REVIEW

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Clinical, histological and therapeutic features of Bowen's disease

TIBERIU PAUL NEAGU[1,2], MIRELA ŢIGLIŞ[3], DELIA BOTEZATU[4], VALENTIN ENACHE[5], CLAUDIA OANA COBILINSCHI[6,7], MUREŞ SEBASTIAN VÂLCEA-PRECUP[8,9], IOANA MARINA GRINŢESCU[3,10]

[1] *Department of Plastic Surgery and Reconstructive Microsurgery, Emergency Clinical Hospital of Bucharest, Romania*

[2] *Clinical Department No. 11, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[3] *Department of Anesthesiology and Intensive Care, Emergency Clinical Hospital of Bucharest, Romania*

[4] *Department of Dermato-Venereology, "Prof. Dr. Victor Babeş" Clinical Hospital of Infectious and Tropical Diseases, Bucharest, Romania*

[5] *Department of Pathology, Emergency Clinical Hospital of Bucharest, Romania*

[6] *Department of Rheumatology and Internal Medicine, "Sf. Maria" Clinical Hospital, Bucharest, Romania*

[7] *Clinical Department No. 5, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[8] *Department of General Surgery, Emergency Clinical Hospital of Bucharest, Romania*

[9] *Clinical Department No. 10, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[10] *Clinical Department No. 14, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Abstract

Squamous cell carcinoma (SCC) *in situ* or Bowen's disease (BD) is a slowly progressive malignancy. However, cases of regression have been reported. Recent reviews cover only certain aspects of this disease; therefore, this paper's aim is to cover all the relevant aspects for medical practice, such as clinical, histological and therapeutic details. BD may affect all regions of the skin and mucosa, but in accordance with the region and etiologic factor, it may embrace different clinical forms, some of them very similar with other skin lesions. Dermoscopy may prove useful for establishing a clinical diagnosis. Several patterns have been encountered and may help distinguishing from other diseases. When in doubt, puncture biopsy or complete excision may be performed in order to obtain histological data that could define BD. Different morphological aspects of the involved components are described in order to reduce the risk of misdiagnose. In order for the approach to be complete, relevant information about treatment has been presented, underlining the pros and cons of each available therapy.

Keywords: Bowen's disease, *in situ* squamous cell carcinoma, intraepidermal squamous cell carcinoma, preinvasive carcinoma, dermoscopy.

Introduction

Bowen's disease (BD) is an epithelial limited squamous cell carcinoma (SCC), frequently diagnosed in elderly people [1, 2]. Progression to the invasive and metastatic form occurs after a long period of time only in 3% to 5% of the cases [3, 4], therefore good outcomes may occur after treatment or in selected cases with no treatment at all [5]. It is usually related to solar radiation, ultraviolet (UV) iatrogenic exposure, radiotherapy, immunosuppression, mostly iatrogenic and, in the past, arsenic exposure, especially in white population [4]. Viral infections such as human papilloma virus (HPV) type 16 [6, 7] and Merkel cell polyomavirus [8] or autoimmune disease, such as primary Sjögren's syndrome [9] are associated with BD and presents different particularities. However, no "cause and effect" hypotheses have been proven [4, 6–9]. Due to sun exposure, head, neck and also limbs, more often in women, seem to be a predilect area for BD [3]. Furthermore, other skin malignancy related to UV exposure may co-exist or develop later [1]. After a literature scan was performed, it has been notice that most of the reviews describe one or two aspects of this pathology. Therefore, the main objective of this review was to synthesize the most significant data for good medical practice as to be able to approach this disease accordingly.

Importance of the matter

BD is a preinvasive carcinoma, which may develop into invasive squamous cell carcinoma (SCC) with 20% chances of metastatic dissemination [1]. Most of the studies revealing information regarding the progression of the BD into SCC are retrospective; therefore, the risk of progression could be higher, with many cases of SCC developing on previous lesions of BD [1, 4]. This disease is commonly encountered in people over 60 years old, with an incidence of 15 cases in 100 000 people per year in United Kingdom [4], 22 cases in 100 000 females and 28 cases in 100 000 males per year in Canada [1], 15 cases in 100 000 people in Minneapolis [3] and between 115 and 174 cases in 100 000 people per year in Hawaii based

on the color of their skin [3]. Therefore, an early diagnosis and therapeutic plan should be available in order to prevent progression and to comfort the patient. In most of the cases, the clinical diagnosis, the histological assessment and the therapeutic approach is easily established, but there are particular forms where little data is available and hardly accessible due to the medical database limitations. This variants of BD are difficult to distinguish from other skin lesion such as bowenoid papulosis, extramammary Paget's disease, seborrheic or solar keratosis [5–10], due to the clinical and histological resemblance Also, there are case reports, studies and reviews in the literature that cover only certain aspects of the BD, thus a summary of the most significant features of this disease ay prove very useful for clinical practice, in order to find all the necessary data as to diagnose, confirm and treat this pathology, in one place. Given this issues, our paper aimed to describe different clinical and dermoscopic forms of BD, specific and misleading particularities in histological assessment, as well as pros and cons for the available treatment options in order to be easily accessed by general practitioner, dermatologist, pathologist and plastic surgeon.

