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Medicine

CLINICAL AND HISTOPATHOLOGICAL CORRELATIONS IN BOWEN'S DISEASE

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ABSTRACT:
BOWEN'S DISEASE (BD) IS AN IN SITU, PREINVASIVE CANCER WITH POTENTIAL FOR PROGRESSION IN SQUAMOUS CELL CARCINOMA (SCC), BEING CLINICALLY CONSIDERED A PRECANCER WITH A HIGH POTENTIAL FOR MALIGNANCY.
THE AIMS OF THE STUDY WERE TO ASSESS THE CLINICAL, HISTOLOGICAL, AND EVOLUTIONARY ASPECTS OF THE BOWEN'S DISEASE AND INVASIVE BOWEN DISEASE.
THE STUDIED GROUP COMPRISES 50 PATIENTS DIAGNOSED WITH BOWEN DISEASE OR INVASIVE BD, HOSPITALIZED IN THE DERMATOLOGY CLINIC OF EMERGENCY COUNTY HOSPITAL OF CRAIOVA, BETWEEN 2010 AND MARCH 2021. THERE WERE 18 MALES AND 32 FEMALES, AGED 30 TO 85 YEARS, 66% OF THE PATIENTS BEING FROM THE URBAN ENVIRONMENT. THE MOST FREQUENT LOCALIZATION OF BD WAS AT THE LEVEL OF THE LIMBS (52%), ON PHOTOEXPOSED AREAS. IN 92% OF CASES, WE NOTICED CLINICAL ASPECT OF BD WITH SINGLE LESIONS AND THE TYPICAL FORM WAS PREDOMINANCE (80%).
THE PATHOLOGY DIAGNOSED 41 BD AND 9 INVASIVE BD (SQUAMOUS CELL CARCINOMA). PRESUMPTIVE CLINICAL DIAGNOSIS IN 31 CASES (57.40%), WAS CONFIRMED BY HISTOPATHOLOGICAL EXAMINATION.
THE CORRELATION OF CLINICAL, HISTOPATHOLOGICAL DATA LEAD TO AN ACCURATE DIAGNOSIS OF BD. BOWEN'S DISEASE, ALONG WITH OTHER KERATINOCYTIC PRECANCERS, BEING A STRONG PREDICTOR OF THE RISK OF DEVELOPING SKIN CARCINOMAS AND MELANOMA, REQUIRING A PROMPT THERAPEUTIC ATTITUDE AND CAREFUL MONITORING.

KEYWORDS: BOWEN DISEASE, SQUAMOUS CELL CARCINOMA, EPIDEMIOLOGY, HISTOPATHOLOGY.

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INTRODUCTION

Bowen's disease is a rare condition, described by Bowen in 1912 as "atypical cancerous epithelial proliferation." Subsequently, the clinical and nosologically framework of the disease extends, including erythroplasia Queyrat, which is distinguished from Bowen's disease by its localization on the mucous membranes[8 9].

Bowen's disease can occur at any age and gender, rarely, cases have been described at the age of under 30 years. Patients are usually affected in the 6-8 decade of life[1,2,3].

The lesions are localized and on areas not exposed to the sun, but there is a predilection for sun exposed areas. The lesions are usually unique, but in 10-20% of patients they are multiple. In men, the lesions are localized especially on the alopecia scalp, anterior ears and thorax and in women on the cheeks and lower limbs.

In immunocompromised patients, BB occurs at younger ages, the lesions are larger, and the trunk, limbs and neck are particularly affected, and they have more frequent relapsing forms compared to immunocompetent people.

In the appearance of the lesion are involved many favorable factors that act synergistically in the development of the tumor in context of an immunosuppression or a genetic predisposition[1,2].

Many factors are involved in the development and tumor progression: chronic arsenic exposure (rarely encountered), in which the lesions are multiple; exposure to insecticides; chronic exposure to the sun, explaining the localizations in 2/3 of the cases on the discovered parts; ionizing radiation; infection with HPV, HHV8 (in the lesions of patients with organ transplantation); immunosuppression; traumatic injuries[1,2,10].

The diagnosis is suggested by the presence of localized ano-genital plaques or glabra areas, a few centimeters in size, well delimited and squamous with moderate erythema, in usually elderly patients; frequently, lesions occur on areas chronically exposed to the sun, women being more frequently affected. Dermatoscopy is useful both in the diagnosis of Bowen's disease and in the posttherapeutic monitoring, the existence of dermatoscopic vascular structures after the treatment being associated with the residual disease[11]. In the pigmented version, the presence of diffuse, irregular pigmentation or irregularly distributed points and globules can be observed[12].

Positive diagnosis of the lesion is based on clinical suspicion, then confirmed by histopathological exam.

AIM

This study objectives were to evaluate epidemiological, clinical evolutive, and histopathological features of BD and invasive BD hospitalized in Dermatology Department of Craiova.

