Clinical Oncology: Case Reports

Case Report

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Cutaneous Squamous Cell Carcinoma and Epidermolysis Bullosa: An Unholy Alliance-Case Report and Review of The Literature

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Abstract

A female patient with a clinical history of Epidermolysis Bullosa (EB) presented with a large, necrotic mass on the posterior aspect of the right leg. The patient had previously undergone a biopsy of the mass at an outside institution that was non-diagnostic for malignancy; the mass had been presumed to be a venous stasis ulcer, and was treated as such. Upon presentation to our clinic, clinical suspicion was that this mass was a wound-derived Squamous Cell Carcinoma (SCC). Repeat biopsy was obtained, with careful consideration to biopsy tumor as opposed to necrotic and granulation tissue within the mass. Pathology confirmed the clinical suspicion and imaging showed that the disease was metastatic. The patient underwent surgery to remove the mass, followed by systemic therapy. This case highlights the phenomenon of skin cancer arising in chronically inflamed or abnormal skin, including scars and/or wounds. This case also elucidates the importance of managing this unique patient population at increased risk of cutaneous malignancy, as well as the salient issues that naturally ensue with obtaining proper diagnosis, including the necessity of repeat biopsy if the initial biopsy results run counter to what clinical suspicion engenders.

Keywords

Epidermolysis bullosa (EB); Squamous cell carcinoma (SCC); Biopsy; Skin cancer; Wound-derived squamous cell carcinoma; Marjolina's ulcer

Introduction

Nonmelanoma Skin Cancer (NMSC) is the most diagnosed malignancy in the United States [1-3]. The number of cases per annum is generally accepted to exceed all other malignancies put together [4]. Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) account for the vast majority of NMSC (>95%) [4].

The overwhelming majority of NMSK patients are managed in the office and do well. The incidence of metastasis and mortality are generally low (see discussion). However, there are recognized patient populations at increased risk for accelerated and aggressive tumor transformation and progression. Early identification of patients at elevated risk in concert with timely initial diagnosis and aggressive treatment is likely to impact the ultimate course of the disease and prognosis. Once metastasis has occurred, survival is significantly decreased [5]. The pathogenesis of cutaneous squamous cell carcinoma is understood to be multifactorial, including both intrinsic and extrinsic factors and their interplay. Extrinsic factors include UV and other ionizing radiation exposure, various chemical carcinogens and induced immunosuppression (organ transplant) [4-6]. Viral etiologies, including HPV, have been associated [7]. Intrinsic factors include chronic scarring and inflammation8. Various genodermatoses are linked to elevated risk and accelerated tumor progression [8,9]. Perhaps the best studied malady is xeroderma pigmentosum, in which an inherited defect in DNA repair prevents the normal host response to UV radiation exposure [10,11].

Epidermolysis Bullosa (EB), likely due to its propensity to cause chronic skin inflammation, is one such example of a disorder that is associated with SCC oncogenesis. EB encompasses a heterogeneous group of genetic skin fragility/blistering disorders, arising from mutations in genes encoding dermal-epidermal adhesion proteins that are crucial for physiologic function of the basement membrane [12-14].

Case Report

An 80-year-old Caucasian female with a clinical history of EB presented with a large, fungating, and necrotic tumor of the posterior aspect of the right leg measuring 13 cm × 15 cm (Figure 1). She had a long history of intermittent skin blistering and desquamation and

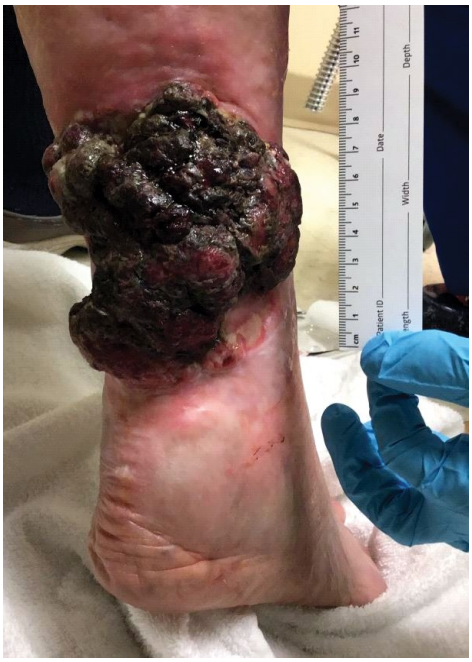

Figure 1: Clinical appearance: Large necrotic mass overlying distal achilles.

