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An Interesting Coexistence of a Classical-Nodular and an Adenoid-Ulcerous Basal Cell Carcinoma in the Same Anatomic Location

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Abstract

Basal cell carcinoma is the most frequent malignant tumor of the skin, and the most common carcinoma found in some countries. The main clinical subtypes of BCC are nodular, superficial, pigmented and morpheaform. The majority of the lesions appear on the head and neck, with a particular predilection on the upper central part of the face. Here we report a 62 year-old woman with two different morphological types of BCC which developed in the same area. The tumors have developed two months apart on the right paranasal region in close proximity. With the clinical examination and histopathological examination of punch biopsy specimens, the diagnoses of the lesions were confirmed as a nodular and an adenoid BCC. The tumors were totally removed with surgical excision. Neither recurrence nor new lesion was observed on the lesional or near areas in a 24-month follow-up period. To the best of our knowledge the presence of the two different morphological types of BCC in the same anatomical location has not been reported previously.

Keywords: Basal cell carcinoma; Nodular; Adenoid; Rodent ulcer; Coexistence

Introduction

Basal cell carcinoma (BCC) is the most common malignant tumor of the skin which was first described by Jacob in 1827 [1]. It represents around 95% of non-melanoma skin cancers [1], 65% of epithelial tumors [2], and account for approximately 70% of all malignant diseases of the skin [3]. It peaks in the sixth decade and more frequently occurs in men [2]. The tumors are frequently located in sun exposed areas such as on the nose, eyelids, at the inner canthus of eyes, and in fair-skinned individuals who have Fitzpatrick skin types I and II [1,2]. On the other hand, both the diagnosis of BCCs and the number of patients who develop multiple BCC (mBCC) [1] have increased considerably in recent years [4]. It is speculated that the increase might be associated with the destruction of the ozone layer, the greater exposure to ultraviolet radiation and, increase in life expectancy and cancer awareness [1]. The multiple tumors can be seen as either multiple lesions on more than one anatomic location [5], or, the coexistence of the same [6,7] or different morphological types in the same [7] or very close location [6]. We also report an interesting case who had a nodular and adenoid BCC located very close to each other in the right paranasal region.

Case

The 62 year-old Caucasian woman was admitted to our outpatient clinic due to an unhealed wound and a small nodule on the right-side of the nose. She has Fitzpatrick skin type IV, and according to the history, the patient worked as a farmer under the sun since the age of 16. A small pink papule developed on the upper-right paranasal region 9 months ago. Two months later, a pruritic, crusted, small eczematous plaque developed just below the first lesion. The second lesion quickly became eroded whereas the first lesion took the form of a nodule. There was no history of exposure to ionizing radiation or trauma on the lesional site, intake of drugs containing arsenic, chronical inflammatory dermatoses or scarring. However, according to family history, the sister of the patient (she was 65 years old) had similar multiple lesions, and they were diagnosed as multiple nodular BCC 7 years ago. In the dermatological examination, a 9 mm-diameter, flesh-colored, hard, oval, telengiectatic nodule, and a 7 mm- diameter, small, pink, crusted ulcer that had a pearly periphery on the right paranasal region were seen (Figure 1a). The lesions were painless. The patient had no regional or systemic lymphadenopathy and no additional pathology. Punch biopsies were taken from both lesions. In the histopathology, a proliferation of basoloid epidermal tumor cells were observed. Whereas the nodular lesion had a classical palisading pattern in the periphery of individual tumor nests which were embedded in a fibrous stroma (Figure 2a,b), in the ulcerated lesion, basaloid cells were located radially in the periphery of gland-like islets (Figure 2d,e). The epidermis of the nodular lesion was slightly atrophic, and in the ulcerous lesion it was destroyed through to the dermis. Immunohistochemical stainings

with anti-bcl-2 monoclonal antibody, S-100, epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) were performed to assist in the diagnoses of the tumors. Both tumors were only stained with bcl-2 positively (Figure 2c,f). The other staanings were negative. With the clinical and histopathological findings, the diagnoses of the lesions were made as nodular and adenoid-ulcerous BCCs. After the diagnoses, each tumor was removed by total surgical excision with a 0.5 cm safety margin under local anesthesia, and the skin defects were closed primarily. Postoperative histopathological examinations of the tumors did not show any subcutaneous tissue invasion, and their surgical margins were intact. Neither recurrence nor a new lesion was observed at the excision site or near areas on the postoperative 60th day (Figure 1b), and in a 24-month follow-up period.

