hyperplastic area without atypia.

Results of treatment of L. S. cases with topical testosterone, of hyperplastic dystrophies with local excision and of mixed with local excision and topical testosterone and corticoids are presented.

Results of treatment of dysplasia with local excision are described.

A unique case of dysplasia without treatment that shows no change in nine years is discussed.

More experience is needed to establish the real significance of dysplasia.

In properly treated patients with chronic vulvar dystrophies followed through many years no evidence of malignancy was found.

Multiple biopsies and careful lifetime follow-up as well as appropriate therapy is mandatory in vulvar dystrophies and dysplasia.

Vulvar dystrophies as a whole have a very low malignant potential. In the present study it was less than 4 percent.

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Squamous cell carcinoma of the vulva takes place in a specialized epithelium that is subjected to rather special environmental, hormonal and functional factors. Today an « at risk » population is beginning to be identified: *a*) patients with other genital carcinomas; *b*) patients previously treated with radiations for vulvar pruritus; *c*) immunosuppressed patients; *d*) patients with history of granulomatous or viral venereal diseases and *e*) patients with chronic vulvar dystrophies and or dysplasia.

Traditionally vulvar dystrophies (previously called leukoplakia and kraurosis) have been considered « the » precancerous lesions of the vulva. This concept was based in the frequency of coexistence (30 to 50 %) of white lesions with carcinoma of the vulva in the radical vulvectomy specimens. White changes are common in the vulva; cancer is rare. Coincidence does not imply a causal relationship. Prospective studies have shown that the likelihood of carcinoma developing within a preexisting area of benign white change is less than 5 percent. However the erroneous concept that leukoplakia and kraurosis of the vulva are premalignant leads to the performance all over the world, of needless vulvectomies in the name of prophylaxis.

In order to correct this misconception and the bias associated with the older inaccurate terminology, the International Society for the Study of Vulvar Disease, has proposed that a new nomenclature should be adopted ([1]).

Dystrophy is to be used as a general heading to denote the disorders of epithelial growth and nutrition which may result in a white surface change on the vulva. Based on easy recognized histologic characteristics, the vulvar dystrophies are subclassified into three subgroups: lichen sclerosus, hyperplastic and mixed.

In the latter two groups epithelial atypia (dysplasia) can sometimes be noted, but the incidence is very low.

Table 1.

	Clinical	Histologic
Lichen sclerosus	Pruritic, thin, parchment « atrophic », introital stenosis.	Thin, loss of rete pegs, homogenization of dermis, inflammatory infiltrate.
Hyperplastic	Pruritic, thick, gray or white plaques.	Acanthosis, hyperkeratosis, inflammatory infiltrate.
Mixed	Areas compatible with both forms present at the same time.	

Without the liberal use of the vulvar biopsy, the accurate diagnosis and proper treatment of vulvar dystrophies is impossible.

Dysplasia is the presence of atypia in the nuclei or in the cytoplasm of the cells from the vulvar epithelia. It can be slight, moderate or severe, depending on the importance of the changes. Notwithstanding the architecture of the epithelium is conserved and this is the difference with carcinoma in situ.

Theoretically the chain of events should be: normal or pathological epithelium changing to dysplasia, then to CIS and then to invasive carcinoma as an interrelated function of time and the status of the patient's defense mechanisms.

Dysplasia then would be the precancerous lesion of the vulva « par excellence » but a great well documented experience is necessary to substantiae this fact.

For this presentation we will consider from the above mentioned « at risk » population, the vulvar dystrophies and dysplasia and make few references to the viral exposed and immunosuppressed patients.

MATERIAL AND METHODS

In the Vulva Clinic of the First Chair of Gynecology of the University of Buenos Aires (Chairman Prof. L. Arrighi), 176 vulvar dystrophies were diagnosed between 1968 and 1979.

They were classified as follows:

Table 2.

1) Lichen sclerosus	125 cases
Lichen sclerosus associated with CIS	2 cases
Lichen sclerosus associated with microinvasive carcinoma and basal cell carcinoma . . .	1 case
2) Hyperplastic without atypia . .	18 cases
Hyperplastic with atypia (dysplasia)	3 cases
3) Mixed without atypia	22 cases
Mixed with atypia (dysplasia) .	4 cases
Mixed associated with microinvasive carcinoma	1 case
Total	176 cases

All diagnosis were based on multiple biopsies, generally oriented by the Richart-Collins test. The macroscopical aspect of the lesions was documented with photographs.

