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Journal
Dermatology Online Journal, 27(2)

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Publication Date
2021

DOI
10.5070/D3272052379

Basal cell carcinoma associated with non-neoplastic cutaneous conditions: a comprehensive review

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Abstract

Basal cell carcinoma (BCC) can be a component of a collision tumor in which the skin cancer is present at the same cutaneous site as either a benign tumor or a malignant neoplasm. However, BCC can also concurrently occur at the same skin location as a non-neoplastic cutaneous condition. These include autoimmune diseases (vitiligo), cutaneous disorders (Darier disease), dermal conditions (granuloma faciale), dermal depositions (amyloid, calcinosis cutis, cutaneous focal mucinosis, osteoma cutis, and tattoo), dermatitis, miscellaneous conditions (rhinophyma, sarcoidal reaction, and varicose veins), scars, surgical sites, systemic diseases (sarcoidosis), systemic infections (leischmaniasis, leprosy and lupus vulgaris), and ulcers. The relationship between the BCC and the coexisting non-neoplastic condition may be coincidental or possibly related to the development of the BCC; alternatively, the development of the BCC may be unrelated to the coexisting non-neoplastic conditions and secondary to either a Koebner isomorphic response or a Wolf isotopic response in an immunocompromised district of skin. This paper reviews several of the case reports and studies that describe the association of BCC with these non-neoplastic cutaneous conditions.

Keywords: basal, carcinoma, cell, collision, condition, cutaneous, dermatoses, neoplasm, neoplastic, skin, tumor

Introduction

Basal cell carcinoma (BCC) is the most common cutaneous malignancy [1]. The molecular pathogenesis of BCC is associated with the hedgehog signaling pathway and mutations in the patched homologue 1 (PCTH-1) transmembrane tumor-suppressing protein [2-4]. Several potential risk factors influence the development of BCC including exposure to ultraviolet radiation, genetic predisposition, genodermatoses, immunosuppression, and trauma [5].

Basal cell carcinoma usually presents as an isolated tumor on sun-exposed skin [6-9]. However, they can occur as collision tumors—referred to as BCC-associated multiple skin neoplasms at one site (MUSK IN A NEST)—in which either a benign and/or malignant neoplasm is associated with the BCC at the same anatomical location [10]. Basal cell carcinoma and non-neoplastic cutaneous conditions can also concurrently be present at the same skin site [11-141].

Discussion

Non-neoplastic cutaneous conditions can be associated with BCC. These conditions may, or may not, influence the pathogenesis of the BCC (**Box 1**), [12-16,19-22,24-26,31-34,38,40,41,46-51,53-61,65-70, 82-109,116,117,120,122-124,127-129]. They include autoimmune diseases, cutaneous disorders, dermal conditions, dermal depositions, dermatitis, miscellaneous conditions, scars, surgical sites, systemic diseases, systemic infections and ulcers (**Box 2**), [12-16,19-22,24-26,31-34,38,40,41,46-51,53-61,65-70,82-109,116,117,120,122-124,127-129].

Box 1. *Non-neoplastic cutaneous conditions associated with basal cell carcinoma.*

Amyloid [31-34]
Calcinosis cutis [38]
Cutaneous focal mucinosis [40,41]
Darier disease [19-22]
Dermatitis[a] [55-61]
Granuloma faciale [24-26]
Leischmaniasis [120]
Leprosy [122-124]
Lupus vulgaris [127]
Osteoma cutis [46-51]
Rhinophyma [65-70]
Sarcoidal reaction [79]
Sarcoidosis [116,117]
Scars[b,c,d,e] [83-117]
Surgical sites[f] [108,109]
Tattoo [53,54]
Ulcers[g] [55,60,85]
Varicose veins [58,59,82]
Vitiligo [12-16]

[a]Dermatitis: allergic contact (nickel), [55], halo [56], radiation [57] and stasis (with chronic venous insufficiency [58-61].
[b]Scars: Burn[c] [83-92], dog bite [90], epidermolysis bullosa [93], infectious[d] [84,94-97], shotgun [98,99], surgical [100-105], trauma [83] and vaccination[e] [84,106,107].
[c]Burn scars: acid [83], cooking oil [89], electric welder flash burn [83], hot fat [83,85], hot metal [83,85,90-92], hot plastic [83], and rubber hose [88].
[d]Infectious scars: chicken pox [84,94], leishmaniasis [95,96], and onchocerciasis nodule [97].
[e]Vaccination scars: Bacillus Calmette-Guerin [107], influenza [106], smallpox [107], and not specified [84].
[f]Surgical sites: Colostomy [108] and hair transplant recipient [109].
[g]Ulcers: Leech bite [55], Marjolin [85], and venous stasis [60].

Box 2. *Etiology-associated categorization of basal cell carcinoma-related non-neoplastic cutaneous conditions.*

Autoimmune diseases
Vitiligo [12-16]

Cutaneous diseases
Darier disease [19-22]

Dermal conditions
Granuloma faciale [24-26]

Dermal depositions
Amyloid [31-34]
Calcinosis cutis [38]
Cutaneous focal mucinosis [40,41]
Osteoma cutis [46-51]
Tattoo [53-54]

Dermatitis [55-61]

Miscellaneous conditions
Rhinophyma [65-70]
Sarcoidal reaction [79]
Varicose veins [58,59,82]

Scars [83-107]

Surgical sites [108,109]

Systemic diseases
Sarcoidosis [116,117]

Systemic infections
Leischmaniasis [120]
Leprosy [122-124]
Lupus vulgaris [127]

Ulcers [55,60,85]

Autoimmune diseases

Vitiligo

Vitiligo is an acquired autoimmune disorder of pigmentation [11]. There is destruction of melanocytes and affected individuals develop patches of pigment loss. Although keratoacanthomas and squamous cell carcinomas have been observed in vitiligo patients, BCC in patches of vitiligo has not frequently been described [12-16].

The first report of BCC associated with vitiligo was described in a Japanese patient with basal cell nevus syndrome and segmental vitiligo in 2005 [12]. Arnon et al. were unaware of this report when they reported a 42-year-old Mexican-American man who developed a nodular BCC in the center of a depigmented patch of vitiligo on his scalp in 2008 [13]. A morpheaform BCC on a depigmented vitiliginous patch was subsequently reported in 2011 in a 33-year-old Caucasian woman [14].

Bhari et al. described a 54-year-old man with a seven-year history of vitiligo who developed three BCCs overlying vitiligo. The investigators attributed the BCCs to the patient receiving five months of phototherapy three times a week with psoralen and ultraviolet radiation five years earlier. The BCCs presented as pigmented plaques on his left shoulder (one BCC, one year following phototherapy) and forehead (two BCCs, four years following phototherapy), [15].

Giant BCC is an uncommon clinical subtype of BCC [9]. Recently, Fiszon-Cerqueira et al. reported a 65-year-old woman with a 20-year history of generalized nonsegmental vitiligo who developed not only a giant BCC of 12cm diameter (with a metatypical

infiltrative pathology), but also an adjacent nodular BCC of 3cm diameter within the same achromatic area on her back. Both tumors were completely excised and the surgical wound was successfully reconstructed using the gluteus muscle and a partial skin graft [16].

Cutaneous diseases

Darier disease

Darier disease, also referred to as keratosis follicularis, is a genodermatosis that has an autosomal dominant mode of inheritance. Mutations in the *ATP2A2* gene causes the condition. The skin lesions present as scaly and crusted papules; in addition, acrokeratosis and nail abnormalities (such as abnormal texture, red and white longitudinal streaks, and subungual hyperkeratosis) can be present [17,18].

Basal cell carcinoma has been observed in the Darier disease lesions of at least four individuals. Latour et al., in 1981, described—to the best of their knowledge—the first Darier disease patient who developed not only two primary BCCs but also a third recurrent BCC. Unsuccessful treatments for his skin condition included not only superficial radiotherapy to the hands during childhood, but also grenz-ray therapy to the legs, arms, and hands; he also had been treated with three courses of oral methotrexate and a topical preparation of 5-fluorouracil [19].

Latour et al.'s patient was a 38-year-old man, with biopsy-confirmed Darier disease which involved his trunk, hands, face, groin, legs and feet, when he developed a BCC on his right leg; it was excised but recurred four years later and was extirpated using Mohs surgical technique. The following year, at age 43 years, he developed two more BCC in areas affected with Darier disease on the left side of his neck and his left arm; these were also excised using the Mohs surgical technique [19].

Subsequently Rapini and Koranda, the following year in 1982, described a patient with Darier disease who developed two BCCs. At 38-years-old, a man with Darier disease since childhood presented with a left lower eyelid pearly 1.5cm nodule of two-years' duration and a 1cm ulcerated area on his left forehead of unknown duration; biopsies of both lesions showed BCC. In addition, Darier disease histology features were also observed in the BCC biopsy specimen from the forehead. Microscopically-controlled excision of both tumors was performed and there was no recurrence at the six month postoperative visit [20].

The development of BCC in Darier disease lesions may be coincidental. Although Latour et al. commented that Darier disease may be managed with medications or treatments that may be carcinogenic, they were not aware of Darier disease lesions being susceptible to malignant degeneration [19]. Rapini and Koranda concurred that it was unlikely that Darier disease patients had any greater risk, as compared to the general population, of developing cutaneous malignancy. Indeed, they were not able to find any other Darier disease patient with a history of cutaneous malignancy when the reviewed the charts of 41 Darier disease patients who had been seen at the University of Iowa Hospitals and Clinics [20].

Nearly a decade later, in 1991, Hamadah and Grande described a man with Darier disease who developed multiple BCCs. His Darier disease had been present since childhood and he received grenz-ray therapy to his face, chest, back, arms, and perianal area over a 10-year-period from age 17 to 26 years old. Approximately four years after his last treatment, he began to develop multiple BCCs on his face, chest and back that were treated with curettage and electrodesiccation or cryotherapy [21].

Hamadah and Grande's patient, at 47-years of age, presented with a recurrent BCC on his right cheek. Mohs surgery was performed to excise the 4.5×2.5cm ill-defined erythematous scaly plaque of BCC. The initial tissue sections of the tumor demonstrated pathologic changes of both BCC and Darier disease; tumor-free margins were obtained after three stages and the final defect measured 7.6×5.0cm. The investigators recommended using Mohs micrographic surgical technique for skin cancers in Darier disease involved skin when erythema and scaling of Darier disease prevent the definitive clinical determination of tumor margins [21].