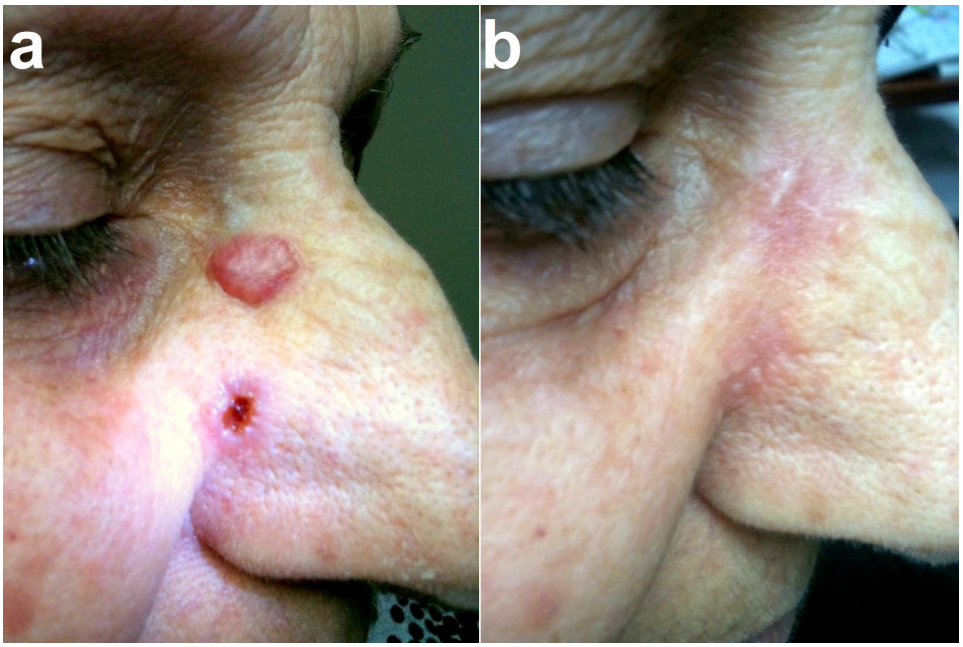

Figure1: The clinical views of the nodular and ulcerous lesions. Preoperative (a), and postoperative 60th day (b).