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MATERIAL AND METHODS

A clinical and histological retrospective study was performed on a lot of 50 patients diagnosed with BD, hospitalized in Dermato-venerology Clinic of Craiova Romania, between 2010 and March 2021. Surgical excision and histopathologic exam were performed for all patients.

All patients have given their consent for surgery and subsequent pathologic exams.

The study material was represented by biopsy or excised lesions, collected under local anesthesia. The biopsy or resealed specimens were examined fresh, subsequently fixed and sent to the Department of Pathology of the County Emergency Clinical Hospital in Craiova, in order to be processed histologically. The biopsy specimens were processed using hematoxylin-eosin stain.

For the purpose of the study, the data obtained prospectively from the patients and recorded in the observation sheets were correlated with the histological diagnostic registers from the Pathological Anatomy laboratory, being subsequently selected from the histotheque of the respective unit.

The recording of data related to the evaluated parameters was done in the database tables of the Microsoft Excel module, component of the Microsoft Office 2007 Professional program package.

The images, representing the main clinical aspects, were taken with the help of a Nikon 10 Mpixeli digital camera; the processing of the images was carried out with the help of AdobePhotoshop, ver. CS3.

The histopathological examination was performed in all cases, performing multiple histological sections, in order to form an image of the tumor in its entirety. The serial sections have a special importance for the discovery of malignant transformation, as well as for the study of peritumor structures, allowing obtaining a diagnosis as accurate as possible.

The morphological study included a usual histopathological study, the resection pieces (excisional biopsy or tumor biopsy fragment) being evaluated from the microscopic point of view, the following objectives being targeted: assessment of the degree of cellular differentiation; assessment of the degree of invasion of neighboring structures; response or reaction of host tissues to the presence of the tumor.

For the microscopic analysis of these parameters, we used Nikon eclipse microscope 55i, Nikon's Image-ProPLUS program, examining fine sections (4 microns), colored by the usual method with Hematoxylin-Eosin.

RESULTS

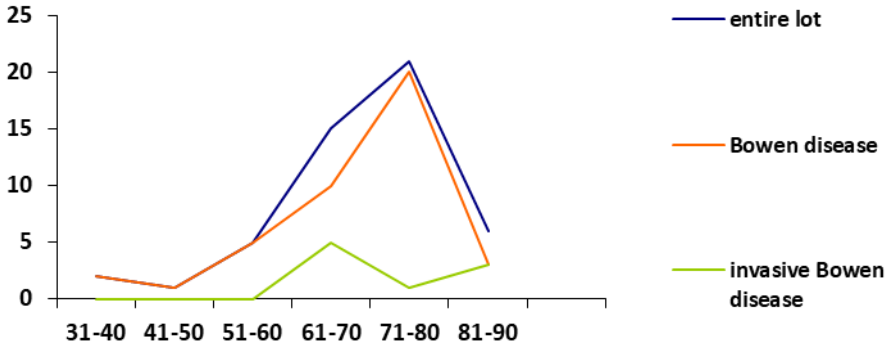
Clinical and morphological data

There were 18 males (36%) and 32 females (64%), while 33 (66%) patients were from the urban environment; urban women are more commonly affected (22 cases) compared to men (11 cases). We also have noticed that in the group with malignant transformation of BD there is an almost equal distribution by genders (5 women and 4 men), 3 women and 3 men were from rural areas.

The mean age of the group with BD was 68.95 years, the age of the patients varying from 30 to 85 years, while for the group with malignancy was 73.82 years, with limits between 65 and 83 years. The mean age in women was 69.31 years, and in men 70.44 years.

BD was more frequently diagnosed in the 8th decade of life, with an increase in the number of cases since the 6th decade.

We observe the same tendency of increasing the number of malignant transformed cases with aging, so that 55.55% of malignant cases belong to the 6th decade of life (figure1).



(figure1) Distribution of patients with Bowen's disease by age group

Following the distribution by age, gender and environment, we noticed that regardless of age and gender BD is more frequently diagnosed in urban areas. In the 6th, 7th and 8th decade of life, women are more frequently affected, so that in the 9th decade of life both sexes are affected, regardless of the environment of origin.

The history of the lesions was between 1 month and 30 years, the size of the lesions being between 0.5 and 7 cm.