Some interesting findings of our population with lichen sclerosus are as follows.

Eighty percent of the cases with L.S. had at the moment of the initial diagnosis between 45 and 69 years of age. The younger case was 20 years old. Twenty percent of our cases were recurrences of the disease after prophylactic vulvectomy.

Ten percent of the L. S. cases had hypochlorhydria or achlorhydria and received gastrointestinal treatment.

Five percent of the cases had extravulvar lesions of lichen sclerosus.

Five cases had asthma or psoriasis. When psoriasis or asthma impaired, pruritus was relieved and viceversa in alternate fashion.

The lichen sclerosus cases were treated with two percent testosterone propionate in white petrolatum topical application. In the first six to eight weeks, two or three times daily, and then once or twice a week for indefinite period of time. Sometimes because of the macerating tendency of ointments, ulceration may occur. Then testosterone should be discontinued and corticoid cream applied for a week or so.

The important features of the L.S. cases associated with CIS and invasive carcinoma of the vulva are as follows:

Case 43. Patient 57 years old, complaining of vulvar pruritus for 6 years. Vulva with typical appearance of L. S. white, with effacement of the labia minora. Biopsy of the paraclitorial area revealed CIS of the vulva. Simple vulvectomy was performed and the specimen study revealed multifocal carcinoma in situ and L. S. Follow up 6 years after operation revealed cure of the CIS and persistance of the L. S. lesions. Treated with testosterone topics.

Case 63. Patient 40 years old, complaining of vulvar pruritus for 2 years. Vulva with white spots around the clitoris. Collins tests positive in the same area. Biopsy: CIS. Simple vulvectomy was performed. Specimen study showed CIS unifocal and L. S. Follow-up 5 years after operation shows cure of CIS and persistance of L. S. Treated with testosterone topics.

Case 161. Patient 52 years old, complaining of vulvar pruritus for 6 years. Vulva with typical appearance of L. S. In the paraclitorial area red velvet lesion that does not healed. Biopsy: microcarcinoma with 4 mm of penetration in depth and 4 mm of diameter and small basal cell carcinoma. Radical vulvectomy with inguinal and pelvic lymphadenectomy. No rests of carcinoma in the specimen. Negative nodes. Follow-up 2 years without recurrence.

In hyperplastic dystrophies age was variable, but generally speaking they were younger than the L. S. group. All of them had pruritus of long chronic evolution. Excisonal biopsy was used as diagnostic and treatment tool. Only one had a big lesion 4 by 4 cm that needed a plastic repair after excisional biopsy.

Three cases had a hyperplastic dystrophy with slight atypia (dysplasia).

Two were young women with the lesion localized in the fourchette. Both have had recurrent herpes genitalis infection and were emotionally unbalanced.

Excisional biopsy was performed and careful follow-up for seven and five years respectively demonstrates non recurrence of vulvar pathology. The other was a 60 year old patient treated for a year with intense systemic corticoid treatment for an erytrodermia. She presented a white non pruriginous lesion located between the urethra and clitoris. Five months after excisional biopsy that showed slight atypia a urethral papilloma was excised showing also slight atypia. Immunosuppressive therapy was discontinued and she is well after two years of follow-up.

In mixed dystrophies age was similar to the L. S. group. Only multiple biopsies can give the diagnosis of mixed dystrophy, because there is not always clear delineation between areas of thin and thick epithelium. When hyperplastic areas are evident, excisional biopsy should be performed followed up by testosterone topics for the L. S. environment. When not, a mixed topical therapy of testosterone and corticoids should be given. These cases should be very carefully followed.

Four cases in our experience had mixed distrophy with slight to moderate atypia (dysplasia). They were patients in their forties and fifties with chronic vulvar pruritus. One of them had a previous prophylactic vulvectomy.

Three had an excisional biopsy of a thick area and then testosterone and corticoid topical treatment for 3 years. New biopsies showed no more atypia. The fourth had a punch biopsy, refused to receive any treatment and nine years later a new biopsy in the same site, showed the same M. D. with slight atypia.