Clinical and dermoscopic features

Bowen's disease is regarded as being *in situ* SCC. The lesion is usually located in areas which are exposed to sun such as the head, neck and legs in neutral skinned elderly people, while in black people, those areas seem to be spared [10]. Theoretical, it can appear on any keratinizing areas of the skin. Therefore, investigators have also reported several cases of Bowen's disease located on the trunk and vulva [11]. Areas such as lip, nipple, palm, feet and the nail bed are rarely affected [11]. Exceptional cases reported in the literature revealed BD of the exterior sheet of an epidermoid and follicular cyst [12], in an area of Mibelli porokeratosis [13], in a scar because of smallpox vaccine [14] and in erythema *ab igne* [15]. Classically, BD it is described as an erythematous little scaly plaque, which enlarges over time in an erratic manner. The scale is usually yellow or white and it is easily detachable without producing any bleeding and with the exposure of a wet, reddish surface. The margins are well defined, the affected area is a little raised above the normal skin, and the surface is leveled but sometimes becomes hyperkeratotic or crusted (Figure 1). The presence of ulcer is most likely a sign of invasive SCC with the exception of the palmar superficial lesion, which can be related to repeated friction.

In some cases, BD can be present in an orthokeratotic manner, as Idriss *et al.* reported 14 patients out of 38 in a recent study [16], in others, hypokeratosis, fissures and scaly rash located on the palms can be suggestive for BD, as Nakai *et al.* reported [17]. When the BD is located periungual, the clinical aspect may vary from leveled, red patches with little scale to verrucous plaques and nail deformity, lysis and necrosis of the nail plate [1]. Saito *et al.* stated that subungual BD can be revealed by a longitudinal melanonychia [18] while Shimizu *et al.* revealed that this is the clinical form of a HPV type 56-associated BD [7]. When the nipple is involved, the skin lesion can resemble the one encountered in mammary Paget's disease, therefore when itching and pain of this region is associated with scaly eczema, BD should be ruled out [19]. Some authors reported two cases of papillomatosis BD, with exophytic growth of the papillae that could be mistaken with solar keratosis [20].

Another clinical presentation is that of Queyrat erythroplasia, which involve penile lesions. The prepuce, the glans and sometimes the urethral meatus can be affected showing reddish wet scaly plaques [21]. In the past, some authors considered that *in situ* SCC of the penile region was a separate entity from BD [22], but during present due to its histological resemblance, erythroplasia of Queyrat is considered the clinical form of mucosa and mucocutaneous epithelium BD [23]. Other authors encountered warts, erosion, nodular and pigmented lesions as being BD according to the histological assessment [24, 25]. However, a significant part of the pigmented ones is considered bowenoid papulosis (Figure 2), which integrates a clinical form resembling condyloma acuminatum and a histological aspect common with BD [26].

Before establishing the diagnostic, the clinician should take into consideration a series of lesions that could resemble BD such as psoriasis, Paget's disease, pagetoid form of basal cell carcinoma, mycoses, papulosquamous dermatoses or solar keratosis [1]; these lesions could be overexpressed in patients with chronic kidney disease, due to uremic milieu or dialysis therapy *per se* [27–30]. For a better assessment of the skin lesions, the use of dermoscopy may come in handy as to establish an accurate diagnostic before biopsy and histological examination. Dermoscopic futures, such as glomerular vessels and scaly erythematous plaques have been described in the literature first in 2004 by Zalaudek *et al.* [31]. Also, Hernández-Gil *et al.* stated that the following aspects may be suggestive for BD: a pattern with multiple components, glomerular vessels, pigmented false network, patches of pigmentation anarchic distributed, smooth distribution of grey or brown pigment, irregular distribution of dots and globules, spots of hypopigmentation and squamous/verrucous surface (Figures 3–5) [32]. With the aim to include and order all dermoscopic findings, a classification regarding different types of BD was first published in 2015 by Payapvipapong & Tanaka [33]. They classified BD in three types, as follows – classic BD, which was associated with the presence of atypical vascular pattern, whitish scale and a pinkish network; pigmented BD, revealing pigmentation without structure, pigmented stripes and crusts; and partially pigmented BD, which was a combination of the other two [33]. It was considered pigmented BD form if more than 50% of the surface was colored in different shades of brown, which was found in only 8% of the patients included in the study [33]. Other authors, reported higher rates (38% to 48%), due to the dermoscopic criteria for pigmented BD smaller than 50% of the area [26, 31], but all of them stated that the classic type is the most encountered.

Therefore, clinical settings are enough to establish the diagnostic, but when there are certain aspects that are less common with classic BD, a punch biopsy followed by a histological assessment should identify or exclude this pathology.