Russo et al. reported a 48-year-old man with Darier disease-associated papules since 12 years of age. He

developed a BCC on the left ear in an area that also demonstrated lesions of Darier disease at age 44 years. The tumor recurred, necessitating excision of the ear and postoperative radiotherapy. Four years later, he developed two more BCCs on the scalp and left supraclavicular fossa. After four weeks of pre-surgery oral etretinate (25mg three times daily), there was significant improvement of his Darier disease lesions permitting the diagnosis of another BCC on the sacrum that had not been clinically evident on the initial evaluation prior to retinoid therapy. All three of the new BCCs were successfully excised [22].

Dermal conditions

Granuloma faciale

Granuloma faciale is a cutaneous condition usually characterized clinically by a solitary reddish-brown to violaceous plaque on the face. However, albeit less commonly, patients can have more than one lesion and extrafacial lesions can occur. A diagnostic morphologic clue that can differentiate granuloma faciale from other conditions in the clinical differential diagnosis is the presence of dilated follicular ostia at the surface of the lesion. A narrow area of uninvolved papillary dermis, a grenz zone, is a frequently observed pathologic finding [23].

Concurrent BCC and granuloma faciale at the same site has been described by Kamolpour et al. in 2009. A 51-year-old man presented with a 2.5cm violaceous plaque on his right cheek. A shave biopsy of the lesion demonstrated a superficial BCC and the residual tumor was excised. At the follow up visit, there was a brown patch at the surgical site; granuloma faciale, without persistent BCC, was diagnosed on the shave biopsy specimen. A review of the initial shave biopsy not only confirmed the presence of superficial BCC but also showed diagnostic features of granuloma faciale in the dermis beneath the BCC [24].

Basal cell carcinoma associated with granuloma faciale at the same cutaneous location had previously been reported by Ortonne et al. in 2005. However, it was not documented whether both conditions had occurred at the same time. In their study of 66 granuloma faciale patients, the investigators commented that at the site of a previously excised BCC granuloma faciale subsequently developed on the scar tissue. The researchers postulated that the occurrence of granuloma faciale at the location was the result of a Koebner phenomenon [25].

Basal cell carcinoma, possibly at the same cutaneous location as subsequently documented granuloma faciale, was reported by Phillips and Hymes in a 44-year-old woman who developed granuloma faciale in a full-thickness skin graft on her left cheek. Previously, on four separate occasions at the same location, a BCC (which presented as small red plaques and for which the diagnosis had been made clinically without pathology confirmation), had been treated with curettage and fulguration. Within months of each treatment a similar-appearing lesion would appear. After the fourth episode, an excision of the lesion was performed and the diagnosis of granuloma faciale was established. The wound was closed with a full-thickness skin graft and within four months intralesional corticosteroid-responsive papules of granuloma faciale appeared at the periphery of the graft [26].

Dermal depositions

Dermal depositions associated with BCC include amyloid, calcinosis cutis, cutaneous focal mucinosis, osteoma cutis and tattoo [27].

Amyloid

The extracellular deposition of amyloid in tissues or organs is referred to as amyloidosis. Amyloidosis can be acquired or hereditary; it can also be localized or systemic. Primary, or AL type, amyloidosis occurs in patients with multiple myeloma and cutaneous nodular amyloidosis. The AL amyloidosis protein is derived from the deposition of immunoglobulin light chain fragments [28,29].

In contrast, secondary, or AA type, amyloidosis occurs not only in patients with cutaneous types of amyloidosis (lichenoid and macular) but also in individuals with chronic inflammatory conditions. In addition, benign tumors and malignant neoplasms can have associated secondary amyloidosis in the adjacent dermis (**Figure 1**). The source of the AA amyloidosis protein is from keratinocytes [30,31].

Several studies have attempted to evaluate the incidence of BCC with amyloid deposition; the results

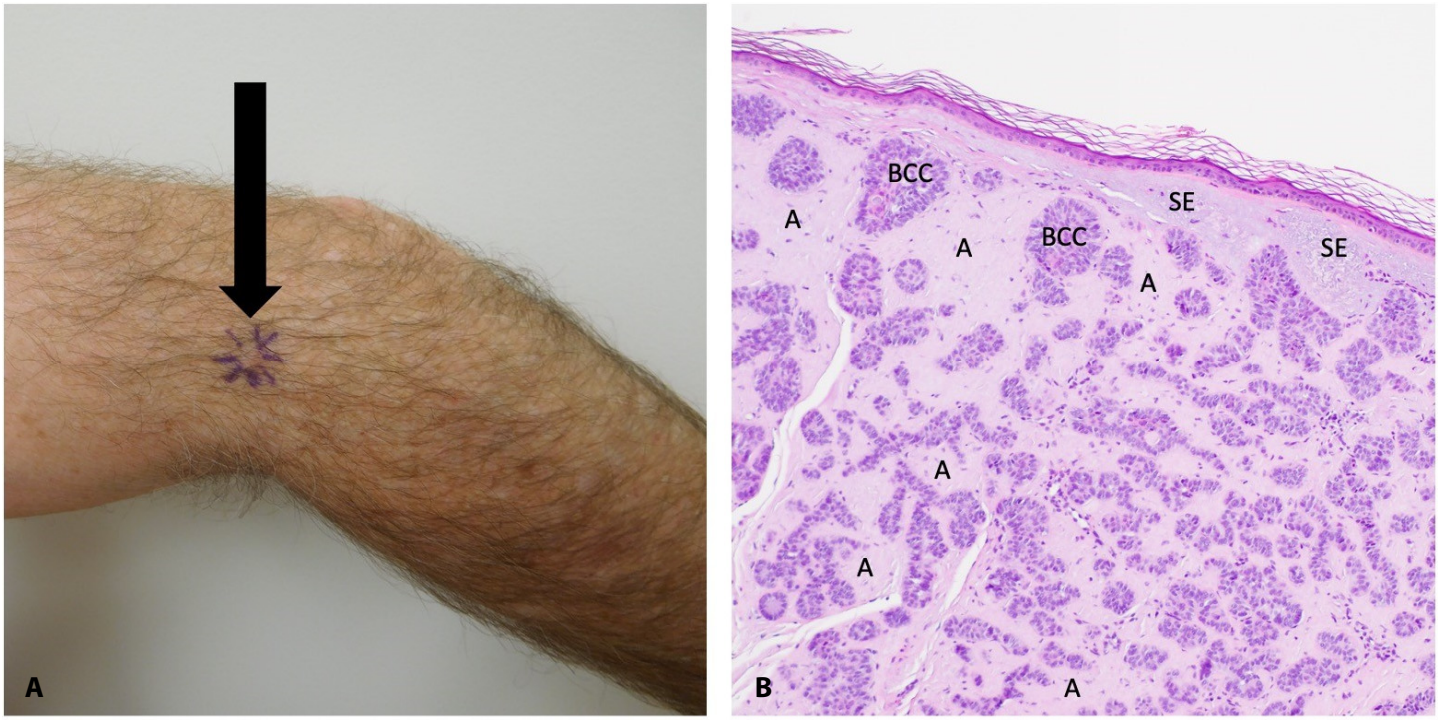

Figure 1. *Basal cell carcinoma associated with amyloid.* ***A)*** *A 68-year-old man--with a prior history of three basal cell carcinomas (BCCs), one squamous cell carcinoma and actinic keratoses—presented with a 6×6mm flesh-colored nodule (thick black arrow pointing to tumor, whose peripheral clinical edge is demonstrated by purple lines, on his left arm of less than six months' duration.* ***B)*** *A skin biopsy using the shave technique was performed; microscopic evaluation showed strands and nodular aggregates of basaloid tumor cells in the upper reticular dermis ('BCC'). Beneath the overlying epidermis and above the BCC in the dermis, there was extensive solar elastosis in the papillary dermis ('SE'); throughout the entire reticular dermis and surrounding the BCC, amyloid is present ('A'). The residual BCC was removed with an elliptical excision. H&E, 10×. The details of this patient have previously been reported; however, the figures included in this manuscript have not previously been published [31].*

range from 11% to 75% (with a calculated incidence of 47%). However, investigators have speculated that the data may have been skewed by studies with lower observed incidences that only evaluated hematoxylin and eosin-stained sections instead of tissue sections also stained with reagents to specifically detect amyloid. Hence, the incidence of BCC associated with amyloid may be higher, ranging from 51% to 75% (with a calculated incidence of 64%), [31-34].

Secondary localized cutaneous amyloid deposits were more frequently observed in BCC with less aggressive histology subtypes and in older individuals. Nodular BCC was the most common tumor subtype and superficial BCC was the least frequent tumor subtype. Solar elastosis was also often present in the dermis [31].

The most common location of amyloid deposits when associated with BCC was the stroma between the tumor aggregates. Other locations of amyloid deposits in the dermal stroma included the papillary dermis above the BCC and the dermis at the advancing edge of the BCC. In addition, BCC-associated amyloid deposits were located within the tumor aggregates [31].

Amyloid deposition did not alter the biologic behavior of the BCC. Therefore, the management of the BCC associated with secondary localized amyloid deposits was similar to that of BCC without amyloid deposits [31].

Calcinosis cutis

The deposition of insoluble calcium salts in the skin and subcutaneous tissue is referred to as calcinosis cutis. Calcinosis cutis has five subtypes of calcification: calciphylaxis, dystrophic, iatrogenic, idiopathic, and metastatic. A local or generalized injury to the skin, including cancer, can result in dystrophic calcification [35-37].

Calcification has been observed in association with benign follicular neoplasms. In addition, cutaneous neoplasms—such as BCC—can be associated with calcification. In a retrospective study by Slodkowska et al., the investigators classified BCC-associated calcification as four types: calcium within the BCC epithelium, calcium within BCC keratinocysts, calcium within tumor necrosis, and free calcium adjacent to the BCC [38].

Slodkowska et al. found that high-risk BCC (mostly infiltrative) had a higher frequency of calcification than low-risk (mostly nodular) BCC. They also noted that BCC associated with calcium were more likely to have active regression, areas of tumor necrosis, background solar elastosis, and a nodular keratinizing phenotype with keratinocyst formation. Indeed, the researchers commented that they considered the detection of free calcium in the dermis of sun-damaged skin (without evidence of BCC) on the evaluation of initial sections of a tissue specimen to be a histologic clue that BCC might be discovered when additional deeper sections of the specimen were studied [38].