Finally to finish the description of our material and methods, the relevant data of the only case in our experience where an early invasive carcinoma developing in the hyperplastic area of a mixed dystrophy was documented in the initial diagnostic biopsy, will be presented.

Case 71. Patient 50 years old, complaining of pruritus for one year. Vulva with effaced structures, shiny and crinkled with white and discromic spots. Nearby the clitoris a red velvet-like lesion (A) and in the inner face of the left labius majus a hyperkeratotic patch (B).

Biopsies of both areas showed: A) Carcinoma with beginning invasion developed in a hyperplastic dystrophy; B) Hyperplastic dystrophy.

Radical vulvectomy and inguinal and pelvic lymphadenectomy. Specimen study: no rests of malignancy, wide area of mixed dystrophy without atypia. Negative nodes. Follow-up for 6 years after operation reveals no recurrences; pruritus is controlled with topical testosterone and mixed dystrophy without atypia was found in repeated control biopsies.

RESULTS

The results of the treatment of lichen sclerosus with topical testosterone were very satisfactory.

Pruritus cured in 95 percent of the cases and dyspareunia in 75 percent.

As side effects clitoral enlargement was observed in 12 percent of the cases, increased libido in 20 percent, increase in the density of preexisting facial hair in two patients, and mild hoarseness in one.

When therapy was discontinued symptoms reappeared. In only twelve cases cure persisted many years after discontinuation of therapy.

Seventy-eight cases of L. S. were followed with close observation, therapy and control biopsies from 3 to 10 years.

None of them developed dysplasia, carcinoma in situ or invasive carcinoma.

In hyperplastic dystrophy without atypia pruritus cured in all patients after excisional biopsy. Only one patient recurred with identical lesion, one year after and same treatment was applied. No recurrence was observed after 2 years follow-up.

Eighty percent of mixed dystrophies without atypia were followed more then 5 years. In all of them pruritus was controlled with treatment and none developed under careful observation dysplasia, CIS or invasive carcinoma.

Hyperplastic dystrophies with atypia did not recur after excisional biopsy after 5 a 7 years of control and after suppression of corticoid systemic therapy.

Mixed dystrophies with atypia are similarly controlled after excisional biopsy and treatment for 3 years.

Interestingly enough one case of slight atypia without treatment did not change after a nine-year observation period.

DISCUSSION

Lichen sclerosus represents the most frequent dystrophy in our experience (72.7 %). The ethiology of the disease is unknown and probably autoimmune.

In the past it has been treated with « prophylactic » vulvectomy.

This erroneus approach was discontinued after many authors demonstrated the high recurrence rate of L.S. after surgery ([2]).

A wide variety of suggestions has been offered for the medical management of lichen sclerosus. Vitamin A ([3]), vitamin B ([4]) and even tattooing with mercuric sulfide ([5]) were once thought beneficial. Mering ([6]) reported that surgical denervation of the vulva, with undermining of the labial skin, could be used when all else failed. Chloroquin and vitamin E ([7]) were also recommended. Yet none of these approaches has proven to be beneficial.

A new approach was undertaken by Cinberg ([8]) who applied topical testosterone to patients with L. S. and reported symptomatic relief.

Later, Richardson and Williams ([9]) confirmed this result. This response to testosterone was surprising to many gynecologists, who considered the vulva as an extension of the vagina, an estrogen-dependent organ. But, in fact as Friedrich stated ([10]) the vulva is skin developed from the embryonal ectoderm and totally unrelated to Mullerian mesodermal anlage.

Papa and Klingam ([11]) studied the effects of topical steroids in the axilla and observed that estrogens produce no effects, corticoids produce marked atrophy and testosterone hyperplastic effect.

Few years ago Zelle ([12]), Friedrich ([13]), di Paola et al. ([14]) and Kaufman et al. ([15]) reassessed the efficacy of topical testosterone in cases of biopsy-proven L. S. and mixed dystrophies which included an element of this change.