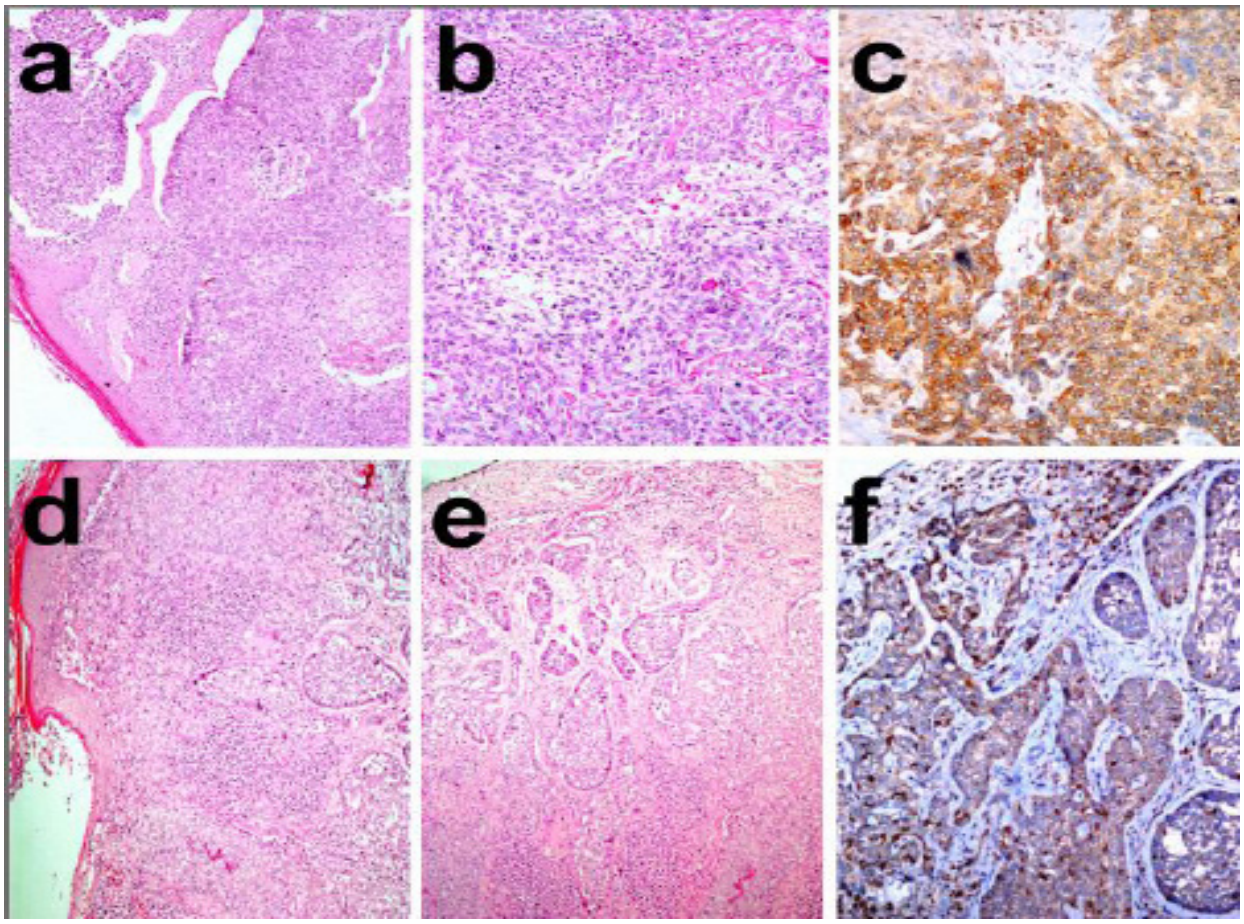

Figure2: Histopathologies of the lesions: Nodular lesion (upper row) (HEX100 (a), HEX200 (b), bcl-2X200 (c)). Adenoid-ulcerous lesion (lower row) (HEX100 (d), HEX200 (e), bcl-2X200 (f)).

Discussion

BCC has been described as the most common malignant neoplasm of humans [3]. According to the previous data, the usual site of origin of BCC has been considered to be the surface epidermis [8]. However, there is considerable morphological heterogenity among BCCs [9]. Thereafter, it has been stated that the tumor may originate from the outer root sheath of hair follicles, and in the 2006 World Health Organization classification, BCCs were classified in the skin adnexal tumor group [8]. On the other hand, the identification of mutations in the patched-1 (PTCH-1) gene has provided important insights into the pathogenesis of BCC, and points to a key role in the Hedgehog (Hh) signalling pathway in its pathogenesis [10,11]. While Hh pathway dysregulation is common to essentially all BCCs, because of the existence of multiple histological subtypes, including superficial and nodular variants, it has raised the possibility that morphologically distinct BCCs may arise from different cellular compartments in the skin. Indeed, Grachtchouk et colliques showed the induction of a major mediator of Hh signaling. The mediator called "GLI2-activator" has been found in stem cells of resting hair follicles in mice. Moreover, it has been shown that a small subset of these cells in the lower bulge and secondary hair germ compartments are capable of developing a nodular BCC. Tumorigenesis significantly accelerates when the GLI2-activator was induced in growing hair follicles. Contrarily, induction of this mediator in epidermis have led to the formation of superficial BCCs, and expression of it at reduced levels contribute to the occurrence of some lesions resembling basaloid follicular hamartomas. Therefore, it has been suggested that the origin of the cell, tissue context (growing stages of hair follicles), and level of oncogenic signaling can determine the phenotype of Hh/Gli-driven skin tumors, with high-level signaling required for the development of superficial BCC-like tumors from interfollicular epidermis, and nodular BCC-like tumors from hair follicle stem cells [9]. On the other hand, genetic mutations in the PTCH gene at 9q22.3 have been described as the cause of nevoid BCC syndrome, in which BCCs usually develop at young ages. In addition, some hereditary syndromes such as xeroderma pigmentosum, Bazex-Dupre-Christol syndrome, Rombo syndrome, and certain genetic polymorphisms may increase the development risk of BCCs, including single nucleotide polymorphism in the genes encoding melanocortin-1 receptor, PTCH, glutation-S-transferase, and cytochrome P450. Also, the TP53 gene, which is classified as a tumor supressor gene, has been seen to alter by point mutations in 40-50% of sporadic BCCs [12]. Another factor in the development of BCCs is ionizing radiation, and the malignancy risk is greater in patients exposed to ionizing radiation before the age of 40 than afterwards, especially in the development of mBCCs [13]. Chronic exposure to inorganic arsenic compounds may induce BCCs, and these BCCs are often of the superficial type. Although the mechanism of its action is not known exactly, a free radical formation and epigenetic DNA changes have been speculated for the reason of the malignant transformation [12]. Immunosuppression is another etiopatogenetic factor for the development of BCCs. There are some case reports describing BCCs in patients who underwent solid organ transplantation, who have HIV/AIDS and hematopoietic malignancies [14]. Additionally, BCCs may develop in chronically damaged skin sites including vaccination scars, pressure sites of medical protheses and chronic inflammatory dermatoses (stasis dermatitis, persistent ulcers, radiodermatitis, lupus vulgaris) [12]. In the etiopathogenesis, the cumulative ultraviolet-B-radiation (UVB-R) with the repeated exposure to the sun over the years is the most important factor in the genetically predisposed patients, and there is a latent period of 20 to 50 years between the beginning of the first UVB-R damage and the formation of the lesion [10]. Scrivener et al. showed that BCCs were seen approximately at the age of 65 years in their study [15]. However, BCCs can also be diagnosed in covered areas such as breast, periungal region, palm, sole, buttocks and intertriginous areas with an incidence from 10 to 15%. The factors responsible for such anatomic distribution are not yet understood [1].