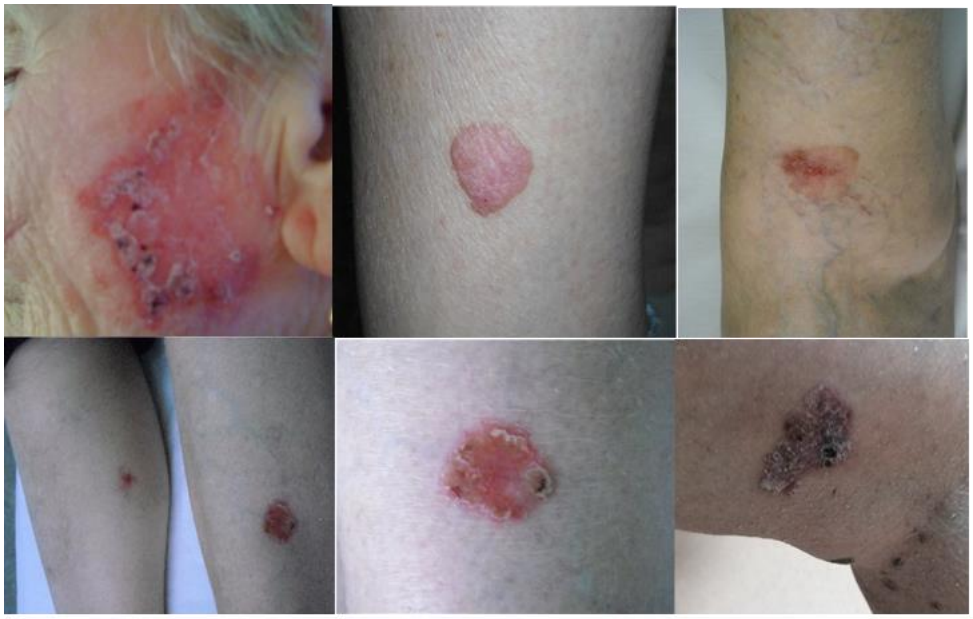
The tumors' topography, both for BD and invasive BD is presented in the table 1.

Topography of lesions by gender and the environment of origin

Localization	Cephalic extremity				Upper limbs				Lower limbs				Thorax				Genital region			
Environment	U		R		U		R		U		R		U		R		U		R	
Gender	F	B	F	B	F	B	F	B	F	B	F	B	F	B	F	B	F	B	F	B
BD*	6	1	-	-	3	2	2	3	6	1	4	1	3	4	1	1	1	-	1	1
IBD**	1	1	1	1	-	2	1	-	1	-	-	-	1	-	-	-	-	-	-	-
No. of cases	7	2	1	1	3	4	3	3	7	1	4	1	4	4	1	1	1	-	1	1
%	14	4	2	2	6	8	6	6	14	2	8	2	8	8	2	2	2		2	2

(table 1)
*- *Bowen disease*, **- *invasive Bowen disease*

In the studied group we encountered in 47 cases the form of BD with single lesions. The appearance of a round-oval, yellowish-brown or pink plaque, with dimensions between 2 and 7 cm, discoid, slightly protruding with clearly delimited edges, covered by scales or crusts, sometimes hyperkeratosis, located on the trunk and limbs, on the photoexposed or traumatized areas was observed in 40 cases; the hyperkeratosic aspect was observed in *6 cases*, clinically the lesion suggesting an actinic keratosis, angiokeratoma, seborrheic keratosis, vulgar wart; in one case the presence of ulceration was observed, announcing a possible malignancy**.** Among the particular clinical forms of BD, the following were observed: BD with multiple lesions – 3 cases (figure 2**);** 1 case of BD with periungual localization and 2 cases of pigmented BD with genital localization and on the thigh.



(figure 2) Clinical aspects in Bowen disease.

We noticed in the studied group the predominance of Bowen's disease with single lesions (92%), located more frequently on the limbs, on areas with chronic sun exposure.

Presumptive clinical diagnosis in 31 cases (57.40%), was confirmed by histopathological examination. In 19 cases the diagnosis of Bowen's disease was established on the basis of histopathological examination, there being no clinical suspicion of Bowen's disease (basal cell carcinoma in 9 cases, squamous carcinoma in 1 case, actinic keratosis in 3 cases, psoriasis in 1 case, seborrheic keratosis, melanocytic nevi, angiokeratoma and vulgar wart in 4 cases, genital leukoplakia 1 case).

The cutaneous manifestations of photo-aging, occurring as a result of chronic sun exposure, we have identified in most patients.

The risk factors involved in the occurrence of Bowen's disease in the studied group were: old age (the mean age in women was 69,31 years, and in men 70,44 years), chronic exposure to the sun (82% of lesions occur on photoexposed areas; 90% of patients recognize repeated and prolonged exposure to the sun), skin phototype (70% of cases belong to phototypes II and III), smoking (30% of the patients being smokers), chemical carcinogens (20%), chronic traumas to the skin (54,54%).

The evolution of the BD lesions was slow, of apparent stagnation, for long periods of time the changes being barely noticeable. Out of the 9 malignant cases in 5 cases, the transformation into invasive squamous carcinoma was clinically suspected, in one case the diagnosis was of basal cell carcinoma, and in 3 cases the clinical diagnosis was of actinic or seborrheic keratosis.