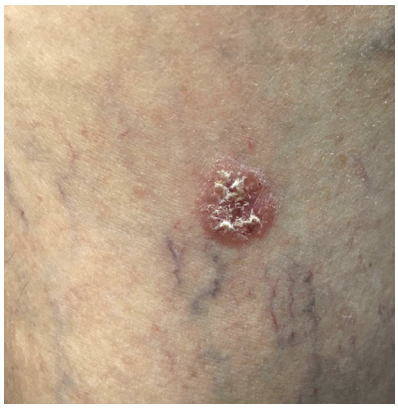

Figure 1 – ***Bowen's disease: clinical aspect revealing well-demarcated hyperkeratotic erythematous plaque sharply border and large scaly surface. Left thigh of a 69-year-old female.***

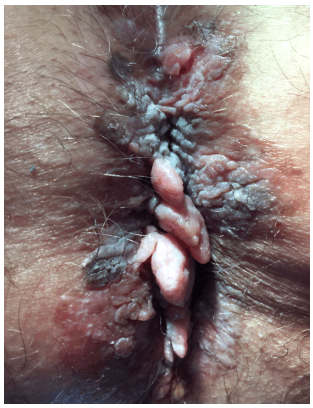

Figure 2 – ***Bowenoid papulosis: clinical aspect revealing papules that resemble verrucas in a 54-year-old male, in the perianal region.***

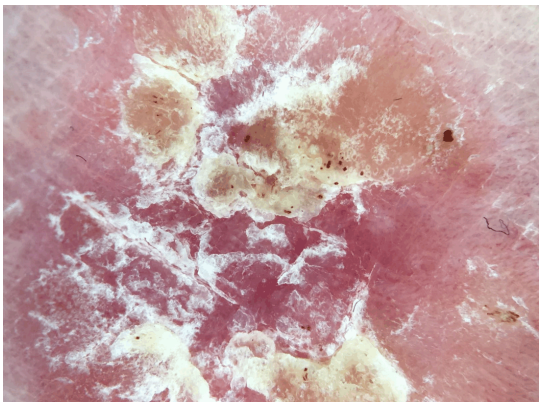

Figure 3 – ***Bowen's disease: dermoscopy revealed a pinkish-white structureless area, glomerular and dotted vessels and overlying whitish scaly areas.***

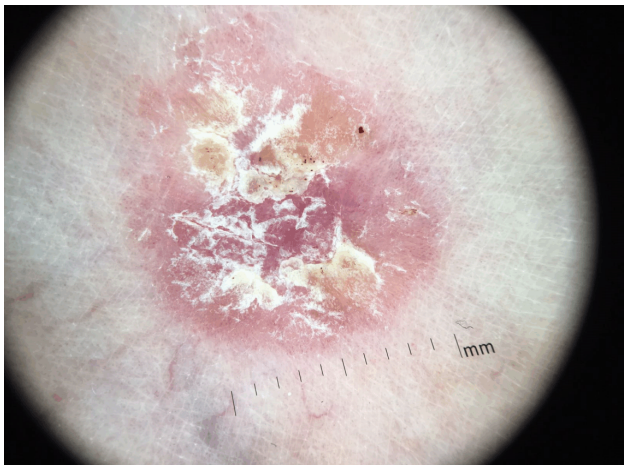

Figure 4 – ***Bowen's disease: dermoscopy revealed a pinkish-white network between the glomerular vessels.***

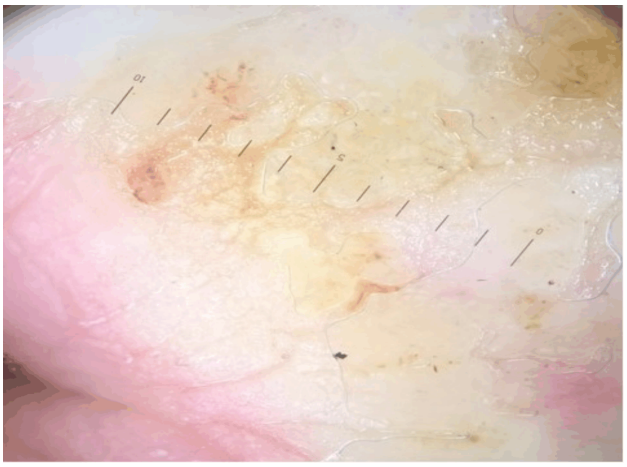

Figure 5 – ***Bowen's disease: dermoscopy revealed a pinkish-white without structured area, glomerular vessels, overlying whitish scaly areas in the palm of a 63-year-old male.***

Histopathological features

Being a form of *in situ* SCC, the whole epidermis is involved in BD and sometimes the epithelium of the pilosebaceous glands [34]. The normal cells are replaced by modified keratinocytes with loss of orientation, hyperchromatic bigger nuclei with a disorderly aspect of the epidermis. The junction between dermis and epidermis is clear (Figure 6), without the unequal acanthosis that is characteristic to the upper layer (Figure 7). Most of the time, there are dyskeratotic cells (Figure 8), atypia and disappearance of the granular layer [34]. Although atypical cells are not present in the dermis, an inflammatory response associated with increased blood flow is often reported (Figure 9) [34].