The number of patients who developed mBCC has been increasing in recent years [1,4]. Wallberg et al. stated that the presence of skin tumors in the family, and sunburn after the age of 60 were independent factors with the development of mBCC [4]. Kiisky et al. indicated that while the age and red hair were significant risk factors for developing a first BCC lesion, factors such as red hair, high educational level, and a first BCC lesion located on the upper extremities were associated with a significantly increased risk of developing multiple BCCs. The authors also stated that the people who developed BCC lesions after the age of 75 were significantly less likely to develop multiple lesions [16]. Husein-El Ahmed et al. reported a case who had three mBCCs that arose from a surgical scar after radiotherapy and they stated that an immunosuppression related to the therapy might have been responsible for the development of the mBCCs. Ferreira et al. reported a case with multiple pigmented BCCs located in the pubic area [6]. In addition, Eisenschultz et al. reported two cases with mBCC in which one had both nodular and pigmented subtypes in different locations, and the other had both types of lesions in close areas [7]. Our patient is 62 years old, and she has Fitzpatrick skin type IV. We did not find any etiological factors such as ionizing radiation, exposure to any carcinogen, immunosuppression, chronic skin wound or inflammation, scarring or previus trauma. In contrast to Wallberg et al., because of the presence of the history of mBCCs in the sister of the patient, we thought that the patient might have a genetic predisposition. Our patient was chronically exposed to the sun due to the fact that she worked as a farmer for 46 years. Therefore, we also thought that the long-term UVR exposure, and the delayed onset of the lesions in the advanced age of the patient might have been responsible for the accumulating UVR doses in the skin, and might have caused the development of these BCCs, which was consistent with the literature.

Most of the BCC lesions arise on the head and neck (75-86%) with a particular predilection on the upper central part of the face [17]. The others develop on the trunk (10%) [2] , and extremities or other anatomical areas [17]. There is a direct relation between occupational sun exposure and risk of head and neck BCCs, especially in the development of the nodular type [18]. The other main clinical types of BCC are superficial, cystic, pigmented and morpheaform types [11,17,19,20]. The superficial BCC generally arises on the trunk [2,19,20]. Therefore, some authors reported that truncal BCC is linked to a genetic susceptibility and a reduced DNA

repair capacity which increased the risk of BCC on the non-exposed areas [18]. In a recent study, the distribution of morphological subtypes of BCC was reported as 49% for nodular, 29% for mixed patterns, 13% for infiltrating, 7% for adenoid, 3% for micronodular, 1% for superficial, and 1% for basosquamous of 103 lesions. Additionally, the authors indicated that only 7 patients had mBCCs on more than one anatomic location, and almost all of the mBCCs were seen on the face and scalp [5]. Nodular BCC is the most common morphological type of BCC [8,12,19]. It begins as a small, waxy nodule that often shows a few small telangiectatic vessels on its surface. The nodule usually increases in size and often undergoes central ulceation. A typical lesion, then, consists of a slowly enlarging ulcer surrounded by a pearly, rolled border. This represents the so-called "rodent ulcer" [8,12]. Koyuncuer et al. showed that the ulceration was detected in 55.3% of all BCC types in their series.