Two percent testosterone propionate in petrolatum is not commercially available. Pharmacists can compound this ointment easily. Testosterone propionate is obtainable in sesame oil from drug houses in multiple dose 10 cc vials containing 100 mg per cc. Thirty millimeters of this mate-

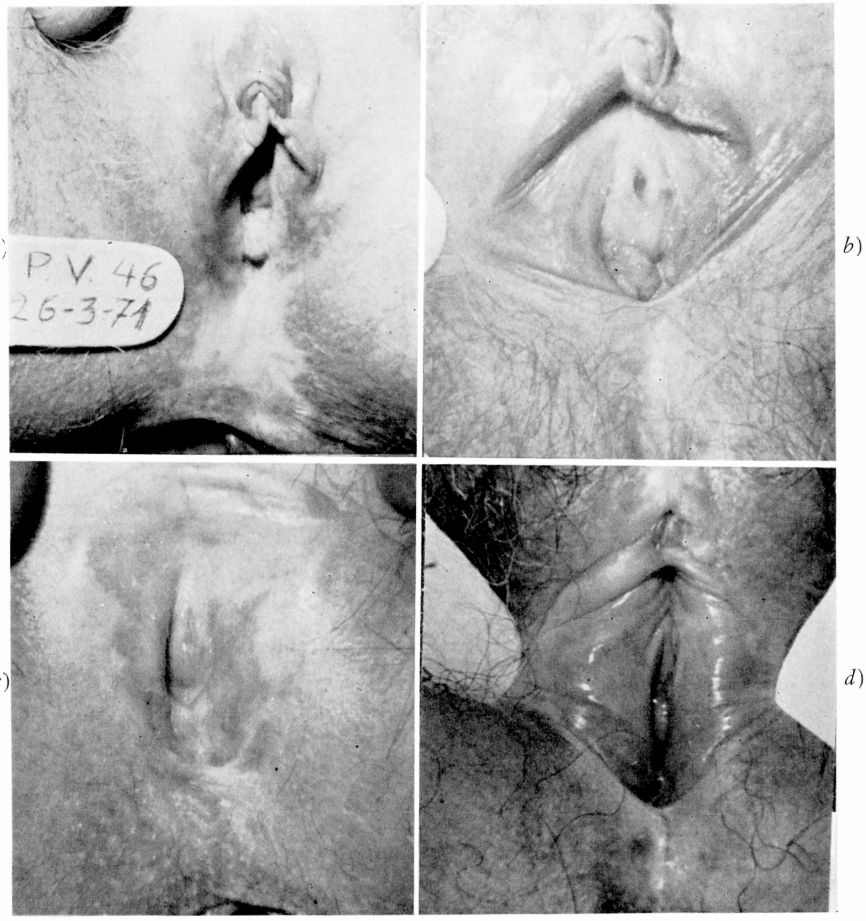

Fig. 1. — *a*) Lichen sclerosus of the vulva localized mainly in the fourchette. *b*) Same case of fig. *a*) after one year of topical testosterone treatment. *c*) Lichen sclerosus with effacement of vulvar structures. *d*) Same case of fig. *c*) after six years of topical testosterone treatment.

rial are mixed thoroughly into 120 g of petrolatum to obtain 2 % ointment.

The good effects in a previously reported ([14]) short term were confirmed in this long term prospective study.

As already mentioned pruritus was relieved in 95 percent of the cases and dyspaurenia in 75 percent.

For achieving these results medication was maintained through the years, with at least two applications per week. When therapy was discontinued symptoms reappear in 90 percent of the cases.

The macroscopical appearance of the lesions improved as shown in the illustrations (fig. 1 to 8). Neovascularization of the sclerotic dermis produces pinker skin colour and there is stimulation of sebaceous glands.

Using acridine orange as an indicator of DNA-RNA localization, Friedrich, Julian and Woodruff ([16]) found a remarka-