There have been encountered several patterns that can be isolated or combined in the same plaque, such as *psoriasiform* (acanthosis, parakeratosis), *atrophic* (lack of organization, atypia hyperkeratosis), *verrucous-hyperkeratotic* (papillomatosis, invaginations, hyperkeratosis) [2], *mucinous or sebaceous* abnormal change of the tissue [35], *papillated* (exophytic, sometimes koilocytosis) [36], *irregular* (unorganized acanthosis, possible inflammation of the underlying dermis) [2], *pigmented* (melanophages under irregular cells with melanin), *pagetoid* (light cytoplasm, lines of normal keratinocytes, sometimes normal basal sheath), or the *clear cell* variant (can be associated with HPV infection) [2]. In the arsenic-induced BD, there are many modified cells, which contain large numbers of vacuoles [34], while in the penile lesions, Yasuda *et al.* described modified keratinocytes with hyperchromatic core and irregular cell cycles spread above melanophages of the dermis [21]. BD of the palms associated with hypokeratosis reveals absence of the corneum and unorganized cell arrangement [17]. There are cases when BD is associated with orthokeratosis and preservation of the granular layer, similar to the irregular psoriasiform or pagetoid variant [16]. Namiki *et al.* reported papillae external projections on histological findings in two cases of papillomatosis BD [20].

Immunohistochemical staining may be of use in order to confirm different variants of BD, such as proliferating cell nuclear antigen (PCNA) pale distribution among the keratinocytes [2, 37], vast expression of cytokeratin 10 (CK10) in most of the BD cases [38], decreasing $CD1a^{+}$ [39], expression of CK 13, 15, 16 in the clear cell variant and CK14 in the progressive BD. In a recent study, it has been proved that p16 staining is well expressed and

follows a distinctive pattern in BD that can be used for support in establishing the histological diagnosis and also to differentiate from actinic and seborrheic keratosis (Figures 10 and 11) [40].

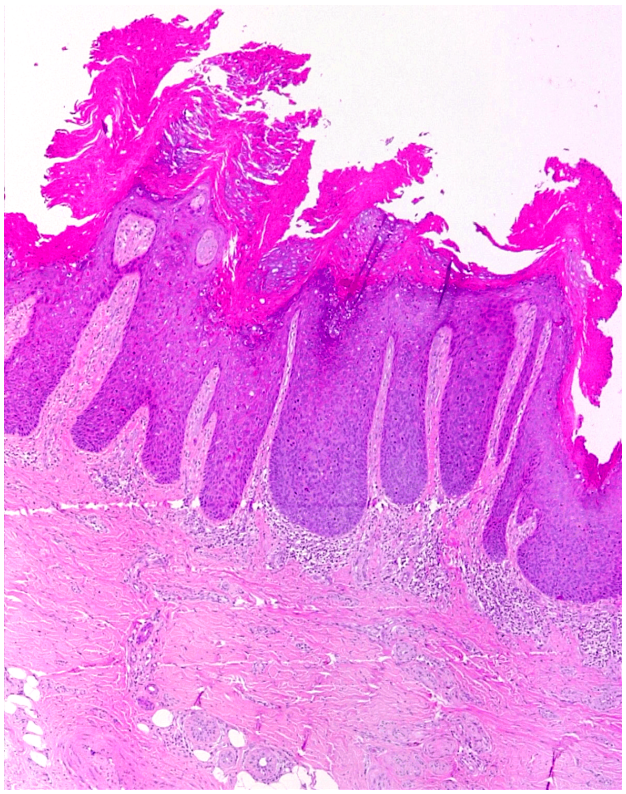

Figure 6 – ***Bowen's disease: hyperkeratosis and hyperacanthosis, irregular architecture of the epidermis, high cellularity of the epidermis, clear limit between unorganized and normal epidermis (HE staining, ×50).***