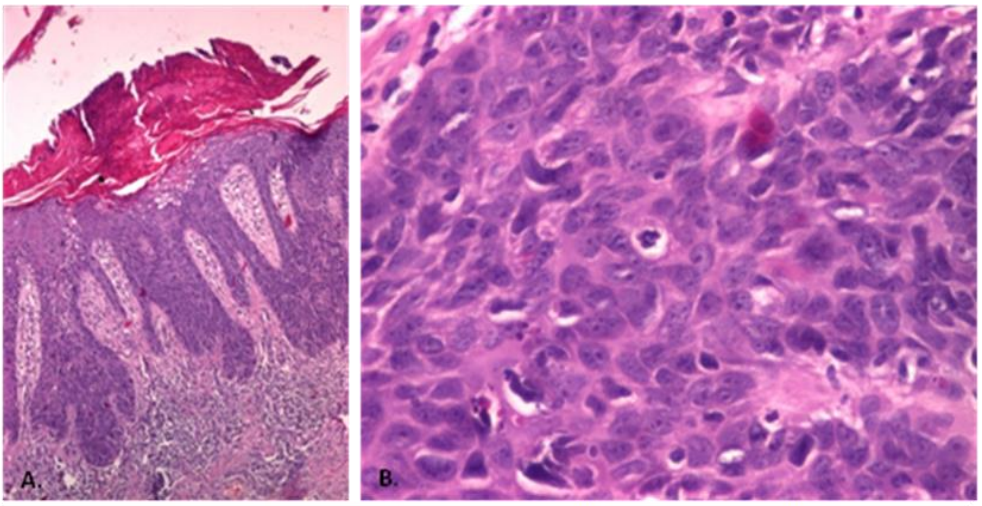
Regarding the association with other carcinomas and cutaneous precancers, 35 patients had a history or had concomitantly: one case SCC; basal cell carcinoma - 5 cases; multiple actinic keratoses located on the face and on the back of the hands in 25 cases, actinic cheilitis in 10 cases, cutaneous horn in 3 cases.

The histopathological study allowed the classification of these tumors in various histological subtypes depending on the growth pattern of the tumors and the assessment

in malignant cases of the degree of malignancy depending on the degree of differentiation of the cells.

For an accurate diagnosis, the pathologist must have at his disposal the entire tumor or a deep biopsy fragment, comprising a part of the tumor and the healthy perilesional skin.

In 41 cases (82%), histopathological examination establishes the diagnosis of BB without invasion. Histological features depend on the evolutionary stage of the tumor; all the tumors studied had the histopathological aspect of carcinoma in situ (figure 3).

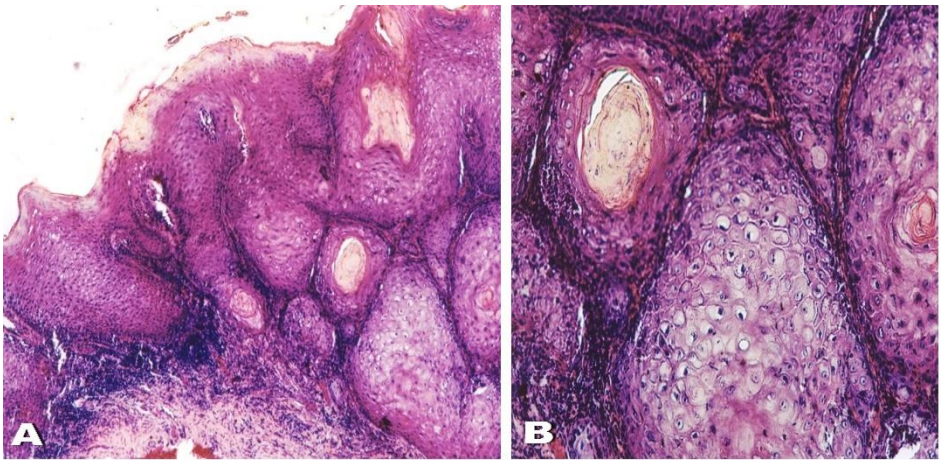


(figure 3) **A.** Bowen's disease: acanthotic epidermis with hyperkeratosis, with large areas of parakeratosis, dyskeratosis, marked nuclear atypia and the presence of atypical mitosis, underlying chronic lymphoplasmacytic inflammatory infiltrate; HE stain x40 **B.** Bowen's disease (detail): marked nuclear atypia and the presence of atypical mitosis; HE stain x400

They have been identified as particular histopathological types of BD: acantholytic type (1 case), hyperkeratosic type (3 cases), pigmented type (2 cases), pagetoid type (3 cases).