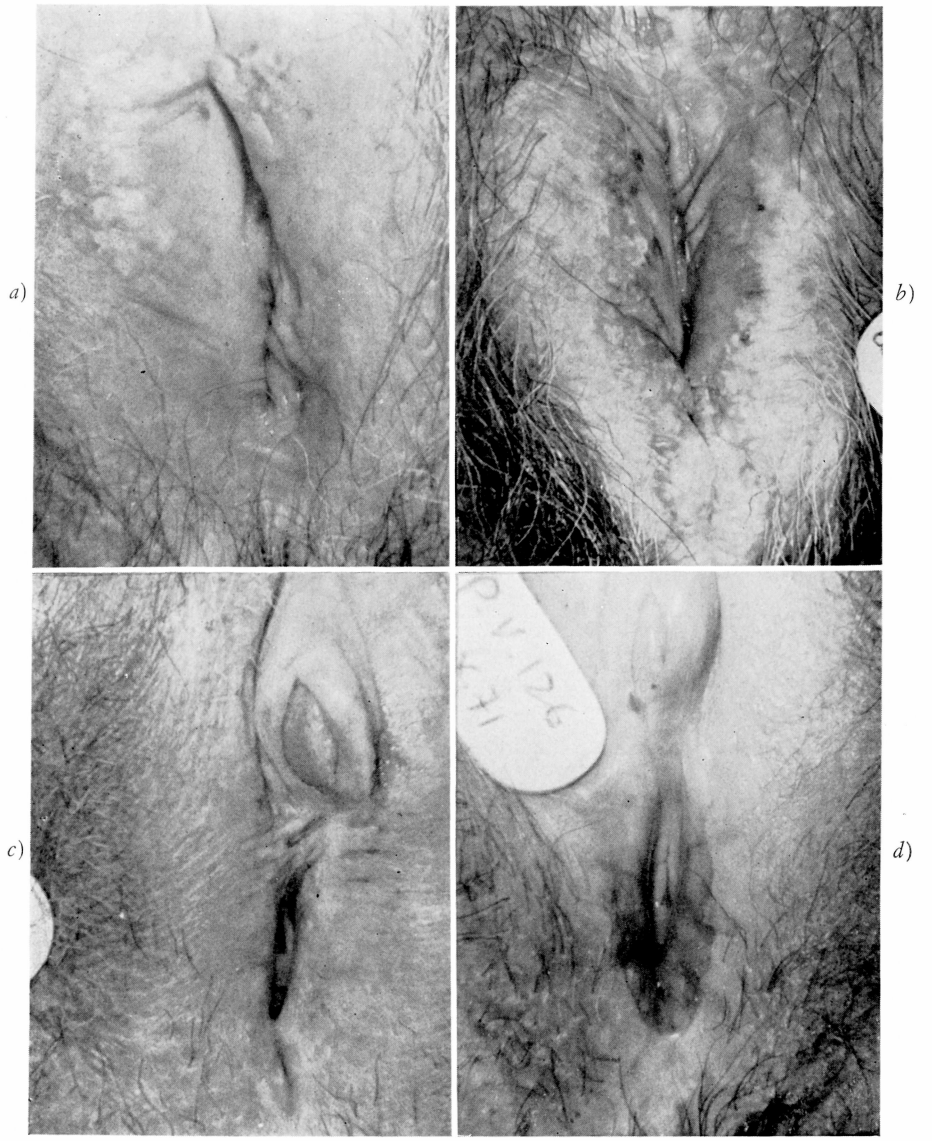

Fig. 2. — *a*) Mixed distrophy of the vulva. *b*) Same case of fig. *a*) after two years of combined corticoid and testosterone topical treatment. *c*) Mixed distrophy of the vulva. *d*) Same case of fig. *c*) after six years of combined corticoid and testosterone topical treatment.

ble concentration of these nucleic acids present in all layers of L. S. vulvar epithelium. The degree of this concentration exceeded that found in normal specimens. With tritiated nucleic acid precursors, Woodruff et al. ([17]) demonstrated a high percentage of labelled cells in L. S. The degree of this activity again exceeded that found in normal tissue and approached the levels noted in cases of carcinoma in situ. Such studies indicated that lichen sclerosus was not really « atrophic ».

However Kaufman et al. ([18]) were unable to demonstrate an increased P 32 uptake in areas of lichen sclerosus when compared to normal skin in the same location. These findings indicated that although nucleic acids were present the mitotic rate was not increased, in spite of the historical concept that « kraurosis » was a highly premalignant potential.

The recent study of Hart et al. ([21]) analyzing retrospectively 92 L. S. patients revealed only one case which eventuated in carcinoma. Even in this single instance the tumor arose not from the areas of L. S. but rather from isolated foci of atypical hyperplasia.

From the 128 cases of lichen sclerosus diagnosed in our Vulva Clinic in the last ten years, three were associated with malignancy in the paraclitorial area in the first diagnostic study.

Does it mean that malignancy arose from the L. S. epithelium or more probably that malignancy appeared in non properly treated and predisposed patients where chronic irritation was the real cause?