Cutaneous focal mucinosis

Cutaneous focal mucinosis is characterized by an accumulation of mucin in the dermis. Clinically it can present as either a solitary papule or multiple lesions. When it occurs as a solitary lesion, there are usually no associated systemic conditions. However, individuals with multiple lesions may have an underlying condition such as lupus erythematosus, thyroid disease, or a paraproteinemia [39,40].

In 2005, Takumura et al. reported a man with cutaneous focal mucinosis [40]. In their paper, they also reviewed the 55 Japanese patients that had previously been described with this condition. One of the individuals not only had diabetes mellitus but also coexistence of cutaneous focal mucinosis and basal cell carcinoma [41].

Osteoma cutis

The formation of bone within the skin is referred to as osteoma cutis; it can be primary or secondary. Idiopathic ossification of the skin in which there is no underlying abnormalities or calcification occurs in primary osteoma cutis. Acquired and congenital plate-like osteoma cutis, Albright hereditary osteodystrophy, fibrodysplasia ossificans progressive, and progressive osseous heteroplasia are the four syndromes associated with primary osteoma cutis [42-44].

Secondary osteoma cutis has been associated with numerous medical conditions. These include not only infectious and inflammatory conditions, but also benign and malignant neoplasms. Bone formation has been observed in association with BCC (**Figure 2**), [45,46].

Basal cell carcinoma with osteoma cutis was originally described by Roth et al. in 1963; they described bone cutaneous ossification associated with BCC in ten patients [47]. There are only a small number of case reports and case series of BCC associated with osteoma cutis [48-51]. However, it has been postulated that BCC and osteoma cutis occurring at the same location may be more prevalent than the number of patients published with this phenomenon suggest [46].

The face is frequently the location of BCC associated with osteoma cutis [46,48]. However, BCC with cutaneous ossification has also been described on the leg [51], scalp [49] or trunk [48]. In three patients, ossification occurred in sites that had previously been treated with electrodessication and curettage [48].

However, the pathogenesis of secondary osteoma cutis in the setting of BCC remains to be determined. It has been speculated that growth factors and bone morphogenetic proteins produced from myofibroblasts may be involved in the development of the osteogenesis in primary osteoma cutis. Whether secondary osteoma cutis in the setting of BCC results from myofibroblast stimulation by inflammation, scarring, or the tumor has not been established [46].

Tattoo

Basal cell carcinoma has been observed to be associated with tattoo [52,53]. A recent review summarized the features of 14 patients with tattoo-associated BCC: eight men ranging from 35 to 76 years old (median, 49 years) and six women ranging

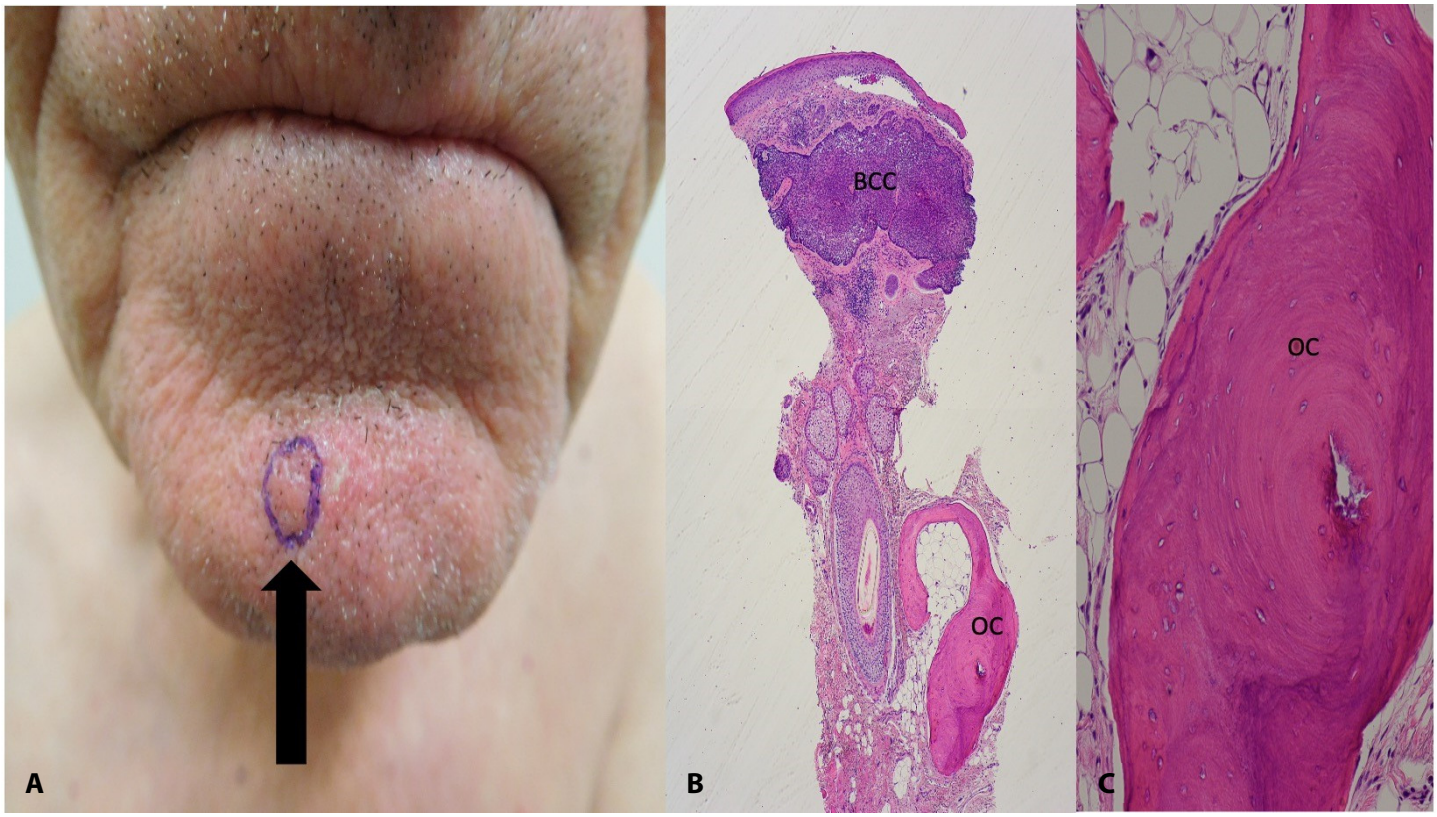

Figure 2. *Basal cell carcinoma associated with osteoma cutis.* ***A)*** *A 79-year-old man—with a prior history of basal cell carcinoma (BCC), normal kidney function and normal calcium level—presented with a 3×3mm tender pearly flesh-colored papule (thick black arrow pointing to tumor that is circled in purple) on the right side of his chin. He did not have acne during his adolescence or adulthood.* ***B)***, ***C)*** *A skin biopsy using the punch technique was performed; microscopic evaluation showed nodular aggregates of basaloid tumor cells in the upper reticular dermis ('BCC') and bone, representing osteoma cutis, in the deeper dermis and subcutaneous fat ('OC'). The BCC and osteoma cutis were excised using the Mohs micrographic surgical technique. H&E,* ***B)*** *2×;* ***C)*** *10×. The details of this patient have previously been reported; however, the figures included in this manuscript have not previously been published [46].*

from 28 to 86 years old (median, 62 years). The tattoos were present from one to 57.5 years (median, 15 years) and were usually dark (11 of 12) and one color (nine of 12); the most common tattoo color was black (eight of 12), [54], **Figure 3**.

The tattoo-associated BCCs were located on the face (six of 14), back (five of 14), and upper extremity (three of 14). They ranged in size from 6×6 millimeters to 20×20 millimeters. Most (11 of 14) were asymptomatic; however, two were pruritic and one was initially painful [54].

The BCC morphology was variable: ulcers, plaques, nodules, papules, and cystic papules. Pathology subtypes were also variable: nodular, superficial, pagetoid, and mixed (nodular and sclerosing). All the tumors were treated with either a routine excision or Mohs micrographic surgery [54].

The pathogenesis of tattoo-associated BCC remains to be established. Some investigators propose that the tattoo influences the subsequent BCC development at that site secondary to a carcinogenic effect of the tattoo pigment and dyes in their native state or after alteration by ultraviolet radiation or the trauma associated with injection of the pigments and dyes, or both. Alternatively, other researchers attribute the observation of a BCC in a pre-existing tattoo to have occurred merely by chance alone [53,54].

Dermatitis

Basal cell carcinoma has been observed in skin affected by dermatitis. The tumor has been reported in association with allergic contact dermatitis to nickel [55], halo dermatitis [56], and radiation dermatitis [57]. In addition, BCC has occurred in the

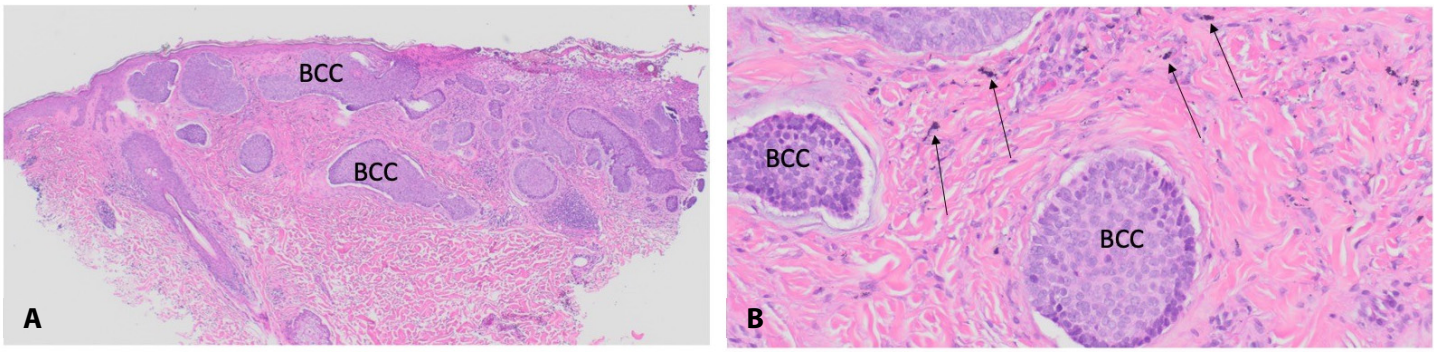

Figure 3. *Basal cell carcinoma associated with tattoo. A 46-year-old man presented with a 12×6mm flesh-colored ulcerated line plaque on his left scapula of 1.5 years' duration. The plaque developed in a black tattoo that had been present for 20 years. He had a history of actinic keratoses, a superficial basal cell carcinoma on his left chest and a squamous cell carcinoma in situ on his left forearm.* ***A)***, ***B)*** *A skin biopsy of the portion of the lesion that was overlying the tattoo, using the punch technique, was performed; microscopic evaluation showed crusted ulceration and nodular aggregates of basal cell carcinoma (BCC) presenting as basaloid tumor cells extending from the epidermis into the dermis ('BCC'). Exogenous pigment (thin black arrows in* ***B)****, representing tattoo, was present in the dermis surrounding the tumor. The BCC was excised using the Mohs micrographic surgical technique. H&E,* ***A)****, 4×;* ***B)****, 20×. The details of this patient have previously been reported; however, the figures included in this manuscript have not previously been published [54].*

setting of stasis dermatitis with chronic venous insufficiency [58-61].