In 9 cases (18%) the transformation into squamous carcinoma was diagnosed. In 6 cases we observed the invasion of the dermis, which initially occurs in a limited area, highlighting the area of carcinoma in situ and microcarcinoma, and in 3 cases it was observed moderately invasively differentiated invasive SCC in the hypodermis.

In order to detect the invasion, serial sections were made through the entire block; inflammatory infiltrate becomes abundant (figure 4).



Cases with malignant transformation occur in 5 women in the 7th and 9th decade of life, representing 15.62% of women and 10% of the total cases of Bowen's disease and in 4 men in the 7th, 8th and 9th decade of life, representing 22.22% of men and 8% of the total studied group.

DISCUSSIONS

Squamous cell carcinoma is an important public health problem, with an increasing annual incidence between 3-8% in all regions of the world and its efficient management consisting primarily in the detection and treatment of precursor precancerous lesions.

Bowen's disease is an *in situ*, preinvasive cancers with potential for progression in SCC, being clinically considered a precancer with high potential for malignancy. The exact incidence of Bowen's disease is not known[1].

In an epidemiological, clinical and evolutionary study, regarding the incidence of cutaneous carcinomas, carried out in our geographical area, the authors report the occurrence of CS in 46,24% of cases on precancerous lesions: actinic cheilitis, actinic keratoses, keratoacanthomas, cutaneous horn, Bowen's disease, erythroplasia of Queyrat, lichen sclerosus, chronic scars[13].

The studied group includes 50 cases of Bowen's disease, diagnosed histopathologically over a period of 10 years. The gender ratio is 1:1.77 in favor of women, results consistent with a number of published studies, while others show an equal distribution by sex, or the predominance of men[1,2,14]. Women seem to be more frequently affected than men, in the studied group they represent 64% of cases, and the lesions predominate on the lower extremities, on the sun exposed areas.

Cases with malignant transformation occur in 15.62% of women, accounting for 10% of all cases of Bowen's disease.

Bowen's disease was more frequently diagnosed in the 8th decade of life, with an increase in cases since the 6th decade, the age of the patients being between 30 and 85 years. We observe the occurrence of cases of malignant Bowen disease, equally, in the 7th, 8th and 9th decade of life, they represent 18% of the studied group.

Regarding the environment of origin, we noticed the more frequent affectation of patients from urban areas (66%), women being more frequently affected.

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Of the 41 cases diagnosed with Bowen's disease, 65.85% came from urban areas, observing the same predominance of women in urban areas (70.37%), men having an almost equal distribution.

Age is an important predisposing factor, in the studied group it is noticed that the prevalence of Bowen's disease increases with age, with values ranging from 10% in the age group 51-60 years, to 30% in people aged 61-70 years and 54% in people aged 71-85 years, most cases being noticed in the 7th and 8th decade of life (72%).

In the occurrence of Bowen's disease are involved many factors, which act synergistically in the development of the tumor, in context of an immunosuppression or a genetic predisposition[1,2,15,16].

The role of chronic exposure to ultraviolet radiation in the etiology of Bowen's disease is very important and is documented by the frequent occurrence of Bowen's disease on the areas chronically exposed to the sun, in the studied group 82% of the lesions appearing on photoexposed areas. Although the majority of patients come from urban areas, 90% of patients recognize repeated and prolonged exposure to the sun.

There were also other arguments regarding the involvement of ultraviolet radiations: the rare occurrence in patients with intensely hyperpigmented skin and the appearance of BB after PUVA-therapy[16].

Photocarcinogenesis is possible after repeated and prolonged exposures to the sun, several hours a day (professional and geographical factor), to which is added the racial phenotypic factor (Caucasians) and skin phototype[7].

In precancerous lesions and in the skin chronically irradiated with UV, there have been found mutation of the p_{53} gene, data that can be regarded as an alarm signal for an already dangerous solar capital[2,17].

The repeated irradiation of the skin by ionizing radiation finds its morphological expression in chronic radiodermatitis, with important malignancy potential, on this lesion can appear keratoses, keratoacanthomas, SCC[1,2].

The risk of developing skin cancers increases if, along with irradiation, the patient will be exposed to ultraviolet, chemical carcinogens or oncogene viruses[1,2,3].

The relationship between chemical carcinogens and the occurrence of Bowen's disease has been documented, these factors acting alone or potentiated by UV[2,17]. insecticides could be involved in the etiopathogenesis of the disease in 10 patients, and smokers accounted for 30% of cases. Exposure to mineral trivalent arsenic (carcinogenic) is associated with the development of actinic keratoses, Bowen's disease, SCC, BCC, internal malignancies; the latency period is 25-30 years. The neoplastic process is whipped by the intervention and other risk factors (UV, HPV)[2,18].

Smoking has been associated with mutations in the p_{53} gene, which reveals another way of involving smoking in the process of carcinogenesis[2].