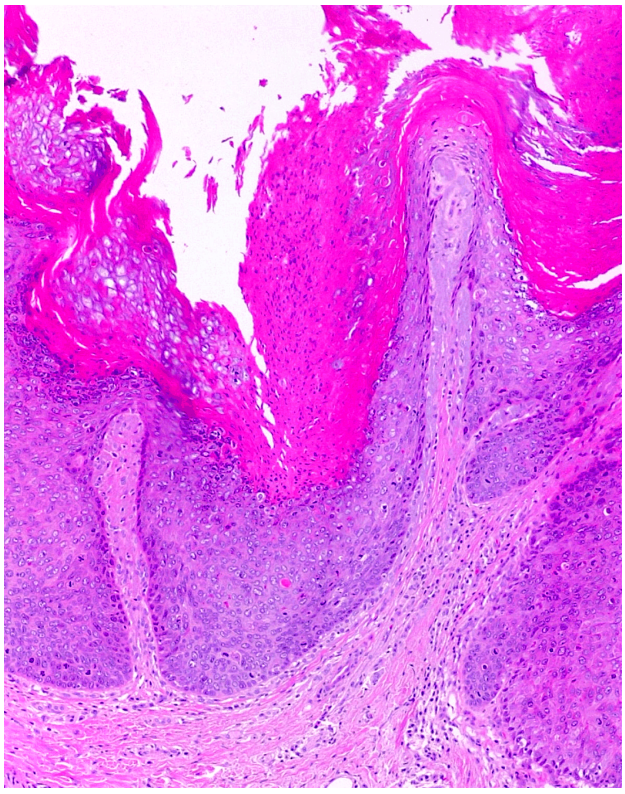

Figure 7 – ***Bowen's disease: hyperacanthosis and papillomatosis of the epidermis; areas of hyperkeratosis alternating with orthokeratosis and well represented granular layer; atypical cells and mitoses (HE staining, ×100).***

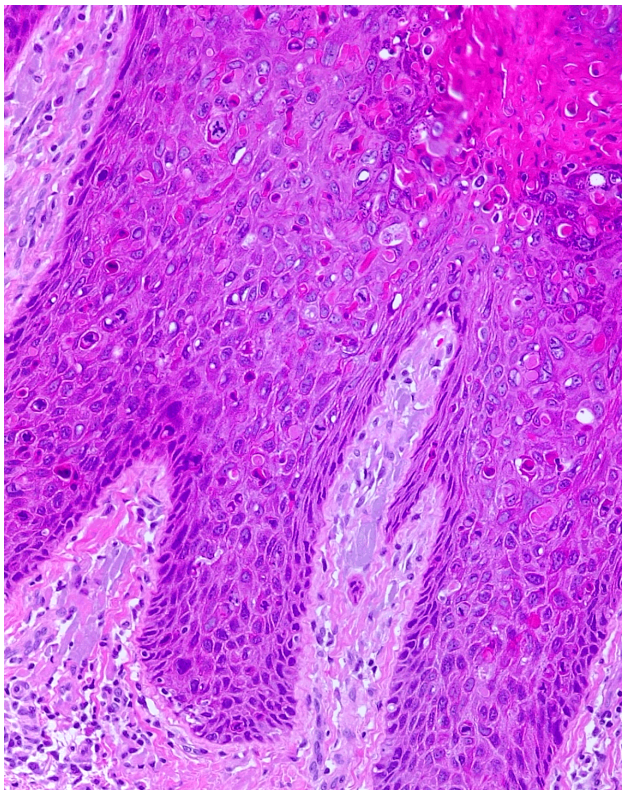

Figure 8 – ***Bowen's disease: nucleocytoplasmatic pleomorphism, atypical mitoses and dyskeratotic cells covering the whole thickness of the epidermis (HE staining, ×200).***

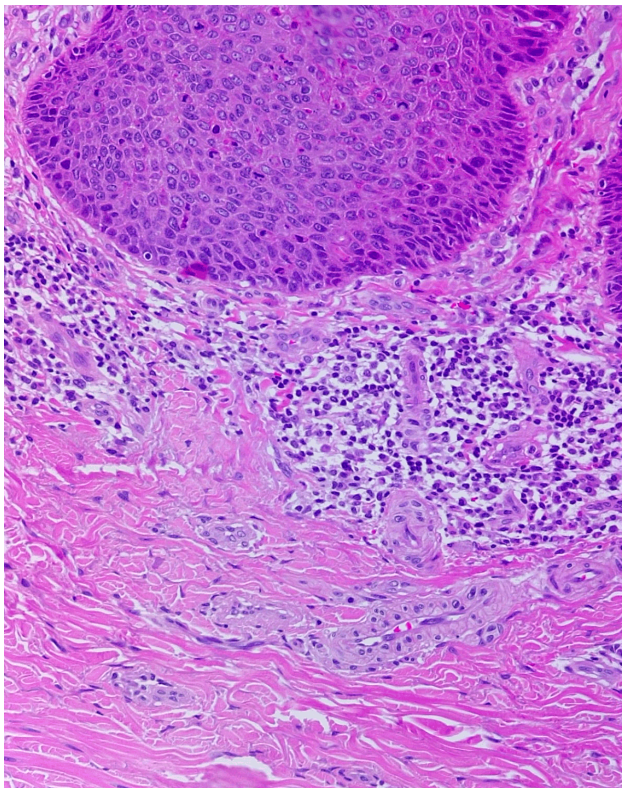

Figure 9 – ***Bowen's disease: disorganized epidermis, massive lymphocytes infiltration around the vessels of the superficial dermis (HE staining, ×200).***