They also stated that the distributions of nodular subtypes according to anatomic locations were 76.9% on the face, 34.7% on the nose, 10.2% on the frontal region, and 10.2% on the orbital regions [5]. Both of the lesions of our case, were found on a sun-exposed area, and the placement of the lesions were consistent with the most frequent location of the BCCs. One of them was clinically the nodular type. Whereas noduler BCC often ulcerates as it enlarges, the nodular lesion of our case did not ulcerate although the lesion began 9 months ago. We thought that the reason for this condition might be related to the relatively small diameter of the lesion.

The second lesion of our patient was ulcerated clinically. Because of its presence near a nodular lesion and the fact that most BCCs can be ulcerated in the course of time, we firstly thought that the lesion might be a second, ulcerated nodular BCC. However, due to the presence of a proliferation of basoloid epidermal tumor cells on the periphery of the gland-like structures, this dagnosis was excluded. The adenoid type is one of the rare variants of BCCs [3]. It is also considered as a rare subtype of nodular disease [17]. The exact incidence of adenoid BCC is not known [21]. However, in the different studies the incidence has been indicated as 1.3% [21], 6.7% [22], 13.1% [23] and 20.91% [24]. This subtype does not have any particular site predilection [2]. However, Hussein et al. reported that the eyelids are preferential locations of adenoid BCC [22]. The other reported locations are face, scalp [5], axillae, back, iner cantus of eye, chin, forehead, and rarely cervix and prostate. The clinical presentations of previous cases have been reported as nodule, papulonodular sessile lesion, pigmented or brownish-black nodule, exophytic tumor, vegetating mass and ulcerative lesion. It is often regarded as a low-grade malignancy [2]. Contrarily, Goto M et al have shown in their recent study that it could invade into deeper tissues as a more invasive subtype of BCC [25]. Our patient indicated that the ulcerous lesion started like a pruritic eczematous plaque and then became rapidly ulcerated. The begining of the lesion (such as an eczematous plaque) did not resemble previously reported cases. However, with the histopathological examination, the diagnosis of adenoid BCC was confirmed. Our lesion was a diferentiated type and it did not invade into the deeper tissues. To the best of our knowledge, this eczematous plaque-like beginning of an adenoid BCC has not been reported previously.

BCC is usually divided into two main histopathological categories according to cell differentiation: differentiated (nodular, adenoid, keratotic, sebaceous) and undifferentiated (superficial, pigmented, infiltrative, sclerosing and micronodular) [20,22]. A sharp dividing line between the two groups cannot be drawn because many undifferentiated BCCs show differentiation in some areas, and most differentiated BCCs show areas lacking differentiation [8]. Additionally, there are some rare morphological variants of BCCs such as cystic, infundibulocystic and miscellaneous (clear-cell, signet ring cell, granular, giant cell, adamantanoid). These rare variants account for less than 10% of all BCCs [3]. Classically, a BCC is characterized by a proliferation of basaloid epidermal tumor cells with a palisading pattern in the periphery of the individual tumor nests, which are embedded in a fibrous stroma [12]. They usually show no pronounced variation in size or intensity of staining and no abnormal mitoses. On the other hand, adenoid variant is one of the differentiated types [8]. Hussein et al. stated that there was an incidence of only 6.67% of the adenoid BCC among all the histopathological types of BCC of the eyelids, and this variant in its pure form is less often seen [22]. The tumor cells of adenoid BCC show differentiation tubular, gland-like structures. These cells are arranged in intertwining strands radially around islands of connective tissue, resulting in a tumor with a lace-like pattern. The stroma has a mucoid appearance. In rare instances, lumina may be surrounded by cells that have the appearance of secretuary cells and the lumina may be filled with a colloidal substance or with an amorphous granular material. However definite evidence of secretuar activity of the lining cells have not been obtained, even with histochemical methods [8]. Each tumor of our patient had the typical histopathological features of their corresponding morphological types of the BCCs.