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Passive smoking also increases the risk of cancer because smoke contains carcinogenic substances. Drug use associated with smoking and alcohol increases the risk of cancer[2].

Repeated local trauma is involved in the production of Bowen's disease, in our study 54.54% of patients with injuries on the hand, report multiple traumas in history.

Mechanical traumas have a role, appreciated differently by various authors, in the production or aggravation of a cancer or precancer; certain proinflammatory cytokines can inhibit the p53 gene, which explains the relationship between chronic inflammation and the development of tumors. They can be unique and brutal, bleeding or of weak intensity, but repeated. This factor is also involved in SCC but also in melanoma[1,2].

In the field of skin cancers, the group of those with mixed pathogenesis, genetic and environmental, is the majority.

In this context, correlations have been noted between the incidence of keratinocyte precancers and carcinomas and the cutaneous phototype, giving a special importance to the individual sensitivity to solar radiations[2].

Epidemiological studies have revealed significant differences in morbidity through cutaneous carcinomas depending on skin pigmentation. The risk of developing cutaneous carcinomas is maximum for phototype I and minimum for phototype VI. In the U.S.A, it has been estimated that whites have a 7 to 8-fold higher frequency of skin cancers compared to blacks (phototype VI)[1,2].

Regarding epithelial precancers, it has been observed that they occur more frequently in people with phototypes I and II.

Immunocompromised patients develop more frequently relapsing forms compared to immunocompetent people. In our study there was only one case with BB with multiple relapsing lesions.

The incidence of cancers in those with significant immune deficiency is 10,000 times higher than in immunocompetents of the same age, and in those with transplants 35 times higher than in the rest of the population[1,19]. Cases with Lewandowski-Lutz verruciform epidermodysplasia or xeroderma pigmentosum in the studied group have not been identified; phototypes I and II, to which chronic exposure to the sun and outdoor occupations are associated, represent 70% of cases.

The presence of Bowen's disease in the studied group makes all patients to be considered susceptible to UV immunosuppression, knowing that the solar spectrum can diminish the immune function of the skin and thus lead to the formation of skin cancer.

To the UV-induced cutaneous immunosuppression is added prolonged immunosuppression related to the presence of systemic diseases, in the studied group a single case of Bowen's disease with multiple lesions having a history of ganglionar tuberculosis and phototype II, 1 case had a history of operated pulmonary neoplasm and phototype II and 1 case had an associated genodermatosis, these factors contributing to the development and evolution of the disease.

Regarding the role of viruses in carcinogenesis, it has been experimentally demonstrated that a chronic antigenic stimulation with herpesviruses (especially cytomegalovirus) in immunodepressed patients, such as those with organ transplantation or AIDS, induces the appearance of lymphomas and skin cancers[1,2].

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The role of HPV in skin cancer remains controversial, but there are evidence of the role of the virus by promoting cancer, through mutagenic effects induced by ultraviolet B radiation, malignant conversion being potentiated by the action of some cocarcinogens (ultraviolet radiation, smoking, ionizing radiation, chemicals, immunodepression)[1,2,12,20].

The role HPV and HHV8 in the production of BD lesions is demonstrated in the localizations at the extremities and respectively in the lesions of the patients with organ transplantation. The association with HPV in extragenital lesions is more common in the black race, the acral localizations, the young age and the hyperkeratotic or verrucous appearance. PCR techniques allow the identification of cutaneous and mucous types of HPV, in some cases of extragenital BD there is a link with high-risk mucous HPV types[21],[22,23,24].

Subtypes 16, 18, 31, 34, 35, 54, 58, 61, 62, and 73 of HPV were detected in lesions of BD[2]. Infection with high-risk subtypes of HPV (HPV 16) may be responsible for BD with localization in the hands or fingers through anal-digital contamination, in patients who also have simultaneous or genital lesions. The prevalence of HPV association of BD lesions is higher on areas of the skin not exposed to the sun compared to lesions on the photo exposed areas[2].

Although the occurrence of BD after burns was cited, in the studied group we did not notice this situation.

Cancers developed on a burn scar, have a latency duration of about 35 years (7 to 62 years), although cases have been described in the child. SCC predominates, but basal cell carcinoma, melanoma can also develop. About 2% of post-burn scars degenerate[2,3,11].

Regarding the topography of the lesions, regardless of gender and the presence or not of the malignant transformation, in the studied group, the most frequent localization of BB was at the level of the limbs (52%), on photo exposed areas, followed by the cephalic extremity (22%), thorax (20%) and genital (6%), suggesting the importance of chronic exposure to the sun in the etiopathogenesis of the disease. Men develop lesions on the upper limb more frequently, and women on the lower limbs, the results being consistent with those in the literature[2].