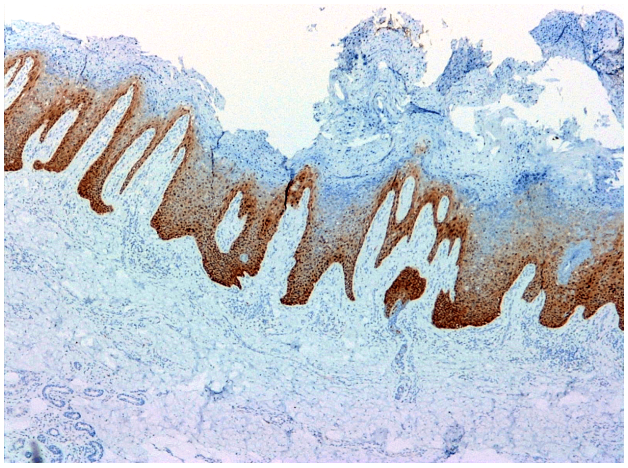

Figure 10 – ***Bowen's disease associated with HPV 16 infection: positive staining for p16 immunohistochemistry (×50) of the dyskeratotic cells inside epidermis; clear limit between dermis and epidermis.***

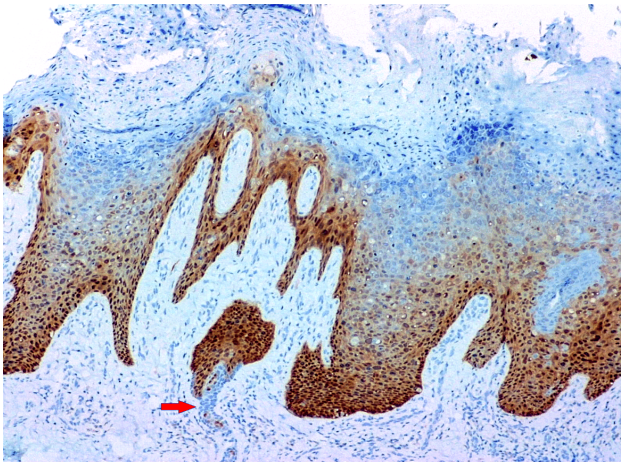

Figure 11 – ***Bowen's disease associated with HPV 16 infection: positive staining for p16 immunohistochemistry (×100) of atypical cells of the epidermis, which extends to the distal part of the excretory duct of the sweat gland (acrosyringium) – red arrow.***

On the other hand, Murao *et al.* reported that HPV can cause BD, but in this case, expression of p16 at high rates is not a marker [6]. In some cases, the absence of p53 may be a marker for HPV-associated BD [6]. Therefore, in order to establish the type of HPV, *in situ* hybridization and polymerase chain reaction (PCR) is needed [6, 7]. Also, in a recent study, PCR was used to identify Merkel cell polyomavirus in BD tissue fragments [8]. Kao stated that progression of BD to invasive SCC revealed large groups of flat epithelial cells without any keratin production spread throughout the dermis [41]. On the other hand, positive staining for surface antigen related to apoptosis (Fas) and other molecules involved in cell death may be signs of spontaneous regression of BD, which should be correlated with the clinical findings of normal skin inside lesions [5].

Some of the histological features of BD are common to other skin lesions. As it was mentioned before, it can embrace many forms. Therefore, BD must be differentiated from solar and seborrheic keratosis (p16 staining pattern, full thickness atypia, sparing of the basal sheath) [40], clonal keratosis that can resemble the pagetoid variant (staining for CK10, which is positive in BD) [34, 38], trichilemmal carcinoma (absence of certainty regarding the presence of trichilemmal keratinization) [42], Paget's disease (Paget cell presenting carcinoembryonic antigen and positive staining for the cystic fibrosis transmembrane conductance regulator) [34, 43], pagetoid dyskeratosis (sparse light cells, with small nucleus) or spreading superficial melanoma (signals for S100 protein) [34, 38, 43]; in addition, calciphylaxis lesions in dialysis patients should not be overlooked [44–47]. One of the most resembling pathology is bowenoid papulosis, which is considered by some a form of genitalia BD, but in fact, even if sometimes the histological features may be misleading, there are two different lesions [34, 48]. In this matter, the electron microscopy could offer intimate details regarding the morphometry of the nuclei in both diseases, underlining that in BD the cores are larger, longish, and more uneven than in bowenoid papulosis [48].

Therapeutic features

There are several therapies available including topical agents [5-Fluorouracil (5-FU) or Imiquimod], surgical removal of the tumor (excision, Mohs micrographic surgery), destructive procedures (cryotherapy and curettage, cautery) light-based procedures [laser therapy, photodynamic therapy (PDT)] and radiotherapy [3]. In some cases, when the lesion is old and has a slow progression rate, some authors prefer no treatment at all if the lesion does not create any discomfort to the patient, especially when there are some comorbidities associated with low healing rate [4]. There are no strict indications for each technique, therefore, the choice remains to the clinician. In order to choose the right therapy, the decision should be made based on the size and site of the lesion, depth, equipment, patient's availability or cosmetic expectations, and also existing healing deficits [4]. Local application of 5-FU implies daily use for a period of three to four weeks with a complete response in 48% to 83% of the cases according to clinical evidence [4, 49]. Most of the patients complained about pain, burning sensations and redness during treatment with 5-FU [3] and some complained of whole limb dermatitis, ulcers and erosions [3, 4]. The other most frequent topical agent used in treatment of BD is Imiquimod, which is an antitumor and an antiviral agent [3]. Clinical evidence show complete response rates between 57% and 86% after six weeks of daily use [3, 50], but most of the patient associate inflammatory reaction of the treated region as an adverse outcome and erythema or hyperpigmentation as a cosmetic deficit [3, 51–53]. Moreover, Gong *et al.* reported extension to the bone of a SCC *in situ* after *Imiquimod* was used [54–58]. *Surgical excision* should be considered when a simple and fast treatment is required. After removing the lesion with safety margins, sometimes, reconstruction procedures are needed in order to cover the skin defect (Figure 12). It is best that this treatment to be performed by a plastic surgeon. In large defects, flaps (Figures 13 and 14) or skin grafts may be required. Ibañez *et al.* reported an advancement flap designed in a V-Y manner in order to cover perianal defect after BD excision followed by chemical colostomy,