Shamsaddini and Babin commented that BCC can develop at the site of a chronic eczematous dermatitis and postulated that this was an etiologic factor for the BCC that occurred at the site of allergic contact dermatitis to nickel of five years' duration on the neck of a 96-year-old woman. The dermatitis had been treated with leech application for six hours; however, the leech had to be removed forcibly. Two years later, a non-healing ulcer at the site was documented to be a BCC [55].

The phenomenon of circular dermatitis around a nevus has been referred to as halo eczema, halo dermatitis, or Meyerson's nevus. However, the same circular eczematous reaction has also been observed in association with benign and malignant tumors. In this setting, the surrounding inflammation does not macroscopically affect the central lesion [56].

Tegner et al. described a 51-year-old man who developed a circular eczematous one-centimeter ring around a tumor on his right trunk one month prior to presentation. The tumor clinically appeared to be a nodular BCC. The dermatitis resolved after two weeks of topical corticosteroid application; the tumor was macroscopically unchanged by the prior inflammation. Excision of the tumor confirmed the diagnosis of BCC. The area of perilesional dermatitis showed acanthosis, parakeratosis, subcorneal vesicles (with amorphous eosinophilic material), some eosinophils, and focal spongiosis in the epidermis with perivascular lymphocytes and few eosinophils in the upper dermis [56].

In a review of BCC on the lower extremities of Japanese patients conducted in 1993, Nogita et al. discovered that 25 percent of the individuals (ten patients) had a pre-existing cutaneous condition or changes (burn in one man, scar in one woman, and radiation dermatitis in three patients) or lesion (seborrheic keratosis in four patients and actinic keratosis in one patient) on their leg. The two men with superficial BCC associated with radiodermatitis were ages 65 and 71 years; their tumors were located on the thigh and popliteal fossa, respectively. The woman with nodular BCC associated with radiation dermatitis was 64 years old and her 10×10-millimeter tumor was located on her knee [57].

Basal cell carcinoma has been noted to develop on the lower extremities in the setting of chronic venous stasis (with varicose veins and stasis dermatitis). The tumor can result as a complication of a chronic stasis ulcer. It can also appear in skin that has stasis dermatitis and the tumor ulceration can mimic a stasis ulcer [59,60].

The leg is a less common location for BCC. In a retrospective histopathology study of 5,475 BCC

during a 5-year period, the investigators were only able to collect 125 BCC occurring on the legs (2.3 percent). Although they observed that stasis changes were found in 25 percent of the individuals with lower extremity BCC (31 of 125 patients), they concluded that chronic venous stasis was not a predisposing factor for BCC development on the leg [61].

More recently, a group of researchers described a 94-year-old man with multiple BCCs that occurred on his lower legs that had varicose veins and stasis dermatitis. The tumors did not respond to cryotherapy. A successful response to photodynamic therapy with aminolevulinic acid was observed on one tumor yet subsequent BCCs did not respond after three treatment sessions. Twice-daily 5-fluorouracil for three weeks with weekly necrectomy was successfully utilized on two separate occasions; however, post-treatment healing required three and five months [58].

Miscellaneous conditions

Rhinophyma

Rhinophyma is an end-stage presentation of rosacea. Clinically, the nose presents with hyperplasia of the sebaceous glands, fibrosis, follicular plugging, and telangiectasias. Pathologic features include hypertrophy of the connective tissue and the sebaceous glands and a proliferation of the blood vessels [62-64].

Several researchers have mistakenly given Wende and Bentz credit for the initial report of malignancy-associated rhinophyma [65-67]. Wende and Bentz presented their pathological analysis of five separate tumors occurring in their patient's rhinophymatous nose lesion. The paper was read at the 28th annual meeting of the American Dermatological Association that was held in Niagara Falls, New York on June 2 and 3, 1904, and subsequently published in October of that year [64]. Wende and Bentz provided a superlative description of their 69-year-old patient's nose and its "…peculiar bulbous enlargement…" [64]. They also characterized his lifestyle; "…he always indulged in drink, beginning with cider, then dallying with beer, and finally becoming a royal subject of King Alcohol" [64]. When he died in 1902, the cause of death was "…diagnosed as cirrhosis of the liver with possible cancer of the stomach" [64].

Although no autopsy was permitted, "…eight hours after his death, five tumors were removed…" from Wende and Bentz patient's nose [64]. Microscopic examination of each tumor showed features of rhinophyma; in some of the tumors, there was increased dermal fibrosis and an absence of sebaceous glands [64]. Indeed, as subsequently affirmed by Acker and Helwig, "…the proof of carcinoma was lacking in this report [of Wende and Bentz]" [68]; none of the specimens showed basal cell carcinoma.

In 2012, Lazzeri et al. reviewed the characteristics of 46 individuals who had malignancies within their rhinophyma. Basal cell carcinoma (28 patients) was the most common neoplasm. In addition, rhinophyma-associated tumors included squamous cell carcinoma (11 patients), basosquamous cell carcinoma (four patients), sebaceous gland carcinoma (one patient), and angiosarcoma (one patient); the tumor was not specified for one patient [65].

The incidence of rhinophyma-associated BCC remains to be established. Acker and Helwig followed 47 patients with rhinophyma at the Armed Forces Institute of Pathology over a 30-year period and detected five BCC; hence, their incidence was 11% [68]. However, based on their evaluation, Brubaker and Hellstrom postulated only a 5% incidence of BCC in rhinophyma patients [66].

Rhinophyma-associated BCC typically occurred in older Caucasian men [65]. Slightly more than half of the individuals (22 of 41patients) had a biopsy of the tumor. The BCC was discovered as an incidental finding in the remaining individuals (19 of 41 patients) when their rhinophymaplasty tissue was submitted to pathology for evaluation. Hence, several investigators recommend that all tissue specimens removed during elective surgical excision of a rhinophymatous nose be submitted for microscopic evaluation [65,67,69].

The most common symptom of rhinophyma-associated BCC is sudden progressive enlargement of an unchanged rhinophymatous nose of long

duration. Serous discharge, bleeding, and ulceration are less commonly observed [70]. However, the most common presentation is for elective surgery to improve the cosmetic appearance of the nose that has significantly grown [65].

Whether rhinophyma predisposes to the development of BCC has not been established. Rhinophyma may be associated with etiologic features of BCC including prior skin trauma, fibrous scarring, and hypertrophic and hyperplastic cellular changes. In addition, investigators have suggested that these features may affect the primary site of malignant degeneration in patients with rhinophyma—the papillary buds of the dilated follicles basal layer [65-67].

Treatment of rhinophyma-associated BCC is usually excision of the tumor with confirmation of clear margins; reconstruction of the site is also often performed. However, for some of the patients, only surgical debulking without achieving tumor-free margins [69] or radiotherapy [70] were performed. Adequate follow was provided for 19 patients; 17 patients were disease free and two patients had either local recurrence or tumor persistence [65].

Sarcoid reaction

A sarcoid reaction is the presence of a sarcoid granuloma in an individual who does not have sarcoidosis [71-74]. Tumor-related sarcoid reaction has been observed [74,75]. However, malignancy-associated sarcoid reaction is seldom observed in patients with cutaneous neoplasms [76-78].

Basal cell carcinoma-associated sarcoid reaction was described in an 80-year-old Japanese man. He presented for evaluation of facial actinic keratoses. Most of the lesions resolved after four weeks of topical imiquimod; however, a lesion on his nose persisted [79].

Cutaneous examination showed a well-circumscribed plaque on his nasal tip. The plaque contained tiny black papules and superficial telangiectasia. He had neither clinical features of rosacea nor systemic findings of sarcoidosis [79].

Microscopic examination of the biopsy tissue specimen from the nasal lesion not only demonstrated BCC in the upper dermis, but also an epitheloid cell granuloma in the deeper dermis beneath the tumor that consisted of both epitheliod cells and multinucleated giant cells. The cells in the granuloma were immunoreactive for CD123 (which the investigators attributed to the presence of imiquimod-induced plasmacytoid dendritic cells) and CD68 (macrophages); in addition, the granuloma was surrounded by CD3-positive T cells. Stains for fungal and mycobacterial organisms were negative [79]. Surgical removal of the residual tumor was performed. A local flap was used to cover the postoperative wound [79].

Varicose veins

Varicose veins are bulging, enlarged, swollen, twisted superficial veins whose valves are faulty or damaged and thereby allow blood to flow in the wrong direction; some of the patients with varicose veins also have microscopic and/or clinical changes of chronic venous stasis [80,81]. Basal cell carcinoma has been observed on the lower extremities of patients with varicose veins [58,59,82]. Investigators debate whether the varicose vein has an etiologic role in the development of the BCC.

One group of researchers retrospectively studied the possible relationship between pre-existing cutaneous changes and the development of BCCs on the lower legs. During a seven-year period, they identified a total of 1053 patients with biopsy-confirmed BCC; 4.5 percent of these individuals (48 patients) had lower extremity BCCs. Varicose veins were observed in ten percent of the patients with lower extremity BCCs (five of 48 patients), [82].