Bowen's disease with single lesions we noticed in 92% of cases, in 80% of cases the appearance is of round-oval plaque, covered with scales or crusts on the photo exposed or traumatized areas. Intense keratotic appearance we observed in 6 cases, clinically the lesion suggesting an actinic keratosis, angiokeratoma, seborrheic keratosis, vulgar wart.

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In 2% of the cases, we noticed the appearance of a prominent plaque with the presence of ulceration announcing a possible malignancy.

Among the particular clinical forms, we have encountered 3 cases of Bowen's disease with multiple lesions, localized on the calves, arm and thorax, or thigh and thorax. Clinical forms with multiple lesions are described in localizations on the trunk, especially the abdomen. This clinical form occurs in 40% of patients, the lesions can appear gradually, over several years[25]. Nishimura Y reports a particular case of Bowen's disease with multiple interdigital, symmetrical lesions in a patient with chronic lymphocytic leukemia[26].

The disease remains for a long time stationary, with slow evolution, of apparent stagnation, long periods of time, of 10-15 years; ulceration and infiltration may be signs of malignant transformation. In the studied group, Bowen's disease evolved in 70% of the cases for 1-2 years, and in 28% of the cases between 4 and 5 years, a single case had an evolution of 30 years. Malignancy is noticed after a shorter latency period than that described in the literature (10-15 years). Also, the risk of progression into invasive carcinoma of 3-5% for Bowen's disease on the skin, described in the literature, is much lower than in the studied group[2,11]. Patients with multiple lesions are more exposed to develop SCC, but in the 3 cases with multiple lesions, the malignant transformation was not revealed.

Most carcinomas, especially SCC, arise by the transition from dysplasia to carcinoma in situ and then to invasive carcinoma[27].

The existence of dysplasia facilitates the development of carcinoma in situ, dysplasia having a regressive or progressive spontaneous evolution. In contrast, there is no reliable evidence that a carcinoma in situ, once developed, can regress spontaneously.

The malignant transformation is suggested by the sudden development of the lesion, not so much in the surface but in height, the lesion becoming more prominent, with the more papillomatous surface and with the infiltration of the base, finally ulcerating, in the studied group two cases presenting these clinical characteristics.

The diagnosis of BD was correctly suspected clinically in 31 cases (57,40%), in the rest of the cases being diagnosed as basal cell carcinoma (9 cases), squamous cell carcinoma (1case), actinic keratosis (3 cases), psoriasis (1 case), seborrheic keratosis, nevocellular nevus, angiokeratoma and vulgar wart in 4 cases, genital leukoplakia (1 case). For malignant cases only in 55.55% of cases, malignancy was suspected.

Most studies suggest a 3-5% risk of progression into invasive carcinoma for Bowen's disease on the skin and 10% for Queyrat erythroplasia[1,11]. Patients with multiple lesions are more exposed to develop SCC. Of the cases in which the transformation into invasive carcinoma occurred, 13% will metastasize, and of these, 10% will die through systemic dissemination.

Studies show that 30-50% of patients with Bowen's disease have developed or will develop cutaneous carcinomas[2]. Regarding the association with cutaneous carcinomas and actinic keratosis, 14% of the cases and, respectively, 76% of the cases, had associated

[25] Avram M.E., Costache I., Georgescu S.R., Benea V., Rusu A. Boală Bowen cutanată cu leziuni multiple. DermatoVenerol. 2007; 52: 157-159

[26] Nishimura Y., Kishigawa T., Tanaka T. Bilateral Bowen's disease. British Journal of Dermatology 2004; 151: 227-228.

[27] Duţu R., Diagnosticul morfologic al Carcinoamelor, Ed. Medicală, Bucureşti, 1985, 37- 88.

cutaneous carcinomas (CBC – 10%, CSC – 4%) and multiple actinic keratosis.

We did not find in the studied group the association with pagetoid epitheliomas and associations with bowenoid papulosis, or internal neoplasia (although classically it was considered that Bowen's disease is a marker for internal malignancies and skin cancers, recent data seem to refute this theory)[2,28]. Other authors report that in the next 5-10 years the diagnosis of Bowen's disease below 10% (less often 25-50%) of patients will get an internal cancer, malignant lymphoma, or skin cancer[29,30,31].

Histopathological examination is the golden standard in the diagnosis of skin cancers, the accuracy of diagnosis increasing when the initial histological results are reassessed by a dermatohistopathologist.

One of the factors that influence the exact estimation of the incidence and prevalence of skin precancers is the lack of histopathological examination in most studies[2,32,33].

Thus, the histological study of the skin precancerous lesions acquires a special importance, all the more so because in our geographical area many of these lesions are not addressed to the histopathologist, and the accuracy of the clinical diagnosis is quite low.

Since the clinical aspect has nothing characteristic, in the studied group the clinical diagnosis was correct in 57,40% of cases.