which required only parenteral nutrition and oral intestinal motility inhibitors, simulating constipation for one week to protect the sutures [59–63]. Similar flaps may be used in order to reconstruct the vulva after skin cancer is removed [64]. Sometimes, wide lesions of the nail, prepuce or urethra are present, distal phalanx or penile limited amputation may be required. In this case, toe tip transfer may be useful in reconstructing hand fingers [63]. Even if there are few clinical studies, most of them associate this therapeutic procedure with excellent outcomes and low recurrence rates [3, 4, 50]. There are several aspects that need to be taken into consideration before choosing this method, such as expected cosmetic result, region, blood flow, quality of the local tissue (absence of regional radiotherapy) in order to avoid complications [3]. When a tissue-sparring technique is required, Mohs micrographic surgery has proven to be useful in removing genital or digital BD [50]. Providing tissue samples for histological assessment in order to confirm diagnosis and quantify spreading of the SCC represents the main advantage of surgery.

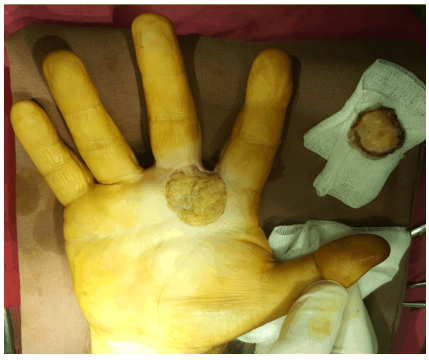

Figure 12 – ***Bowen's disease: intra-operative view of a skin defect due to the surgical excision of a palmar wide in situ SCC.***

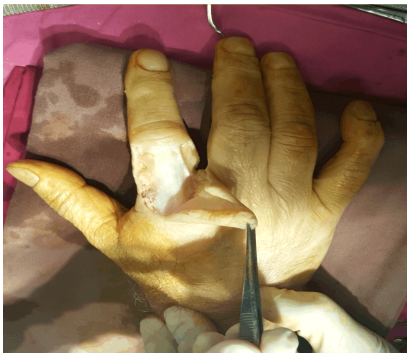

Figure 13 – ***Bowen's disease: harvesting a dorsal digital flap in order to cover skin defect after BD excision.***

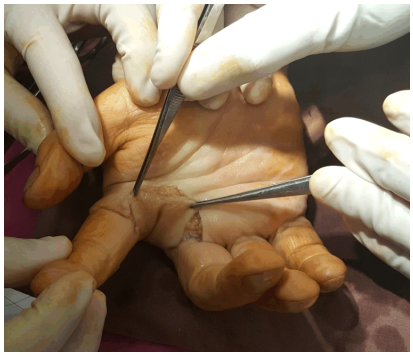

Figure 14 – ***Bowen's disease: reconstruction using dorsal index flap passed through the interdigital space in order to cover palmar defect after excision.***

Other operator-dependent techniques include curettage and cautery (2%, 10% or 20% recurrence rate according to clinical evidence), but also cryotherapy, which is associated with a 61% clearance rate [52, 53]. Despite low costs and fast procedures, Morton *et al.* reported that one in four patients presented ulceration of the region where cryotherapy was used [53]. On the other hand, cosmetic outcomes were significantly better where PDT associated with local application of lipophilic methyl ester (methyl ester methyl aminolevulinate – MAL) was used [53]. Usually, two or three sessions are required for clearance (rates between 68–89%) [53, 54]. There is little data regarding the use of lasers in treating BD, limited to case reports and series. The results seemed to be good, with a clearance rate of 86% in a 44 patients' study [55], but associated with limited penetration of the epithelium. Further improvements of this technique are expected in order to be used for treating genital or nail BD [53, 55]. When other techniques have failed or the region is surgically demanding with few reconstruction options available, radiotherapy should be considered [57].

