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Basal Cell Carcinomas and Trichoblastomas Associated With Epidermal Nevus

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Abstract

We herein report a case of multiple basal cell carcinomas (BCCs) and trichoblastomas associated with a linear epidermal nevus. An 84-year-old woman had a large, brown papillomatous lesion on her back that had been present since birth and was diagnosed as a linear epidermal nevus 20 years earlier. A black papule first appeared 11 years earlier within the lesion and was diagnosed as basal cell carcinoma. Over the subsequent 13 years, approximately 40 similar papules appeared, 17 of which were diagnosed as basal cell carcinoma. However, upon retrospective review of the available histological slides, five of these lesions were re-diagnosed as trichoblastoma. The association of basal cell carcinomas with epidermal nevus is rare, and trichoblastoma associated with an epidermal nevus has not been previously reported. Therefore, we described this unique case in detail.

Categories: Pathology, Dermatology
Keywords: basal cell carcinoma, epidermal nevus, multiple, secondary tumor, trichoblastoma

Introduction

Epidermal nevus is a hamartoma that is typically present at birth [1] and is characterized by multiple papillomatous or hyperkeratotic papules, often arranged linearly along the lines of Blaschko. The association of secondary tumors with epidermal nevus is considerably uncommon; therefore, epidermal nevus is generally not recognized as a hamartoma often associated with secondary tumors. Nevertheless, such tumors associated with epidermal nevus have been sporadically reported over the years. Among the secondary tumors, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and several trichogenic/adnexal tumors have been described [2]. Regarding BCC, 11 cases have been reported over the past five decades [2]; moreover, as for trichogenic tumors, two cases each of trichoepitheliomas and trichilemmomas have been reported [2-4]. However, the association of trichoblastoma with an epidermal nevus has not been previously reported.

Sebaceous nevus is another congenital hamartoma, and various tumors are known to develop within the lesion [5]. It is usually present at birth and is characterized by hair loss in early childhood, followed by the development of papillomatous plaques with a yellowish hue [1]. Although controversial, BCC and/or trichoblastoma are considered to be principal tumors associated with sebaceous nevus [6,7].

BCC is a malignant neoplasm that is thought to originate from the epidermis or occasionally from the outer root sheath of the hair follicle and is characterized histologically by the proliferation of basaloid cells forming tumor nests [8]. Palisading at the outermost layer of the nests is a characteristic feature, and the formation of artificial clefts adjacent to the nest is commonly observed [8]. On the other hand, trichoblastoma is a benign follicular neoplasm showing differentiation toward follicular germinative cells, and it shares some histological features with BCC [9,10].

One of the distinguishing histological features of trichoblastoma is the occasional presence of follicular germ/papillae structures within and around the tumor, which are absent in BCC [10,11]. In addition, compared with BCC, trichoblastoma typically exhibits a more orderly packed architecture, smoother borders, and more abundant fibrous stroma surrounding the tumor and generally lacks extensive necrosis [10,11]. Similar to BCC, peripheral palisading is usually observed in trichoblastoma. However, artificial cleft formation around the tumor nests is uncommon; instead, they are seen within the fibrous stroma rather than around the tumor nests [10,11]. Despite these histological differences, not all cases of BCC and trichoblastoma exhibit the typical features described above, and sometimes, the histological appearances of the two tumors may be similar. Distinguishing between these two tumors is important for subsequent management because malignant tumors generally require complete excision, whereas complete removal is not always essential for benign tumors. Nevertheless, because of occasional several histological similarities, distinguishing between these two tumors is often challenging.

We experienced a case of a large epidermal nevus associated with multiple BCCs and trichoblastomas. This

case highlights the rare occurrence of secondary tumors within epidermal nevi. We herein present the rare case and review the relevant literature.

Case Presentation

An 84-year-old woman with no known history of other tumors presented with a wide, brownish papillomatous lesion on the left side of her back, that extended linearly onto the left upper extremity and had been present since birth. Twenty years earlier, she visited a hospital because the lesions on the back of her finger had become painful. The lesions on the finger were excised, and histopathological examination revealed hyperkeratotic lesions with marked elongation of the rete ridges and focal inflammatory cell infiltration (Figure *1A* and Figure *1B*). The lesions were diagnosed as a linear epidermal nevus (Table *1*). Eleven years earlier, the patient noticed an elevated black lesion within the linear pigmented lesion on the left forearm and underwent excision. Histopathological examination revealed tumor nests in the superficial dermis with connection to the epidermis (Figure *1C*). The tumor was composed of atypical basaloid cells with peripheral palisading (Figure *1C*, arrow in the inset) and an artificial cleft (Figure *1C*, asterisk in the inset). Many melanocytes were scattered throughout the tumor nests (Figure *1C*). Based on these findings, a diagnosis of BCC was made (Table *1*).