Scars

Cutaneous neoplasms, including BCC, may develop in scars. Trauma to the skin, resulting in the subsequently development of a scar, is postulated as the causative event. Indeed, scar tissue may be more likely to promote the development of cancer since the site has diminished blood supply, atrophy of adnexal structures and epidermis, and increased sensitivity to the effects of ultraviolet radiation [83,84]. Basal cell carcinoma has occurred in scars from various primary etiologies: burns [83-92], dog bites [90], epidermolysis bullosa [93], infections [94-

97], shotgun [98,99], surgery [100-105], trauma [83], and vaccinations [84,106,107].

Burn scars

Treves and Pack were the researchers responsible for the classic analysis and report of 34 patients who developed cancer in their burn scars. In their paper, they not only share a biographical note on Jean-Nicolas Marjolin for whom the eponym 'Marjolin ulcer' describes the carcinomatous ulcers that originate in degenerating scar, but also report their observations of the 1,374 patients with BCC that were treated at the Memorial Hospital in New York City from January 1, 1917, to January 1, 1929. Seven of the 1,374 BCC developed in burn scars. Hence, they estimated that 0.3% of BCC originate on skin that has experienced a thermal injury [85].

Burn scar carcinomas are classified as acute and chronic. Acute burn scar carcinomas occur within a year after the injury. In contrast, chronic burn scar carcinoma has a longer latency between the injury and the subsequent development of the BCC [85,86].

Acute and chronic burn scar BCC has occurred at the site of flame burns. An acute burn scar BCC developed in a 28-year-old man who was burned by some flaming sparks on his right cheek; the wound never healed and within a year he developed a nodule in its center. Carbon dioxide snow cauterization had no effect and the tumor recurred after excision a year later. Seven years after the injury, the biopsy-confirmed BCC was successfully treated with the application of radium to the ulcer [85].

Chronic burn scar BCC occurred in a 74-year-old man at the site of a flame burn he acquired on his left lumbar area of his back more than 50 years earlier. Within the 19×19cm scar, he had developed a 21×35mm patch of erythema. Initial treatment with topical fluorouracil resulted in ulceration of the tumor; the ulcer was excised and microscopic evaluation showed a nodular BCC in the scar tissue [87].

In addition to fire, several other sources of thermal injury can result in burn scar BCC. These include acid [83], burning rubber hose [88], cooking oil [89], electric welder flash burn [83], hot cinders [85], hot fat [83,85], hot metal [83,85,90-92], hot plastic [83], and molten metal [85].

Dog bite

In a case report about BCC occurring in burn scars, Connolly described a 45-year-old smelter worker who noticed a scaly induration developing in the scar on his chest from a molten metal burn five years earlier; two years later the growing tumor was excised and diagnosed as a BCC. In the paper's discussion, the author commented that he was also aware of another patient who developed a BCC in the scar on the dorsum of the hand which was the site of a prior dog bite [90].

Epidermolysis bullosa

Squamous cell carcinoma has often been observed to develop in the scars of patients with epidermolysis bullosa. However, albeit rarely, BCC has been described to occur at the lesion sites of epidermolysis bullosa. A 33-year-old man with epidermolysis bullosa had biopsy-confirmed skin cancers: an ulcerative BCC that developed on his left thigh and a squamous cell carcinoma on his left elbow. He had a brief beneficial response to superficial ionizing radiation. However, in spite of multiple attempted skin cancer-directed therapies, he continued to develop biopsy-confirmed BCC and squamous cell carcinomas. When he died at age 46, in addition to cutaneous BCC, his autopsy also demonstrated metastatic squamous cell carcinoma in his left axillary lymph node [93].

Infectious scars

Basal cell carcinoma can develop in scars caused by infectious agents such as virus [84,94], protozoa [95,96,128], and parasites [97]. In 1980, Hendricks reported a 71-year-old man who developed a BCC in an old chicken pox scar on the right side of his chin [94]. Subsequently, in a study of trauma as a possible etiologic factor in BCC development, Noodleman and Pollack observed four BCCs that developed in chicken pox scars [84].

Suster and Ronnen reported a 53-year-old man who developed a BCC at the site of a healed Leishmania scar. Three years earlier, he had a biopsy-confirmed leishmaniasis lesion (early ulcerative form) on the angle of his nose; he responded well to treatment

and the site healed with an irregular atrophic 1.5cm scar. Two years after completing his treatment for leishmaniasis, he developed a firm nodule at the site; biopsy showed a BCC and the tumor was excised [96].

Ghahery et al. presented a paper at the 30th Annual Meeting of the American Society of Dermatopathology of a 32-year-old middle-eastern man who developed a BCC that was located at the scar of his previous cutaneous leishmaniasis infection on his face. Four years earlier, at 28 years of age, he presented with a facial lesion that was diagnosed as cutaneous leishmaniasis. The leishmaniasis infection was treated with antimonate (glucatime). After four months of therapy, his infection had healed with a facial scar; 42 months later, the BCC was diagnosed in the scar [128].

Subsequently, Gurel et al. described a 50-year-old farmer with a leishmanial scar on his left cheek that had healed 40 years earlier and who developed a BCC at the scar site. He had cutaneous leishmaniasis when he was 10-years old; the affected area on his left cheek spontaneously healed and there was a visible scar. He developed a one-centimeter biopsy-confirmed ulcerated and crusted BCC within the scar at age 50. Two years later, after the tumor had enlarged to three centimeters, he had the BCC completely excised [95].

Dermatologic manifestations of onchocerciasis present as onchocercal dermatitis (pruritic papules) and onchocercomas (mobile subcutaneous cysts); it is a filarial disease caused by *Onchocerca volvulus* adult worms and microfilaria. Aram and Barsky described a pigmented BCC that arose in the scar of an onchocerciasis nodule. A 41-year-old man developed onchocerciasis characterized by widespread pruritic erythematous papules on his trunk and extremities and a nodule in the right scapular area; skin snips from both lesions showed free-swimming microfilaria and immunofluorescence serologic tests were positive for onchocercosis on several occasions. He was initially treated with diethylcarbamazine, 100mg daily, for three weeks. During the next two years treatment was repeated twice and all the skin lesions resolved. However, at 45 years of age, he presented with a two centimeter asymptomatic pigmented nodule, with a depressed pale center, at the site of the scar from the ochocercoma; biopsy demonstrated a pigmented BCC and fibrosis with mixed inflammation in the dermis. The tumor was completely excised without recurrence. The researchers speculate that the scarring and proliferation process of the filarial disease contributed to the development of the BCC at the site [97].

Shotgun scar

A 68-year-old man developed a BCC as a late complication of an injury he sustained 14 years earlier at the site of a shotgun pellet entry wound. At age 54, a man—while grouse shooting—was accidentally shot in the left temple with a Purdy 12-bore shotgun; the shot was removed and the site healed. Fourteen year later, he developed a 5×4mm ulcerated nodule arising from the left temple scar; an excision of the tumor demonstrated a BCC. The investigators postulate that injury to the site contributed to the subsequent BCC development [98].

Lambert et al. had described the appearance of a metatypical BCC in a gunshot wound. A 70-year-old man developed a BCC in the shoulder of a gunshot wound. The BCC had metastasized to the ipsilateral axillary lymph nodes [99].

Surgical scar

Basal cell carcinoma occurring in surgical scars has not been frequently described. The most commonly reported scar type is following sternotomy (three patients), [100,101]. Other surgical scars in which a patient has subsequently developed a BCC include the following surgeries: cleft lip repair [102], inguinal hernia repair [103], thyroidectomy [104], and tracheostomy [105].

The sternotomy scar-associated BCCs occurred in two men (ages 53 and 62 years) and one woman (age 68 years). The latent period between valve replacement and the appearance of the BCC ranged from 9 months (in the 53-year-old man) to 16 years (in the 68-year-old woman); the median was five years (in the 62-year-old man). The sites healed without BCC recurrence following excision of the tumor in all patients [100,101].

The other patients ranged in age from 54 to 69 years at the time of diagnosis of their BCC. The latent period between surgery and tumor presentation ranged from two years to three years (following inguinal hernia repair or thyroidectomy) to 27 years or 67 years (following tracheostomy or cleft lip repair, respectively). The investigators have suggested that the pathogenesis of BCC at these sites was associated with skin trauma, scar formation and carcinogenesis [102-105].

Traumatic scar

Ewing, in 1971, discussed the possible relationship between a single injury and the development of BCC. During his general surgical practice, over a period of approximately 20 years, he had 13 patients with BCC who gave a history of a well-remembered injury at the site of their subsequent skin cancer. A burn was the etiology for seven of the patients; the source of the thermal injury was either hot fat (three patients), acid (one patient), hot metal (one patient), hot plastic (one patient), and a flash burn from an electric welder (one patient), [83].

The remaining six BCC patients that Ewing observed had BCC that developed in the traumatic scars created by either blunt or sharp injury to the skin. They included abrasion (three patients), cut (two patients) and a chip of metal that flew off and penetrated the skin while the patient was cutting a steel pipe with a cold chisel. The injury occurred between three months and five years (median, 15 months) before the BCC was diagnosed [83].

Noodleman and Pollack also evaluated the possibility of trauma as an etiologic factor in the subsequent development of BCC at that location. During August 1979 and January 1986, 1774 BCC were treated by Mohs surgery at Duke University Medical Center; trauma at the skin site had occurred for 7.3% of the cancers (129 of 1774 BCC). The most common types of trauma included sharp trauma (60 lesions), blunt trauma (25 lesions), and burn (34 lesions). The remaining tumors occurred at the site of a chicken pox scar (four lesions), a vaccination (three lesions), or more than one type of trauma (three lesions), [84].

Trauma-related BCC were larger and occurred more commonly in slightly younger men. The tumors were also clinically deceptive. Often, five or more Mohs surgery stages were necessary to remove the cancer. However, based on their histologic type, the BCC was not particularly aggressive [84].

Vaccination scars

Vaccination sites may subsequently develop scars. Melanoma and non-melanona skin cancers have occurred in vaccination scars; the most common vaccination site-associated cutaneous neoplasms are BCC and squamous cell carcinoma [84,106,107]. Basal cell carcinoma has been at the sites of inoculation of the following vaccines: Bacillus Calmette-Guerin [107], influenza [106], and smallpox [107].