The prospective study of 78 cases of L. S. observed during three to ten years demonstrates that properly treated and free of symptoms none of them developed with the control of repeated biopsies, any degree of malignancy.

Hyperplastic dystrophies represent a 12 % of our experience with vulvar dystrophies.

The circumscribed appearance of hyperplastic dystrophies allows using excisional biopsy as an efficient diagnostic and treatment tool.

Pathological study of the specimen is more satisfactory and almost all patients have no more pruritus once the lesion is removed.

For this reason we prefer excisional biopsy to the topical corticoid therapy proposed by other Authors as Friedrich ([22]).

In only one instance of our experience it was necessary a plastic surgical repair of the raw area because it was a large lesion.

Slight atypia appeared in 3 of the 21 hyperplastic dystrophies (14 %).

Two of them were young patients with proven exposure to herpes virus type 2 and a psychological pattern of marital maladjustment.

The exposure to herpes virus in young pregnant patients associated with vulvar atypia was observed by Friedrich ([23]) and careful control proved a spontaneous cure some months after delivery.

In our two cases, atypia did not recur after excisional biopsy. Prolonged follow-up of 7 a 4 years proved a satisfactory evolution free of disease coincidental with solution of emotional conflicts and good therapeutic support.

It should be stressed the consideration of the emotional factors (anxiety with vulva as target organ) plus the correction of the irritative factors.

The other case of H. D. with slight atypia occurred in a patient with prolonged immunosuppressed therapy.

It is well known that immunosuppressed organ homograft recipients have a 50 to 60 % incidence of de novo malignancies at some time after transplantation. Also gynecological malignancies have been encountered in nontransplant patients who were treated with immunosuppression agents or cancer chemotherapy. One explanation is that immunosuppres-

sion impairs the immunologic surveillance function of the lymphoreticular system. In consequence potentially malignant cellular mutations are not detected and destroyed and become established as overt cancers ([24]).

Our case had erytrodermis and has been treated for a year with high doses of prednisone. In five months period developed a H. D. with slight atypia and urethral papylloma with sligh atypia.

This cases should be very carefully controlled.

Mixed dystrophies are considered as having a malignant potential no more than 4 to 5 percent.

In our experience mixed dystrophies were a 15.3 % of the cases. Eighty percent of M. D. without atypia were followed for more than 5 years. In all of them pruritus was controlled with proper treatment and none developed dysplasia or malignancy under careful observation and control biopsies.

The case 71 where in the initial diagnostic biopsy an early invasive carcinoma developing in a hyperplastic area of a mixed dystrophy was found, represents a 3 percent (one in 27 cases) of malignant potential. This is coincidental with current concept in the field of vulvar pathology of assigning to mixed dystrophies less than 5 percent of malignant potential.

Three of the four cases of mixed dystrophy with slight to moderate atypia were treated with excisional biopsy and followed with corticoid and testosterone topical therapy and after 3 to 8 years of control, none of them recurred.

The most interesting is the fourth where no treatment was given and nine years later the lesion was without change in the same location.

From the reduced experience we have on dysplasia it can be said that these changes do not evolve necessarily to further steps. They can stay without aggravation for as long as nine years. They also can regress with appropriate treatment that eliminates local irritation.

It is rational to say that much more experience is needed to establish the real significance of dysplasia. But the new terminology proposed by the International Society for the Study of Vulvar Disease represents a real progress because allows the collection of well documented cases in different centers through the world under the same parameters. With time and careful prospective data a better understanding will arrive.

In relation to dystrophies it can be said that chronic irritation from scratching can induce in predisposed patients atypical changes in a small proportion of cases.

This is the explanation of the rare association of L. S. with carcinoma in situ or microinvasive carcinoma and the beginning early invasive cancer that started « de novo » in a hyperplastic area of a mixed dystrophy without previous steps.

In properly treated patients with chronic vulvar dystrophies (L. S., hyperplastic or mixed) followed through many years no evidence of malignancy was found. We think that this is the rational prophylaxis in this « at risk » population.

Multiple biopsies and careful lifetime follow-up as well as appropriate therapy is mandatory in vulvar dystrophies and dysplasia.

Vulvar dystrophies as a whole have a very low malignant potential. In our experience it was less than 4 percent.

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