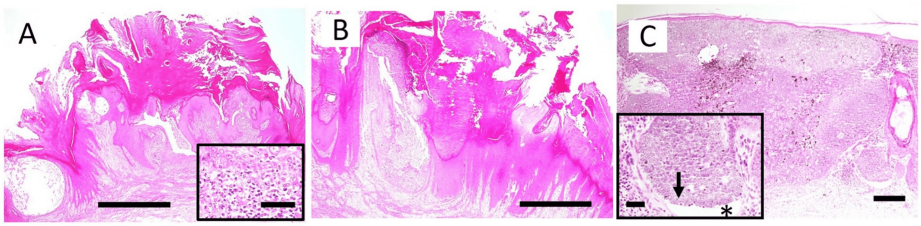


FIGURE 1: Histological images of the lesions

Lesions excised 20 years earlier (A and B) and 11 years earlier (C). Clinical photographs of these lesions were not available; however, panels A and B correspond to the sites labeled “1A” and “1B” in Figure 2F, and panel C corresponds to a site labeled “1C” in Figure 2E. The inset in A shows inflammatory cell infiltration beneath the basal layer. The inset in C shows palisading (arrow) and an artificial cleft (asterisk) around a tumor nest. Scale bars indicate 2 mm in A and B, 200 μm in C, and 50 μm in the insets.