Surgical sites

Basal cell carcinoma has also occurred at surgical sites. The tumor originated at the mucocutaneous junction of a woman's long-standing colostomy site [108]. It also presented at the hair transplant recipient site on the central scalp of a man [109].

A 75-year-old woman presented with an ulcerated skin lesion of one year's duration extending from her colostomy. At 42 years of age, adenocarcinoma of the rectum was diagnosed; she was only treated with radiotherapy—initially 4,624 rads and subsequently six months later with an additional 2,200 rads because residual tumor was still present. A year following her diagnosis, she required a sigmoid colostomy to resolve intestinal obstruction from a stricture of the rectum; she only used toilet paper as a dressing and never used a colostomy appliance. Nearly 32 years after the colostomy had been performed, she was evaluated for a three-to-four centimeter tumor all around the colostomy opening. The biopsy showed a BCC and a wide local excision was performed. The colostomy was relocated to a different area and the non-functioning distal colon was closed intraperitoneally and the abdominal wall opening was repaired with a split-thickness skin graft. Her physicians speculated that bad hygiene and reluctance to use a colostomy appliance caused irritation and frequent ulceration around the colostomy site and subsequently promoted the development of the BCC [108].

A man developed male pattern alopecia by age 27 years. Nine years later, at age 36 years, he underwent

hair transplantation. All 69 transplants harvested from the occipital area healed normally. Five years after the transplant, at age 41, he presented for evaluation of a gradually enlarging painful scalp ulcer of six months' duration located at the recipient site of a hair transplant plug on his central scalp. The area was excised; microscopic examination showed an infiltrative ulcerated BCC and fibrosis (consistent with scar tissue) and an incidental foreign body granuloma containing doubly refractile linear particles. He had no prior history, or subsequent development, of non-melanoma skin cancer [109].

Systemic diseases

Sarcoidosis

Sarcoidosis is an inflammatory disease that affects multiple systems of the body [110,111]. It is characterized by the formation of granulomas and most commonly occurs in the lungs, lymph nodes, and skin. Less often, other organs are affected such as the brain, eyes, heart, and liver [112-114]. Malignancy-associated sarcoidosis can be related to either the cancer or the treatment for the neoplasm [73,74,115].

Ogata et al. described a patient with systemic sarcoidosis in 2013. The individual developed cutaneous sarcoidal plaques. The patient developed a BCC; within the dermal stroma surrounding the tumor, epitheliod cell granuloma were observed [116].

Subsequently, in 2015, Ishikawa and Yamamoto reported a 77-year-old Japanese woman with systemic sarcoidosis who developed a BCC on her back eight months after trauma to the area caused by hitting her back against a tree. Cutaneous examination showed a 23×17mm round brownish plaque on her lower back. Microscopic examination of the biopsy specimen revealed a superficial BCC [117].

The residual tumor was excised with a 5mm margin of normal-appearing skin. Similar to the biopsy specimen, the excision specimen also showed superficial nests of basaloid tumor cells. However, in the subcutaneous fat beneath the superficial BCC, sarcoidal granulomas consisting of CD68 immunoreactive histiocytes and giant cells [117].

The investigators speculate on the association of the BCC and the sarcoidal granulomas. They comment that the Koebner phenomenon (in which a dermatosis occurs at the site of trauma) may be seen in sarcoidosis and that trauma (such as the bruise on the patient's back) resulting in epidermal injury may be a causative factor for the development of BCC. Hence, they hypothesized that the traumatic injury from the tree to her back may have been an event that promoted both the tumor and the granuloma to occur at the same anatomic location. However, they also postulated that if cutaneous subcutaneous sarcoidal granulomas exist asymptomatically in patients with systemic sarcoidosis, the simultaneous occurrence of a cutaneous neoplasm and granuloma at the same skin site may not be so rare. Since the researchers did not perform a random biopsy from a normal-appearing skin site, they could not establish whether the subcutaneous sarcoidal granuloma was only present in the areas with overlying BCC (similar to what has been observed in systemic sarcoidosis and disease-related acquired ichthyosis vulgaris), [117,118].

Systemic infections

Leischmaniasis

Cutaneous leishmaniasis is a parasitic infection of the skin caused by a protozoa [119]. However, the occurrence of leishmaniasis and BCC at the same cutaneous site is rare [129]. Morsy et al. described a 17-year-old man in whom cutaneous leishmaniasis and BCC were identified in the same lesion; the investigators speculate that leishmaniasis infection was a predisposing etiologic factor for the development of the man's BCC [120].

Subsequently, 20 years later, Asilian et al. described a 52-year-old immunocompromised woman who developed a BCC superimposed on a cutaneous leishmaniasis lesion. She had received a renal transplant four years earlier and her daily therapy included mycophenolate mofetil and cyclosporine. The lesion on her nose appeared 14 months earlier; two months later (and one-year prior to presentation), based on a positive smear of the lesion showing leishmania bodies, a diagnosis of leishmaniasis had been confirmed yet no treatment had been initiated. The nasal tip lesion was now a

3×3cm ulcer with elevated borders. Leishmaniasis therapy was started: weekly intralesional glucantime injection [129].

The nasal tip cutaneous leishmaniasis lesion persisted after 20 weekly intralesional glucantime injection treatments and was therefore considered to be glucantime therapy resistant. Surgical excision of the lesion was performed, and microscopic examination showed a BCC. Although the investigators suggested that their patient's immunocompromised status (secondary to her solid organ transplant and chronic immunosuppressive therapy) may have been a risk factor for the development of her skin cancer, they concluded that cutaneous leishmaniasis could have a possible role as a predisposing factor for the development of cutaneous malignancy [129].

Leprosy

Leprosy is caused by *Mycobacterium leprae* bacillus infection [121]. Basal cell carcinoma within the same cutaneous lesion as leprosy has been observed predominantly in patients with lepromatous variant of the infection. Although it has been a consideration that lepromatous leprosy-associated immunosuppression may have been an etiologic factor in the occurrence of the BCC, this is unlikely since the *Mycobacterium leprae*-associated immune response is specific for the mycobacteria and not related to the development of BCC. Hence, the large number of *Mycobacterium leprae* bacilli in patients with lepromatous leprosy probably accounts for the coexistence of the mycobacteria and the BCC in the same lesion [122-124].

Michalany, in 1966 not only reviewed the previously published literature on malignant tumors of the skin among leprosy patients but also performed a retrospective study on the subject that evaluated a series of 60,000 pathology specimens (between the years of 1934 to 1965) from the Department of Leprosy of Sao Paulo in Brazil. His literature review identified 94 leprosy patients (with 96 tumors); the cutaneous neoplasm was recorded for 85 tumors: squamous cell carcinoma (40), basal cell carcinoma (37), squamous cell carcinoma in situ (four), melanoma (two), and sarcoma (two). The relationship between the presence or absence of leprosy in the tumor was addressed in 51 neoplasm. *Mycobacterium leprae* were identified in 51 percent of the tumors (26 of 51 cancers) but the specific neoplasms containing mycobacteria were not provided [122].

He discovered 539 malignant tumors of the skin among persons with leprosy. The tumors included basal cell carcinoma (272), squamous cell carcinoma (194), squamous cell carcinoma and actinic keratosis (28), sarcomas (25), melanoma (14), and adnexal carcinoma (6). Leprosy and cancer were found in the same anatomic site in 35.6 percent of tumors (192 neoplasms), [122].

Subsequently, nearly 30 years later in 1994, Ratoosh et al. described a 62-year-old man with exposure not only to the sun chronically but also to armadillos, whose excisional biopsies of BCCs on the head and neck also demonstrated *Mycobacterium leprae*. In addition to the BCCs, he had a leonine face and infiltrated erythematous plaques on his abdomen. The biopsies from both the BCC and the abdominal plaques demonstrated organisms in the dermis that stained with Ziehl-Nelson stain and Fite-Faraco stain, establishing the diagnosis of leprosy [123].

Recently, another group of investigators reported a 49-year-old man with multiple BCC of five years' duration on the sternal region. He also had a BCC on his nose and a melanoma on his right temple. All the chest tumors were resected in a single elliptical excision; the 'dog ears' at the edges of the surgical wound were removed and a linear closure was performed. Microscopic evaluation of the dog ears showed numerous Fite-Faraco positive staining bacilli in the dermis, establishing the diagnosis of lepromatous leprosy in the same lesion as the sternal BCC. Subsequent examination of the patient revealed multiple cutaneous stigmata of lepromatous leprosy: ciliary madarosis, rarefaction of the distal eyebrows, ear skin thickening, and bilateral thickening of the ulnar nerve [124].

Lupus vulgaris

Mycobacterium tuberculosis can cause skin lesions. Lupus vulgaris is the most common presentation of cutaneous tuberculosis. It typically presents as nodular lesions on the face [125,126].

Dr. Abraham J. Orfuss presented a 61year-old woman with lupus vulgaris and superimposed BCC. The woman lived in Warsaw, Poland for the first 48 years of her life and her father had died from tuberculosis. As a child, her lips and chin had been severely burned. Since age 18 years, she had confluent erythematous plaques with central scarring on her cheeks, chin and neck; diascopy of the lesions showed apple-jelly nodules. A clinical diagnosis of lupus vulgaris was established [127].

Beginning at age 31 years until age 44 years, she underwent various treatments for the lupus vulgaris. These included chemocautery (pyrogallic and trichloroacetic acids), cryotherapy (slush and solid carbon dioxide), sodium glucosulfone and streptomycin ointment (topically), ultraviolet light (Alpine and Kromayer lamps), vitamin D (orally), and other oral preparations (of uncertain nature). By age 46 years, the lupus vulgaris lesions were considered to be resolved and she was lost to follow up until age 61 years [127].

At age 61 years, apply-jelly nodules (by diascopy) were noted on areas of erythema, atrophy, and hypopigmentation on her cheeks, chin, and lips. In addition, there were crusted pearly-bordered lesions on her chin, under her nose, and on the vermillion border of her upper lip. Biopsies of the apple-jelly nodule showed lupus vulgaris, and one of the other three lesions showed BCC. However, Dr. Bahram Sina who was attending the meeting commented that the lupus vulgaris and the BCC were not present on the same slide [127].