In order to improve efficacy of the mentioned therapies, the outcomes of different association between them, such as 5-FU and lasers, cryotherapy and Imiquimod, 5-FU and Imiquimod ± topical Tazarotene, PDT and Imiquimod, or such as PDT and radiotherapy, have been presented in case reports and series [4, 53, 58]. Sotiriou *et al.* reported a case with a BD measuring 100 cm^2 that was treated using a single session of MAL-PDT and daily topical Imiquimod application for a period of six weeks [59]. On the other hand, five weeks are enough when immunocryosurgery is performed [60]. This combination of topical Imiquimod and cryosurgery at the end of the second week was successfully used to treat BD of four renal transplant recipients without any recurrence according to Gaitanis *et al.* [60]. In selected cases, other therapies that are not conventionally specific for BD have been useful, such as a combination of oral cyclooxygenase enzyme inhibitor and local Imiquimod, phenol peels, topical Tazarotene, or such as ultrasonic surgical aspiration [4]. Napolitano *et al.* reported the use of intra-arterial administration of Methotrexate and 5-FU in order to obtain full remission of extensive BD of the vulva, perineum and anus [61].

There are several factors that could influence the choice of treatment [4]. Therefore, in lesions less than 2 cm in diameter with normal healing, curettage is the best option followed by cryotherapy [3, 52, 60]. In case of multiple lesions, cryotherapy may be the first choice [3, 52]. When poor healing may occur, PDT is the first choice, followed by topical Imiquimod and 5-FU [3, 50, 52–54, 59]. In facial lesions, curettage followed by topical therapy and PDT is preferred [3, 52]. Penile BD is usually treated using PDT, topical and radiotherapy [4, 52, 57, 60]. Surgical excision can be used in most of the cases but in order to have good cosmetic results, it is better to perform it when the lesion is small or affects the nail and to be the last resort in large, multiple, facial or penile lesions [4]. In immunocompromised patients or in organ transplant recipients, PDT, cryotherapy and curettage seems to be the correct treatment [4, 49, 59, 60]. Another important aspect is the necessity of anesthesia, which sometimes is better to avoid if important comorbidities are associated [65]. Some of the procedures may be performed without or under loco-regional blocks, but extensive reconstructive surgery usually requires general anesthesia [66].

Practical approach

BD is usually suspected in old patients with slowly spreading skin lesions such as reddish scaly plaque with good defined margins, usually located in sun-exposed regions [1, 2, 4]. However, there are various clinical forms of BD, sometimes induced by etiological factors [4], therefore establishing a clinical diagnosis may be difficult

even for the most experienced clinicians. Most of the rare variants were clinically described after surgical excision with safety margins or biopsies followed by histological confirmation of the diagnosis, being treated initially as a tumor with uncertain progression [5, 9–26]. History of other simultaneous skin malignancies, HPV infections or arsenic exposure may support the diagnosis [1, 2, 4].

In most of the classic BD, visualizing glomerular vessels and scale reddish lesions during dermoscopy may be sufficient to establish diagnostic and therapeutic options [31, 32]. When there is any doubt and the clinical settings resemble other skin lesions that impose different treatment from BD, histological assessment may be the next logical step. Even so, due to its multiple components and the possibility of taking different forms similar to other skin diseases (such as seborrheic keratosis, Paget's disease or bowenoid papulosis), a positive diagnosis may require advanced techniques such as immunohistochemistry or electron microscopy in order to study irregular nuclei morphology [34–43, 48]. Therefore, positive and distinctive patterns of p16 or CK10 staining may be used in difficult cases [40, 42].

After the diagnosis has been established, there are a series of treatment options [3]. Although there are some factors that should be considered as to proceed with the most adequate treatment, most of the times the therapy is selected based on the practical knowledge of the specialist. In most of the cases surgical treatment may be performed in order to obtain good results even if relevant clinical evidence regarding efficiency is limited [59–63]. Facial, genital and nail involvement may be difficult to treat in order to preserve function and esthetics, however, PDT, cryotherapy, topical therapy and curettage may be useful in this case [48–58]. The prognosis is usually very good when correct treatment is applied [1, 2, 4, 48–52] with minimal chances of recurrence, and even when this occurs, other therapeutic options may be considered in order to obtain tumor-free status.

Conclusions

There are some clinical forms of BD, which resemble very intimately with other skin lesions making it difficult to diagnose, even with the use of dermoscopy. In this case, histological assessment, including modern techniques, may imply revealing different patterns in order to distinguish BD from other pathologies. Even so, after the diagnosis has been established, choosing the right treatment may be a challenge due to poor clinical evidence regarding surgery, topical therapy and other treatments, limited to small retrospective studies and case reports. There is also a lack of comparison between treatments, most of the studies providing data about the rate of remission. Therefore, further research is required in order to establish the appropriate conduct regarding different forms of BD.

Conflict of interests

The authors declare no conflict of interests.

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Corresponding author
Tiberiu Paul Neagu, Assistant Professor, MD, PhD, Department of Plastic Surgery and Reconstructive Microsurgery, Emergency Clinical Hospital of Bucharest, 8 Floreasca Avenue, Sector 1, 01446 Bucharest, Romania; Phone +4021–599 23 00, e-mail: dr.neagupaul@gmail.com

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