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although her disease was never subtyped, she did show the clinical changes consistent with the broad diagnosis (Figure 2). She, in addition, had a multiple year history of a chronic and progressive wound of the posterior aspect of the right leg. The wound was presumed to be a venous stasis ulcer and was treated with compression therapy including Unna boot applications, without resolution. The patient had previously undergone a skin shave biopsy of the mass, which was interpreted at an outside institution as necroinflammatory changes, non-diagnostic for SCC (Figure 3). Initial physical exam confirmed the presence of a foul smelling, fungating tumor of the posterior right leg, superficial to the Achilles tendon. She had an ipsilateral enlarged inguinal lymph node consistent with metastatic disease. Subsequent internal review of that initial outside biopsy and a subsequent biopsy would confirm the clinical impression of invasive squamous cell carcinoma.

Staging imaging was scheduled and an expedited palliative surgical resection was performed after maggot infestation was reported. The tumor was resected with free gross margins. The resection site was left open pending final pathology and completion of staging imaging.

Histologic sections of that resection specimen showed a poorly differentiated squamous cell carcinoma, composed of large atypical cells with epithelioid morphology, large nuclei, and prominent nucleoli exhibiting marked acantholysis accompanied by foci of tumoral necrosis. There were rare foci in which the poorly differentiated tumor cells could be seen arising from a focus of more well-differentiated squamous cell carcinoma (Figures 4, Figure 5). Epithelial lineage of the tumor cells was immunohistochemically confirmed with positive staining for pan-cytokeratin and p40.

The postoperative course was uneventful and the open wound

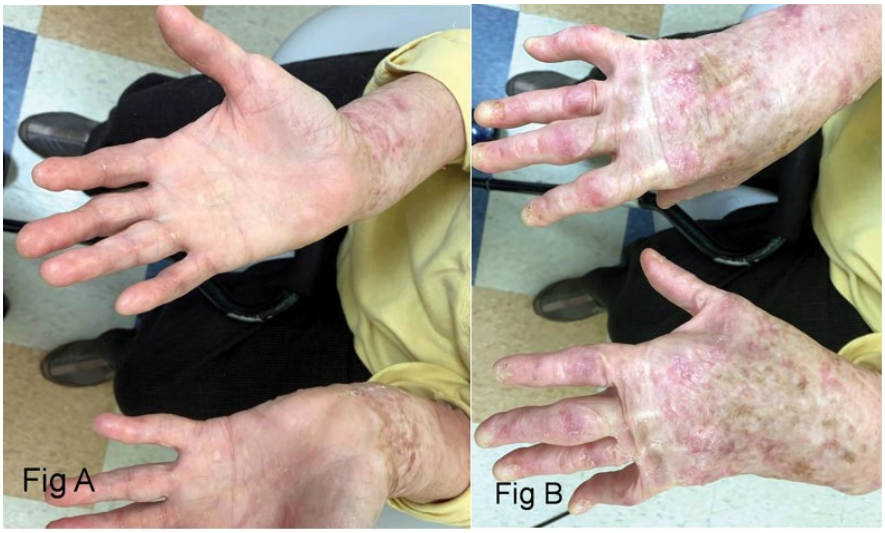

Figure 2: Skin and joint changes consistent with clinical history of EB. Note thickened fibrotic skin with mild blistering and characteristic nail and joint changes.