Even if the histopathological criteria still continue to be important in the histological diagnosis of a BCC, the immunohistochemistry is an adjunct technique for the differential diagnosis [3]. Also, it can be performed to identify the aggressiveness of the tumors [26-29]. As prognostic factors in BCC, bcl-2 and p53 have been proposed. Bcl-2 expression was directly correlated with nonaggressive BCC and a favorable clinical follow-up, whereas the expression of p53 was correlated with the aggressive histotypes [27,28]. Moreover, the expression of the proliferation marker Ki67/MIB1 also directly correlates with aggressiveness [29]. Even though we could not perform the latter prognostic stainings (p53 and Ki67/MIB1), both lesions of our patient were stained positively with bcl-2, and they were differentiated and nonagressive types at least histopathologically.

In differential diagnosis of BCCs, a trichoepithelioma and especially its desmoplastic variant should be considered due to the clinical and histological similarities. The trichoepitheiomas have characteristic horny cysts and consist fully keratinized center surrounded by basophilic cells, but they have not high-grade atypia or mitoses. Tumor cells can be arranged in a lacelike or adenoid pattern [8]. In the adenoid BCC, the staining of the cytoplasms of the cells with bcl-2 is homogenous throughout the lesion but m-

ore prominent at the periphery of the lesion. This feature is useful in differentiating BCCs from trichoepitheliomas [3]. Differentiation of BCC from squamous cell carcinoma (SCC) can sometimes be difficult. However, the fairly common presence in BCC of areas of retraction of the tumor from surrounding tissue, and deeply basophilic staining, aid in the diferentiation of BCC from SCC [8]. Another rare tumor with a similar histopathological picture is the cutaneous adenoid cystic carcinoma (ACC) which often originates in salivary glands. It is a firm, slow growing, ill-defined nodule commonly found on the scalp. Its cutaneous localization may also result from direct extension of ACC of minor salivary glands situated in the paranasal sinuses, and rarely a distant cutaneous metastasis of a primary salivary gland ACC. The tumors originating in salivary glands have local recurrence and widespread metastases; whereas cutaneous ACC is considered to be indolent or locally recurrent. Cutaneous ACCs are characterized by basaloid cells in the mid-to deep dermis in cords and tubules with a cribriform pattern, and few small cystic spaces containing mucinous material that stains positively for hyaluronic acid. Lack of connection to the overlying epidermis or adnexal structures and perineural invasion are important distinguishing features from adenoid BCC. Some observational evidence suggests that this tumor might be apocrine in origin. The other similar lesion to adenoid BCC is primary cutaneous cribriform apocrine carcinoma (CAC), which is a rare low-grade cutaneous apocrine carcinoma. Histologically, it is a non-encapsulated dermal tumor with a cribriform pattern. The aggregations of neoplastic cells are pleomorphic as opposed to the monomorphous appearance of BCC, and arranged in solid nests and tubules. In the lumina of tubules, some papillary protrusions of basophilic cells are seen. No perineural invasion is seen. It does not have metastatic potential or recurrence. Because of the lack of connection to the overlying epidermis, peripheral palisading of the basaloid islands of cells and retraction artefact of the surrounding fibrous stroma, the diagnosis of adenoid BCC can be excluded [3]. In the histopathologic examination, we did not see findings that suggested that the adenoid lesion was ACC or CAC.

BCCs generally show a favorable clinical behavior, but a percentage of them grow aggressively, infiltrating contiguous structures [30]. Infiltrative and micronodular tumors are more likely to be incompletely excised; thus they recur more frequently and are considered aggressive [31]. Treatment options of BCCs are topical 5% imiqoimod, 5-fluorourasil, curettage, cryotherapy, electrodesiccation and surgical excision [32,33]. We preferred surgical excisions for the therapy of each lesion.

Conclusion

The development of the different mBCCs in the same anatomic location is a relatively rare condition. Multiple BCCs which had had the same or different morphological types of BCC located on the same or different areas have been reported previously. However, to the best of our knowledge, our patient, is the first case in literature regarding the coexistence of a nodular and an adenoid BCC in the same location in close proximity. Adenoid BCC is usually considered rare, differentiated and a low-grade malignancy. However, it sometimes can be locally invasive, so differentiating it from ACC and CAC can be difficult, even histologically. Making the correct diagnosis is crucial because of their prognostic differences. In addition, similarly to the previously mentioned mechanisms, we anticipate that the adenoid BCC can be originate from stem cells of rudimentary adnexal epithelium depending on the location and severity of oncogenic signals. We hope that the pathogenesis of the development of different BCC types, and other tumors originating from epidermal appendages will be enlightened in the future through the understanding of the exact role of GLI-activator-like mediators in the human skin.

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