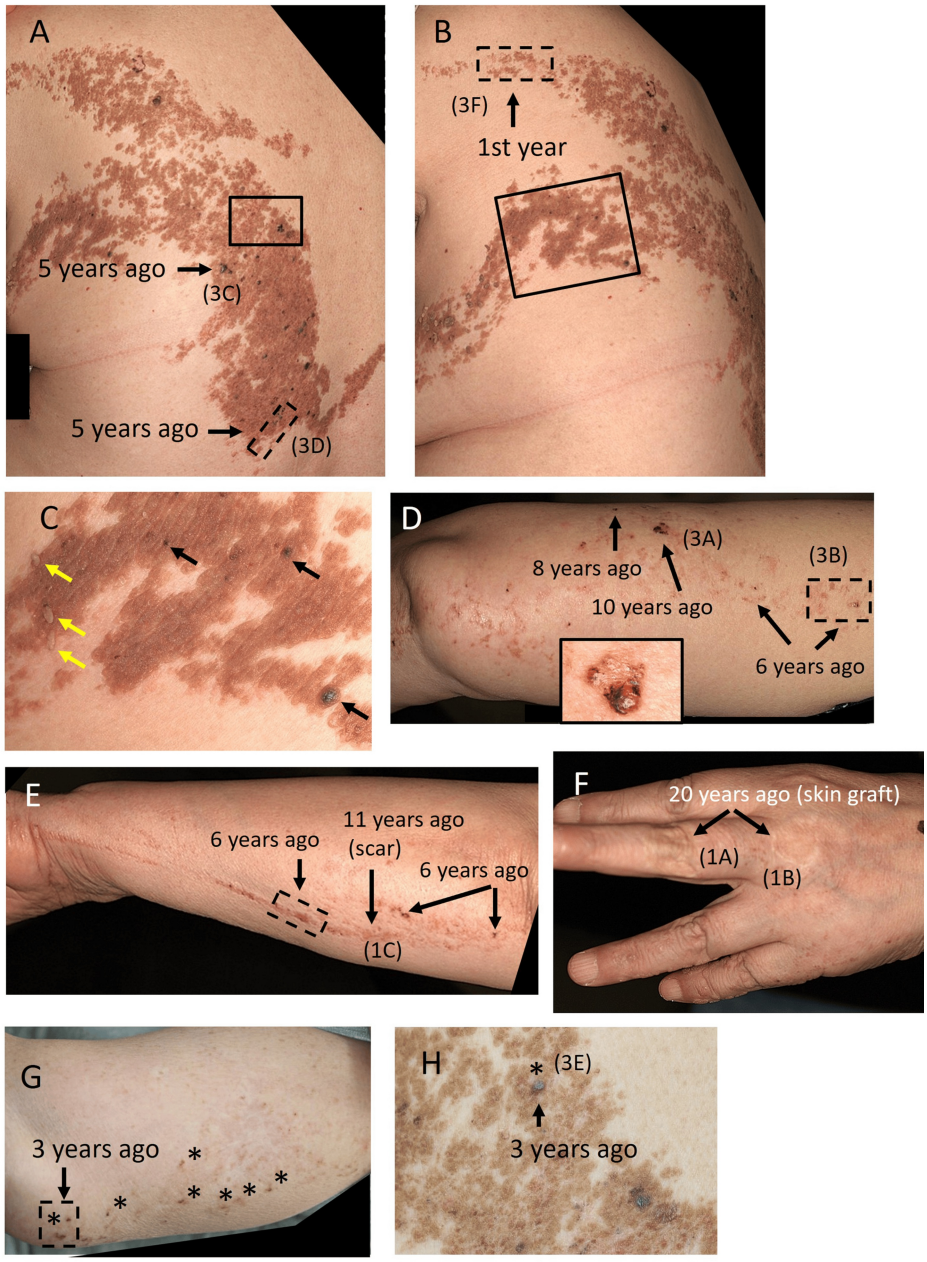


FIGURE 2: Clinical appearances of lesions before visiting our hospital

A-F: Photographs taken 10 years earlier. A: Left side of the back. B: Lateral view of the trunk. C: Close-up view of the area enclosed by a solid-line box in panel B. Papillary projections are indicated by yellow arrows, and black papules are indicated by black arrows. D: Left upper arm. The inset shows a close-up view of the lesion labeled “3A”. E: Left forearm. The arrow (labeled “1C”) indicates the scar after excision of the previous lesion. F: Dorsal aspect of the finger. Arrows indicate grafted skin (labeled “1A” and “1B”) after excision of the previous lesions. G and H: Photographs taken five years earlier. G: Left upper arm. H: Close-up view of the area enclosed by the box in panel A. In A, B, and D-H, black arrows with indications of the year denote excised lesions and the years of excisions. Asterisks in G and H indicate newly appeared lesions. Papules labeled “1A”-“1C” and “3A”-“3F” correspond to panels A-C in Figure 1 and panels A-F in Figure 3, respectively.