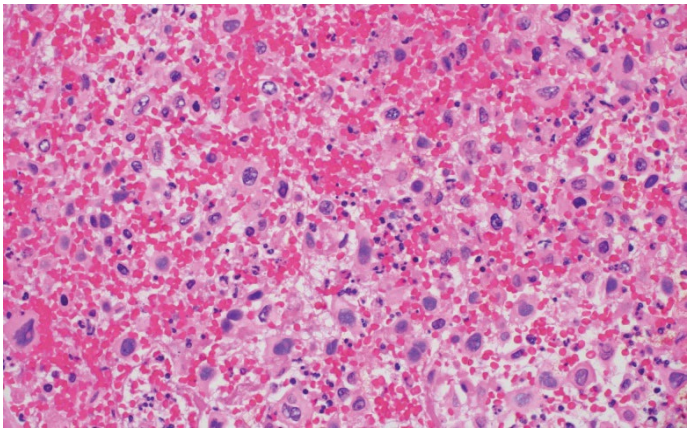

Figure 3: H&E 400x magnification. Initial skin shave biopsy (punch biopsy) of right tibial mass, interpreted by an outside pathologist as granulation tissue with necroinflammatory changes. The biopsy was subsequently reviewed after a repeat biopsy confirmed the clinical suspicion of SCC and was felt to be consistent with SCC. This particular focus shows malignant epithelial cells exhibiting marked acantholysis within a background of neutrophilic inflammation and hemorrhage.

was easily managed with dressing changes. Imaging studies were completed and showed extensive pulmonary and ilioinguinal metastases (Figures 6, Figure 7).

Systemic treatment was initiated with Cemiplimab, an anti-PD1 drug with demonstrated response rates in advanced or metastatic SCC [15].

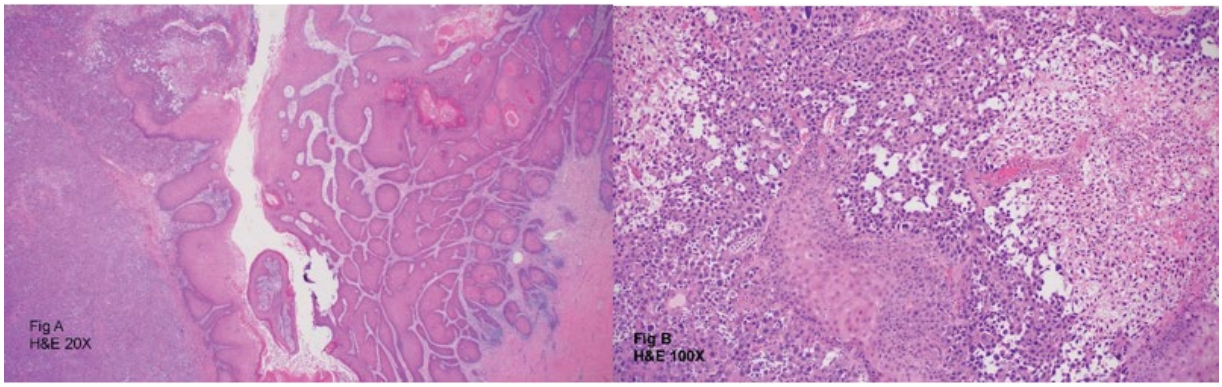

Figure 4: Surgical specimen. The low magnification image (left) shows a focus of invasive well-differentiated squamous cell carcinoma (right and middle) manifest as irregularly shaped islands of malignant epithelial cells with glassy eosinophilic cytoplasm, which are seen to focally give rise to the poorly differentiated acantholytic squamous cell carcinoma which is evident at the left side of this image. In this slightly higher magnification image on the right (Part B), there is clear evidence of the poorly differentiated acantholytic squamous cell carcinoma spilling off of a peninsula of well-differentiated squamous cell carcinoma.