The lupus vulgaris was treated with isoniazid and pyridoxine hydrochloride for two years, until age 63 years. The BCC under the nose and on the lip were excised using the Mohs micrographic technique and the tumor on the chin was treated by electrodesiccation and curettage. Follow up, at age 64 years, showed no lupus vulgaris activity and no persistence or recurrence of the BCCs [127].

Dr. Orfuss emphasized that the BCCs on her chin and upper lip were at the same skin sites where she had erythematous scaly plaques of lupus vulgaris for over 40 years. He also commented that it was impossible to exclude the possibility that either the childhood burns or the scarring modalities initially used to treat the lupus vulgaris or both may have had a role in the development of the BCCs. Dr. Sina added that he considered the development of the BCCs on cutaneous locations of lupus vulgaris only to be a coincidental association since lupus vulgaris destroys the adnexal structures and leaves nothing to form a BCC [127].

Ulcers

Chronic ulcers, regardless of their primary etiology, may undergo malignant degeneration. Subsequently, non-melanoma skin cancer may develop within the prior ulcer or at a cutaneous location characterized by chronic non-healing and ulceration. Marjolin ulcer is the eponym that designates the underlying lesion in which a malignant neoplasm appears as a carcinomatous ulcer in a degenerating scar [85].

Jean-Nicolas Marjolin was born on December 6, 1780. He studied medicine at the University of Paris, won first prize as a clinical intern in 1801, and received his doctorate in 1808. As he progressed in his medical career, he became second surgeon to the Hotel-Dieu of Paris in 1819, chair of surgical pathology in 1819, and consultant surgeon to Louis-Philippe after 1830. However, in 1828, he published his classic lucid description of the degenerating scars in which the cancerous ulcers develop in Dictionnaire de Medecine pratique [85].

In December 1930, Treves and Pack published their seminal study on the development of cancer in burn scars. During a 12-year period they evaluated 1,091 squamous cell carcinomas and 1,374 BCCs. They observed that 28 of the cancers developed in burn scars, many of which were ulcers or ulcerated. Indeed 21 of 1,091 (two percent) of the squamous cell carcinomas and seven of 1,374 BCCs (0.3 percent) arose in the scar of a burn [85].

There are other examples of BCC occurring in association with an ulcer. A 96-year-old woman had a plaque of chronic allergic contact dermatitis to nickel on her neck. After 5 years of persistent dermatitis, with periodic glucocorticoid ointment-associated improvement, traditional therapy with

leech application directly to the plaque surface to allow blood sucking for six hours through the lesion was initiated [55].

After the forcible removal of the leech, prolonged bleeding occurred for several days and the site did not heal. Subsequently the area did not heal. During the next two years, a gradually enlarging ulcer, which increased to a diameter of 12.28cm, developed that extended from the midline of her jowl to include her right mandibular and ipsilateral ear areas [55].

A biopsy of the ulcer demonstrated a BCC. Surgery was determined to not be possible (because of the risks associated with general anesthesia. Conservative therapy was initiated; however, six months later she experienced a cardiac arrest and died [55].

Basal cell carcinoma has also been observed in chronic venous stasis ulcers. Gosain et al. reported a 72-year-old man who developed a multifocal BCC in a large ulcer on his right lateral leg that extended distally to the lateral malleolus. He had previously received successful treatment for a venous stasis ulcer on the same leg eight years earlier. Five years later, a new ulcer on the right leg appeared that continued to enlarge and did not heal over the subsequent three years [60].

Six biopsies of different areas of the 8×12cm ulcer all showed sclerosing BCC. The tumor was completely excised and the wound was covered with a split thickness skin graft which successfully healed without recurrence of the BCC. Proximally, another primary BCC was discovered and excised. Also, five additional areas (which clinically presented as hyperpigmented patches) were biopsied and all showed stasis dermatitis. Although venous stasis ulcers typically present on the medial malleolus, the biopsy-confirmed stasis changes support the investigator's assertion that the BCC on the patient's distal lateral leg occurred in association with a chronic venous stasis ulcer [60].

The researchers summarized their review of the previously published patients with BCC associated with chronic venous stasis ulcers. They found that the BCCs were often multifocal, had an aggressive histology subtype (such as sclerosing), and often only extended into the reticular dermis but not the subcutaneous fat. They recommended that an incisional biopsy be performed for treatment-resistant non-healing lower leg ulcers assumed to be secondary to venous stasis [60].

Relationship between non-neoplastic cutaneous conditions and BCC

The relationship between the BCC and the coexisting non-neoplastic condition may be coincidental or possibly related to the development of the BCC. Alternatively, the development of the BCC may be unrelated to the coexisting non-neoplastic conditions and secondary to either a Koebner isomorphic response or a Wolf isotopic response in an immunocompromised district of skin. The proposed relationship between non-neoplastic cutaneous conditions and BCC are summarized in **Box 3** [1-141]; some non-neoplastic cutaneous conditions are listed in more than one category.

Possibly related

There is a possible relationship between several of the non-neoplastic cutaneous condition and the development of the BCC in the same cutaneous site. In certain circumstances, the non-neoplastic cutaneous condition promoted the development of the BCC: dermatitis, leishmaniasis, rhinophyma, scar, tattoo, and ulcer. However, in other circumstances, the BCC promoted the development of the non-neoplastic cutaneous condition: amyloidosis, calcinosis cutis, osteoma cutis, sarcoid reaction, and sarcoidosis.

The non-neoplastic cutaneous condition promotes the development of the BCC in both allergic contact dermatitis—in the patient with nickel-associated dermatitis—and halo dermatitis. The altered immune response resulted in a predisposition for the area to be the site of the BCC [55,56]. In addition, several of the researchers considered the cutaneous leishmaniasis infection to be a predisposing etiology for the development of BCC [120,129,130]. Some of the investigators for the rhinophyma patients considered the fibrous scarring and the cellular changes in the dermis to affect the papillary buds of the dilated follicles in the basal layer of the epidermis and predispose to the development of BCC [65-67].

Box 3. *Relationship between non-neoplastic cutaneous conditions and basal cell carcinoma*[a].

Possibly related[b]
Amyloidosis[c]
Calcinosis cutis[c]
Dermatitis (allergic contact dermatitis and halo dermatitis)[d]
Leishmaniasis[d]
Osteoma cutis[c]
Rhinophyma[d]
Sarcoid reaction[c]
Sarcoidosis[c]
Scar[d]
Tattoo[d]
Ulcer[d]

Coincidental[e]
Cutaneous focal mucinosis
Darier disease
Granuloma faciale
Leprosy
Lupus vulgaris
Sarcoid reaction
Tattoo

Probably unrelated[f]
Dermatitis (radiodermatitis and stasis dermatitis)
Granuloma faciale
Lupus vulgaris
Osteoma cutis
Rhinophyma
Sarcoidosis
Scar
Tattoo
Ulcer
Vitiligo

[a]Some non-neoplastic cutaneous conditions are listed in more than one category
[b]The non-neoplastic cutaneous condition possibly promotes the development of the basal cell carcinoma or the basal cell carcinoma promotes the development of the non-neoplastic cutaneous condition.
[c]The basal cell carcinoma promotes the development of the non-neoplastic cutaneous condition.
[d]The non-neoplastic cutaneous condition promotes the development of the basal cell carcinoma.
[e]The occurrence of the non-neoplastic cutaneous condition and basal cell carcinoma being present at the same skin location is merely by chance.
[f]The basal cell carcinoma occurring at the site of the non-neoplastic cutaneous condition is probably unrelated to the condition by results from either a Koebner isomorphic response or a Wolf isotopic response in an immunocompromised district of skin.

Scars can result not only in decreased blood supply but also atrophy of both the epidermis and the adnexal structures in the dermis. In addition, scars are more sensitive to ultraviolet radiation. Therefore, scars may predispose the cutaneous site to the development of BCC [83,84].

Tattoo pigments and dyes may have a carcinogenic effect on the skin into which it is injected. This may occur secondary to these elements in their native state. In addition, the potential cancer-associated effect of tattoos may occur after the pigment and dye are altered by ultraviolet A radiation [53,54].

Cutaneous malignancies have been observed to develop in ulcers. Malignant degeneration of the ulcer and the subsequent development of cancer can occur. In addition to squamous cell carcinoma, BCC may occur in ulcers [85].

In other situations, the BCC may promote the development of the non-neoplastic cutaneous condition. In amyloidosis, calcinosis cutis, and osteoma cutis, the dermal deposition direct or indirectly result from the presence of the BCC. In patients who have BCC-associated amyloidosis, the BCC promotes cytokines that stimulate keratinocytes to make AA amyloidosis protein resulting in secondary amyloidosis in the dermal stroma adjacent to the tumor [30,31]. In patients with BCC-related calcinosis cutis, it is hypothesized that the BCC acts as a source of skin injury causing dystrophic calcification in the surrounding dermis [35-38].

Secondary osteoma cutis occurs in association with BCC. There are several postulated mechanisms for its development in this situation. Some investigators suggest that the BCC tumor cells stimulate myofibroblasts to secrete growth factors and bone morphogenic proteins. However, researchers also speculate that BCC-related inflammation or scarring is the source of myofibroblast inflammation [46].

Basal cell carcinoma can also promote the onset of sarcoid reaction and sarcoidosis. It was hypothesized that soluble antigenic factors shed from BCC tumor cells cause the induction of a T-cell mediated host reaction resulting in the formation of an epithelioid cell granuloma in individuals with BCC-associated sarcoid reaction [79]. In patients with BCC-related sarcoidosis, similar to individuals with cutaneous sarcoidosis associated with acquired ichthyosis vulgaris, the cutaneous sarcoidosis granulomas are only present in the dermis or subcutaneous fat adjacent or beneath the BCC and not in the surrounding normal-appearing skin [117,118].

Coincidental

The occurrence of the non-neoplastic cutaneous condition and BCC being present at the same skin location may merely by chance. These include cutaneous diseases (Darier disease), dermal conditions (granuloma faciale), dermal depositions (cutaneous focal mucinosis and tattoo), miscellaneous conditions (sarcoidal reactions), and systemic infections (leprosy and lupus vulgaris). Cutaneous focal mucinosis and BCC has only been described in one Japanese patient; that person also had diabetes mellitus [40,41].