By comparing the histopathological diagnosis with the clinical one in the studied group, the accuracy of 57,40% for the clinical diagnosis and of only 55,55% in identifying malignancy, emphasizes the need for histological examination in these lesions.

Histopathological point of view Bowen's disease is an in situ squamous cell carcinoma, in which neoplastic cells originally appeared multicenterly, in small but expansive areas, and proliferate for a variable period of time only intraepidermal[1,2].

The histopathological aspects observed in Bowen's disease are similar, regardless of the sex of the patients, the environment of origin, the location of the lesions, the clinical form. Lesions located on areas chronically exposed to the sun are accompanied by actinic degeneration of collagen fibers. In 82% of the cases the histological picture reveals typical epidermal changes, consisting of hyperacantosis with Malpighian cells of different sizes, cramped, set disorderly, with voluminous atypical nuclei (Bowen cells), with early individual keratinization (cells with mantle, round bodies). The basal membrane is intact, as in all carcinomas in situ.

Damage to the appendages, especially the pilosebaceous complex, may be present, but it has not been encountered in the studied group. Hyperpigmentation along the basal layer and proliferation of dermal melanophages is accentuated in the pigmented version, also found in 2 cases in the studied group. Pagetoid and clear-cell variants have been reported[3]. The

[28] Iosif S., Tatu A., Costache M. Boala Bowen cutanată şi pigmentară pe abdomenul inferior. Dermatovenerologie. 1998; 43: 119-121.
[29] Reymann F., Ravnborg L., Schou G. Bowen's disease and internal malignant diseases. A study of 581 patients. Arch Dermatol. 1988; 124:677-679.
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[31] Jaeger A.B., Gramkow A., Hjalgrim H. Bowen disease and risk of subsequent malignant neoplasms. Arch Dermatol. 1999; 135:790-793.
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invasion of the dermis occurs in 3-5% of cases, especially in the lesions of the head and neck, of the elderly or middle-aged people, and occurs initially in a limited area, and for its detection it is sometimes necessary to make serial sections through the entire block[2,3]. In the studied group we observed the dermal invasion in 18% of the cases, the lesions being located on the back of the hand, forearm, face, calf and thorax, in both sexes in the 6th, 7th and 8th decade of life.

Both in cases with single lesions and in the clinical form with multiple lesions, the histopathological aspect is identical, suggestive of the diagnosis of carcinoma in situ. The invasion of the dermis initially occurs in a limited area, highlighting in 6 cases the area of carcinoma in situ and microcarcinoma, and in 3 cases it was observed the moderately differentiated SCC invasive in the hypodermis. In order to detect the invasion, serial sections were made through the entire block. Inflammatory infiltrate becomes abundant in cases with the invasion of the dermis. Some authors have described the phenomenon of fibrosis regression and scarring of the papillary dermis[34]. Amyloid deposits are described in the injured and perilesional tegument, being the result of the degradation of cytokeratins from the dyskeratotic keratinocytes[26].

The appearance of the invasive process is announced by the accentuation of pseudoepitheliomatous hyperplasia, the presence of squamous cells with atypical mitosis, hyperchromatic nuclei, their number increasing with the number of undifferentiated cells, the appearance of discontinuities of the basal membrane, the accentuation of the reactional inflammatory infiltrate. The histopathological differential diagnosis was made mainly with bowenoid actinic keratoses, bowenoid papulosis, pagetoid in situ melanoma, actinic keratosis. Bowenoid actinic keratosis and bowenoid papulosis are histopathologically identical to Bowen's disease; however, these tumors are small and are usually completely excised by biopsy, for differentiation being useful immunohistochemical staining.

CONCLUSIONS

Although Bowen's disease is still considered by some clinicians a cutaneous precancer, histopathologically it is a potentially invasive in situ carcinoma. Age over 60 years, chronic exposure to the sun, chronic trauma and immunodepression are factors that intervene in the occurrence of the disease in the studied group. Age-related immunodepression and ultraviolet exposure are factors that intervene in the malignancy process. The positive diagnosis of the lesion is based on the clinical suspicion confirmed by the histopathological examination, which is mandatory for a diagnosis of certainty and to exclude invasive SCC.

The polymorphic clinical aspect explains that the diagnosis of BD was correctly suspected clinically in 57.40% of cases, and malignancy of lesions was clinically suspected only in 55.55% of cases.

BD tends to persistence and evolution towards an invasive squamous carcinoma, observing the malignant transformation of BD in 18% of cases, in both sexes in the 6th, 7th and 8th decade of life, the lesions being located on the photodamaged skin.

Early diagnosis of BD, correct treatment and careful monitoring of patients carry out prophylaxis of squamous carcinoma, a tumor with the potential for lymphatic or blood metastasis.

[34] Murata Y., Kumano K., Sashikata T. Partial spontaneous regression of Bowen's disease. Arch Dermatol. 1996; 132:429-432.

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