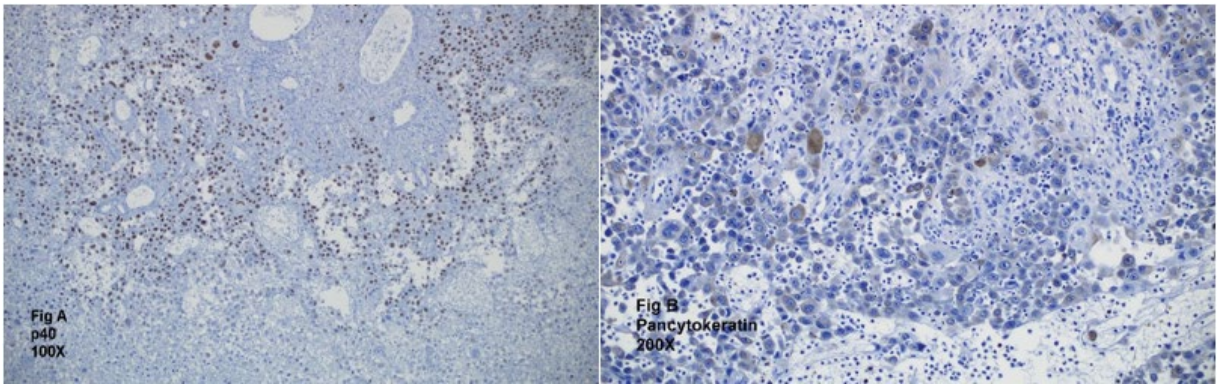

Figure 5: Immunohistochemistry stains consistent with diagnosis of squamous cell carcinoma: Fig A (left) p40 immunohistochemical stain; 100x magnification. The tumor cells exhibit positive immunoreactivity for p40 (nuclear marker for squamous epithelial cells). Fig B (right) Pancytokeratin immunohistochemical stain; 200x magnification. The tumor cells exhibit variably positive (weak to moderate) immunoreactivity for pancytokeratin stain.

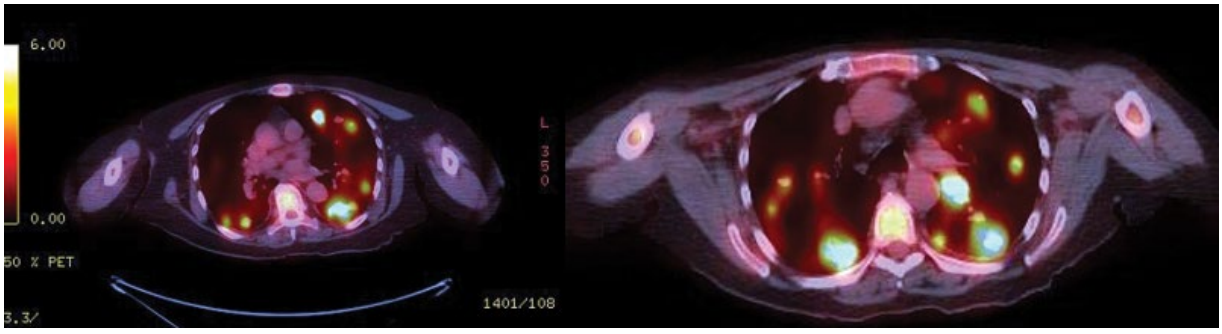

Figure 6: Extensive pulmonary metastases noted on PET/CT.

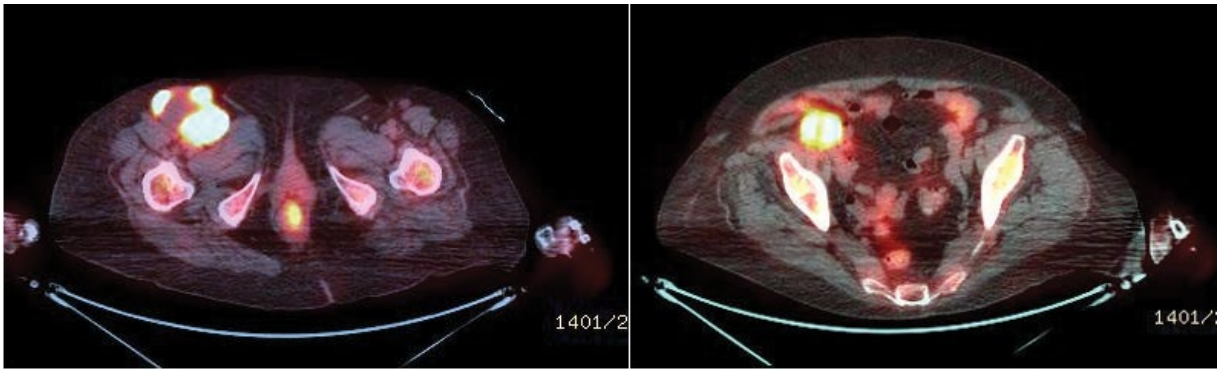

Figure 7: FDG avid tumor lesions in the superficial ipsilateral groin (left) and pelvic iliac chain (right).

Discussion

Incidence of NMSK

It is generally accepted that the incidence of NMSC exceeds all the other malignancies put together [4] with an annual cost of $8.1 billion [16]. However, the actual number of NMSC cases is unknown because such cases are not reported to cancer registries, so incidence data is derived from medical claims data, survey data, and special studies [17-19]. It should be noted that melanoma statistics are in fact reported [1], which underscores the fact that clinically, NMSC tends to be underemphasized. The most recent study of NMSC occurrence estimated that in 2012, 5.4 million cases were diagnosed among 3.3 million people [1].