Rapini and Koranda reviewed the charts of 41 Darier disease patients who had been seen at the University of Iowa Hospitals and Clinics. With the exception of the patient they described who had multiple BCC concurrently present in his Darier disease skin lesions, they were not able to find a history of skin cancer in any other Darier disease patient. Hence, they concluded that compared to the general population, Darier disease patients were not at any greater risk of developing a cutaneous malignancy [20].

Latour et al. also described a man with Darier disease who developed multiple BCC in the disease skin lesions. They commented that although some of the therapies used to treat Darier disease may be carcinogenic, they were not aware of malignant degeneration of the Darier disease lesions [19]. Similarly, Rapini and Koranda suggested that the development of BCC in lesion of Darier disease in an afflicted individual was coincidental [20].

Granuloma faciale was a coincidental dermatosis present in the BCC lesion on the right cheek of the man described by Kamolpour et al. The presence of granuloma faciale was not appreciated when the dermatopathologist originally evaluated the tissue specimen and diagnosed the BCC. However, the excision specimen of the residual BCC also demonstrated granuloma faciale prompting the dermatopathologist to review the initial tissue specimen and confirm its presence [24].

The presence of systemic infections, such as leprosy and lupus vulgaris, in BCC tumor specimens is also likely to be coincidental. The altered immune response in patients with leprosy is specific to *Mycobacterium leprae* and is not related to the development of BCC [124]. Also, the evaluation of normal-appearing skin not only patients with lepromatous leprosy with its high bacterial load but also in individuals with other types of leprosy demonstrates organisms. Hence, since the pathogen can be observed in normal-appearing skin of leprosy patients, the detection of mycobacteria in lesions of BCC is unrelated to the presence of the tumor [123,131,132].

The occurrence of BCC and lupus vulgaris, a cutaneous *Mycobacterium tuberculosis* infection, at the same skin location is likely secondary to chance. The infection destroys the adnexal structures of the affected skin. Hence, there may not be sufficient or suitable germinative tissue to allow the development of BCC [127].

Basal cell carcinoma is common in elderly patients. However, in patients with melanoma and non-melanoma skin cancers, malignancy-related sarcoid reaction is rare. Indeed, the concurrent presence of BCC and sarcoid reaction has only been described in one patient. Therefore, some investigators consider BCC-associated sarcoid reaction to be coincidental [79].

Tattoos are commonly applied to both sun-exposed and sun-shielded sites of the body. Basal cell carcinoma typically occurs in sun-exposed locations. Many of the patients with tattoo-associated BCC have their tumor on a sun-exposed site. Hence, the development of BCC on the tattoo may merely be secondary to the chance occurrence of the skin cancer occurring on a tattoo that is present on a sun-exposed site [52-54].

Probably unrelated

For several conditions, the development of a BCC at the same site as the non-neoplastic cutaneous condition is probably unrelated to the condition; it merely represents the skin cancer occurring in an immunocompromised district of skin. Indeed, the BCC at the site may result from either a Koebner isomorphic response or the sequalae of a Wolf isotopic response [135-141].

The Koebner phenomenon—originally presented in 1872 (at a meeting) and reported in 1877—described the appearance of psoriasis lesions in the healthy skin of psoriasis patients following local cutaneous trauma. The term isomorphic (referring to equal shape) response has been used to extend the definition of the Koebner phenomenon to the appearance of other diseases, such as lichen planus and vitiligo, at site of skin trauma. Subsequently, the concept of the isomorphic phenomenon of Koebner has been expanded to describe the development of a new condition that the person did not previously have prior to the skin trauma (such as a basal cell carcinoma) at the site of the cutaneous injury [135,136].

Wolf (post-herpetic) isotopic response—initially reported in 1995—describes a new skin condition occurring at the same location as a previously-healed unrelated cutaneous disorder. In the original description, the healed skin disorder was a herpesvirus infection resulting from either herpes simplex virus or varicella-zoster virus. The isotopic response observed at the site of the prior herpesvirus infection include comedonic-microcystic reactions, dysimmune reactions, granulomatous reactions, infections, leukemic or lymphomatous infiltrations, other miscellaneous conditions, and malignant solid tumors (such as basal cell carcinoma), [137-139].

The nomenclature of Ruocco immunocompromised district (of skin) was coined in 2009 as a unifying concept for lymphoedematous, herpes-infected and otherwise damaged cutaneous sites. It describes a site of regional neuroimmunocutaneous destabilization of skin secondary to chronic lymphoedema, paraplegia, infections, or trauma. The concept of an immunocompromised district unites the different phenomenon such as the isomorphic response of Koebner and the isotropic response of Wolf [140,141].

Basal cell carcinoma can occur on the lower extremities of patients with varicose veins and stasis dermatitis. Researchers of a retrospective histopathology study noted the presence of stasis changes in 25 percent of the BCC patients with lower extremity tumors. However, the investigators did not consider the observed incidence of BCC in this setting to be of sufficient significance to attribute the individual's chronic venous stasis as a predisposing etiology for the development of the BCC at that site [61].

In one review, BCC occurred on the lower extremity of three patients with a history of radiodermatitis at the location. The thigh and popliteal fossa were the sites of superficial BCC and the knee was the site of a nodular BCC. In this setting, the tumor occurring in the location of the pre-existing cutaneous radiation dermatitis represented Wolf isotropic response [57].

In a review of 66 granuloma faciale patients, the researchers mentioned that the condition occurred at the site of the scar of a previously excised BCC. Hence, the dermatosis appeared at a site of prior trauma to the skin. Therefore, in this patient, the granuloma faciale represented a Koebner isomorphic response [25].

Basal cell carcinoma occurred at the same location as lupus vulgaris, a cutaneous *Mycobacterium tuberculosis* infection, in a 61-year-old woman. She had the infection since the age of 18 years; prior treatments had included chemocautery, cryotherapy, and ultraviolet light. In addition, as a child, she had experienced a severe burn to the lupus vulgaris and BCC affected her lips and chin. Although the investigators speculated that the BCC developing at the sites of lupus vulgaris may have been coincidental since the infection destroys the adnexal structures in the dermis, they also hypothesized that BCCs occurred as a Koebner isomorphic response to the childhood burn or scarring from the lupus vulgaris treatment modalities, or both [127].

Boyd and King described the features of five patients who had BCC with ossification. The tumors had previously been treated with electrodessication and curettage in three of the individuals: a 73-year-old woman with a pigmented nodular BCC of 4.5 years' duration on her left back with intratumoral bone, a 67-year-old man with a nodular and infiltrative BCC of four years' duration on his left sternum with bone in the reticular dermis, and a 77-year-old man with a micronodular BCC of 11 years' duration on his right cheek that had bone within a pilosebaceous unit. In

these individuals, the osteoma cutis at the prior site of treatment and subsequent recurrent BCC was likely a Koebner isomorphic response secondary to the trauma from the initial management or the resulting scar or both [48].

It remains to be established whether the development of BCC within a rhinophymatous lesion is caused by the rosacea disease process or unrelated to the pathogenesis of the rhinophyma. Prior skin trauma, fibrous scarring, and hypertrophic and hyperplastic changes— causes of BCC—can result in the development of rhinophyma. Hence, the development of not only rhinophyma but also BCC at the same location may represent a Koebner isomorphic response to earlier injury or subsequent skin changes [65-67].

A Koebner isomorphic response was postulated as the cause of BCC at the site of cutaneous sarcoidosis. Basal cell carcinoma developed at the site where a tree had hit the back of a 77-year-old Japanese woman; examination of the tumor excision specimen sarcoidal granulomas in the subcutaneous fat beneath the superficial BCC. The investigators favored that BCC resulted from a Koebner isomorphic response as a result of the trauma from the tree to the location on her back [117].

Basal cell carcinoma occurring at the site of a scar is also suggested to be the result of a Koebner isomorphic response. Trauma (and subsequent scar formation) was proposed as the single injury responsible for the development of BCC at the site of the injury in 13 patients [83]. Similarly, 7.3 percent of the BCC occurred at the site of a traumatic scar—representing a Koebner phenomenon—for 129 of the 1774 BCC in a study of BCC treated by Mohs surgery at Duke Medical Center [84].

Tattoo-associated BCC may be more prevalent than indicated by the 14 published reports of this phenomenon. The investigator's hypotheses regarding the pathogenesis of BCC within tattoos vary. Some consider that the tattoo promotes the development of the BCC at that location or that the occurrence is merely coincidental. However, other researchers propose that a Koebner isomorphic response is occurring from the trauma associated with the injection of the pigment and dyes [53,54].

A 96-year-old woman had been treated with traditional leech application therapy directly to the location of a chronic allergic contact dermatitis to nickel. The area on her neck did not heal following the traumatic removal of the leech and developed into an enlarging ulcer during the next two years; a biopsy was performed which demonstrated BCC. It was proposed that the non-healing ulcer—with subsequent malignant degeneration into a BCC—was caused by the trauma-induced Koebner isomorphic response from the trauma of the forcible leech removal from the site [55].

Vitiligo is characterized by depigmentation of the skin, mucous membranes and hair. Indeed, the affected skin has an absence of melanin. However, vitiligo patients, based upon their genetic and autoimmune profile, have a decreased risk of developing melanoma and non-melanoma skin cancers [133,134].

Therefore, it is not surprising that BCC has only been described in five individuals [12-16]. One of the patients, a 54-year-old man developed three BCCs at sites that had been treated with psoralen and ultraviolet radiation; the researchers postulated that his treatment (directly or indirectly as a Koebner isomorphic response) caused the development of the tumors [15]. However, other investigators had demonstrated that not only narrow-band ultraviolet B treatment but also other types of phototherapy do not increase the risk of cutaneous malignancies in vitiligo patients [133,134].

Conclusion

Basal cell carcinoma may occur as a solitary neoplasm. In addition, BCC can concurrently appear with either a benign tumor and/or a malignant cancer or a non-neoplastic cutaneous condition. The relationship between the BCC and either the coexisting neoplasm or non-neoplastic condition can be coincidental or possibly related to the development of the BCC. However, for some of the conditions, the development of the BCC was likely to be secondary to either a Koebner isomorphic response or a Wolf isotopic response in an

immunocompromised district of skin. Awareness of the various non-neoplastic cutaneous conditions that have been observed at the same anatomic location as a BCC may be useful for the evaluation and management of patients with BCC.

Potential conflicts of interest

Dr. Cohen is a paid consultant for ParaPRO; however, this activity has no influence as a potential conflict of interest with regard to the manuscript.

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