The mortality risk associated with NMSC is low: A study that examined deaths due to NMSC in Rhode Island between 1988-2000 showed mortality rates of 0.29 and 0.08 per 100,000 people per year for nongenital SCC and BCC, respectively [20]. Similarly, NMSC metastasis risk is relatively low; metastasis is thought to occur in <0. 1% of BCC patients [21,22]. However, metastasis in SCC is higher and is commonly reported as occurring in approximately 3%-9% of patients [23,24]; in this SCC cohort with metastatic progression, metastasis occurs most frequently to the regional lymph nodes and then systemically (often to the lungs, bone, and brain). Factors that may increase the risk of SCC metastasis include tumor diameter >2 cm, depth of invasion >4 cm, poor differentiation, scar carcinoma, perineural invasion of nerves >0.1 mm in diameter, immunosuppression, and history of previous treatments [4,5]. The 5-year survival rate for patients with metastatic cutaneous SCC remains guarded, at 34% [5].

Pathophysiology

There is a clear and definitive link between Ultraviolet (UV) skin exposure and SCC; this causative relationship is highlighted by a correlation between SCC incidence and geographic latitude, with SCC incidence doubling with each 8 to 10-degree decline in geographic latitude towards the equator [25,26]. Ultraviolet-B light (290 nm to 320 nm) is the most carcinogenic [27] and thus, is most implicated in SCC carcinogenesis. While UV-exposure is responsible for approximately 90% of NMSC cases [28-30], there is a subset of SCC patients in which SCC originates in abnormal skin, as described previously, with pathology arising from varied clinical entities as burns, varicose ulcers, Human Papilloma Virus (HPV) infection, chronic inflammation, carcinogenic chemicals, chronic immunosuppression, chronic wounds, and several genetic syndromes. Perhaps most relevant to this report is Marjolin's ulcer, a SCC that develops in old scars and/or chronic wounds, with latency periods of up to 30 years [31,32]. Marjolin's ulcer represents a more aggressive clinical course with metastasis occurring between 18% to 38% of the time [33] and mortality rates as high as 32.6% [34].

Intrinsic and extrinsic risk factors

Numerous risk factors have been identified which increase the likelihood of developing SCC, and portend a poor prognosis due to early and aggressive metastatic behavior. Whether multiple risk factors have an additive or synergistic impact is not known; however, clinical experience suggests the latter.

In a subset of patients, SCC is associated with long-standing wounds, irritation, or inflammation, which is clinically pertinent given that long-standing wounds have a 2% risk of harboring a SCC [35]. SCC associated with long-standing wounds was first described in the setting of burn wounds (Marjolin's ulcer), however, malignant degeneration may occur in any chronic wound with features that include venous stasis ulcers, decubitus ulcers, hidradenitis, and chronic osteomyelitis. The possibility of malignancy should be considered in any chronic wound, and a biopsy should be performed, with particular attention paid to ensure biopsy of the tumor, as opposed to surrounding fibrotic or granulation tissue. Timely diagnosis is crucial, given that wound or scar-associated SCC tends to be more aggressive than its UV-induced counterpart, with metastases occurring more frequently (from 20% to 30%) [36,37], and overall prognosis for patients with metastatic disease being relatively poor, as previously described [38].

Indeed, Marjolin's ulcer can arise in a chronic blistering wound as result of EB. EB is a broad diagnosis and includes a number of entities which have a common clinical presentation- skin fragility manifest as blistering in a setting of minimal to insignificant trauma (e.g rubbing); histologically this appears as subepidermal pauciinflammatory blistering. It is suggested that EB patients should be considered a population at elevated risk for SCC. This proposition has been confirmed for some of the EB subtypes. Particularly, severe recessive dystrophic EB (RDEB-S), is associated with increased risk of aggressive mucocutaneous SCC [39].

Four types of EB are recognized clinically, characterized by the

level of skin cleavage/blistering: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB) [14]. SCC in the EB patient arises in tissue with phenotypic features of chronic skin blistering, wounds, and fibrotic scarring [40]. Furthermore, in EB-associated malignant degeneration, multiple primary SCC's often develop and have a propensity towards progression and metastasis [14]. As previously mentioned, a subtype of DEB termed severe recessive DEB (RDEB-S) has been described, in which SCC oncogenesis occurs almost invariably in all patients and is associated with a very aggressive biological behavior and attendant high morbidity and mortality [40]. According to the USA National EB Registry, the risk of developing at least one SCC for RDEB-S patients is 67.8% by age 35 and approaches 90.1% by age 55 [39]. Furthermore, EB-associated SCC's are the leading cause of death in individuals with recessive DEB (RDEB-S) [39]. A study from Robertson et al. highlights the risk of SCC in EB (and particularly RDEB-S), ultimately showing that among 44 EB patients with SCC, 70% had RDEB-S and among RDEB-S patients, SCC tended to present earlier as compared to all other collective EB subtypes (median age 29. 5 years compared to 47.1 years) [14]. Furthermore, RDEB-S SCC patients tended to have multiple tumors (mean 5.8) as well as high rate of mortality (64.5%), with median survival after first SCC of 2.4 years [14].

Despite the clear link between EB (and especially RDEB-S) and SCC, further investigation is needed to understand the molecular mechanisms responsible for the development of SCC in EB patients [40]. Recent evidence suggests that mutations in the COL7A1 gene represent an important antecedent of SCC tumorigenesis in RDEB-S patients, with COL7A1 knockout in fibroblasts, keratinocytes, and extracutaneous tissue preceding a complex series of pro-tumorigenic molecular processes that include inflammation, angiogenesis, and tumor cell invasion [40]. Moreover, chronic inflammation plays a role in EB pathogenesis, which is supported by cytokine imbalance, and especially excessive plasma levels of the pro-inflammatory cytokine Interleukin-6 (IL-6) [41,42] in both EB animal models and patients; this evidence suggests that inflammation contributes to pathological perturbation of the dermal microenvironment while simultaneously leading to exacerbation of systemic disease manifestations [40]. These pathophysiological mechanisms are not mutually exclusive; instead, they can, and do, occur in concert: this is supported by a COL7A1 knockout mice model, which shows excessive inflammation in the upper dermis [43] as well as increased serum concentrations of IL-6 [40,41].

While more needs to be learned about the unique pathophysiological mechanisms that underlie SCC development in the EB patient, it is clear that this patient population remains a unique challenge to treat and ultimately necessitates a multidisciplinary care approach from surgical oncology, medical oncology, radiation oncology, and dermatology alike. This patient also demonstrates the difficulty in diagnosing SCC when present in tandem with chronic wounds, as the initial biopsy did not render a diagnosis of a carcinoma. This indicates that SCCs arisen from chronic wounds and/or EB may require multiple biopsies to confirm either the presence or absence of a carcinoma. While surgical excision is curative for localized disease in up to 95% of patients [44], systemic treatment is necessary if SCC has metastasized. In the SCC patient with metastatic disease, a common combination chemotherapy regimen initiated post-surgery is cisplatin, 5-fluorouracil, paclitaxel, and methotrexate [45]. Second-line options of epidermal growth factor receptor (EGFR) inhibitors such as cetuximab or erlotinib may be employed in patients with advanced, unresectable SCC if polychemotherapy fails [46,47]. Importantly, the first anti-PD1 drug cemiplimab was recently approved by the US Food and Drug Administration in September 2018 and is an effective therapy with demonstrated responses in roughly 50% of SCC patients with advanced or metastatic disease [15]. This may be an appropriate choice for patients unable to tolerate the toxicity of front line therapy. Response statistics underscore the need for better systemic therapy perhaps guided by relevant biomarkers.

Conclusion

Ultimately, for the vast majority of patients, SCC is a highly curable disease with surgical excision providing durable cure. However, there are a subset of patients who may be identified as being at elevated risk for the development of an aggressive form of SCC and for whom metastatic potential and mortality rate are significantly elevated. These high risk group patients can be identified according to both extrinsic and intrinsic factors including EB as described. Patients at elevated risk should benefit from increased surveillance perhaps in a multidisciplinary skin cancer clinic. Importantly, a high index of clinical suspicion should be present in this group- particularly in patients having multiple risk factors as the case described. Clinicians should be aware of the possibility of sampling bias in any tumor, especially a large necrotic superficially sampled one. Additional sampling is warranted when a superficial subtotal biopsy read is not in keeping with the clinical impression of malignancy.n.

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