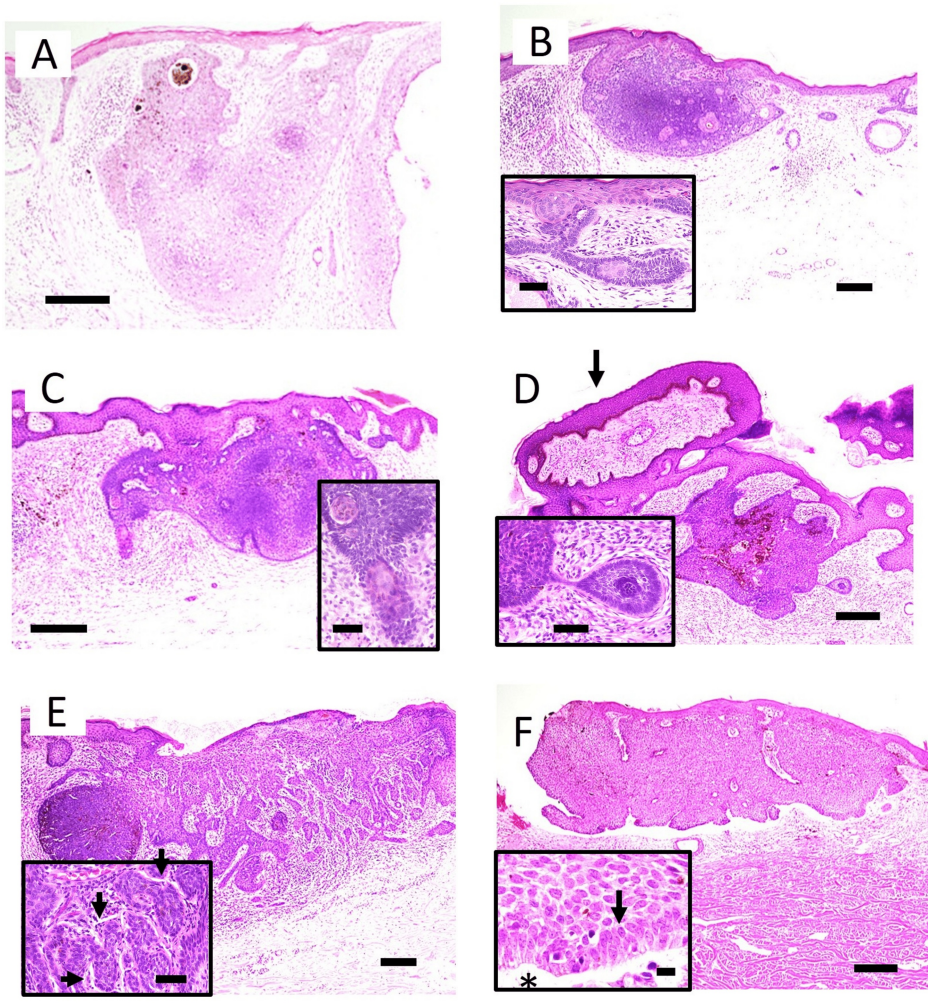


FIGURE 3: Histological images of lesions shown in Figure 2

Lesions excised 10 years earlier (A); six years earlier (B); five years earlier (C,D), three years earlier (E), and the first year (year of the patient's first visit to our hospital) (F). Panels A-F correspond to the lesions labeled "3A"-"3F" in Figure 2A, Figure 2B, Figure 2D, and Figure 2H. The arrow in panel D indicates a papillary projection indicative of an epidermal nevus. Insets in panels B-D indicate close-up views of immature follicular structures. The inset in panel E indicates a close-up view of artificial clefts (arrows). The inset in panel F indicates a close-up view of palisading (arrow) and artificial cleft (asterisk) at the periphery of a tumor nest. Scale bars indicate 200 μm, and scale bars in the insets indicate 50 μm.

Year	Month	Event	Operation site	Initial diagnosis	Revised diagnosis	Figure number
20 years ago	5	Visit a hospital	-	-	-	-
20 years ago	11	Excision 1	Left finger	Epidermal nevus	Same	1A
20 years ago	11	Excision 1	Left finger	Epidermal nevus	Same	1B
11 years ago	11	Excision 2	Left forearm	BCC, epidermal nevus	Same	1C
10 years ago	8	Excision 3	Left upper arm	BCC	Same	3A
10 years ago	8	Excision 3	Back	Hyperpigmentation	Same	-
10 years ago	9	Transfer to a clinic 1	-	-	-	-
10 years ago	10	Excision 4	Left upper arm	BCC	ND	-
6 years ago	5	Excision 5	Left upper arm	BCC	Trichoblastoma	3B
6 years ago	6	Excision 6	Left upper arm	BCC	ND	-
6 years ago	6	Excision 6	Left upper arm	BCC	ND	-
6 years ago	6	Excision 6	Left upper arm	BCC	Trichoblastoma	-
6 years ago	9	Excision 7	Left forearm	BCC	ND	-
6 years ago	9	Excision 7	Left forearm	BCC	ND	-
6 years ago	9	Excision 7	Left forearm	BCC	ND	-
5 years ago	10	Excision 8	Back	BCC	Trichoblastoma	3C
5 years ago	10	Excision 8	Left waist	BCC	Trichoblastoma	3D
3 years ago	3	Excision 9	Back	BCC	Same	3E
3 years ago	3	Excision 9	Left upper arm	BCC	Trichoblastoma	-
1st year	9	Excision 10	Left shoulder	BCC	Same	3F
1st year	9	Transfer to our hospital	-	-	-	-
1st year	11	Excision 11	Back	BCC	Same	5A, 5C
1st year	11	Excision 11	Back	Seborrheic keratosis	Same	-
2nd year	3	Excision 12	Back	BCC	Same	5B, 5D
2nd year	3	Excision 12	Back	Seborrheic keratosis	Same	-
2nd year	3	Excision 12	Back	Seborrheic keratosis	Same	-
2nd year	6	Transfer to a clinic 2	-	-	-	-

TABLE 1: Summary of diagnoses of excised lesions

The year of the patient's first visit to our hospital was designated as the first year, and the years in which events occurred are indicated in the left column. Initial and revised diagnoses are shown in separate columns. "Same" indicates that the revised diagnosis was the same as the initial diagnosis. "ND" indicates that the diagnosis was not re-evaluated because the histological slides were unavailable.

BCC: basal cell carcinoma

The patient revisited the hospital 10 years earlier because of lesions on her back, and the photographs documenting the entire lesion were available (Figure *2A*-*2F*). A large pigmented plaque with many papules was observed on the left side of the back (Figure *2A*-*2C*). Small papules were arranged linearly, extending forward from the back to the left side of the chest (Figure *2B*). Small papillomatous papules (Figure *2C*, yellow arrows) and black papules (Figure *2C*, black arrows) were distributed within the plaque. The linearly arranged papules extended along the left upper arm (Figure *2D*) and forearm (Figure *2E*), where a scar from a previous excision was observed (Figure *2E*, labeled "1C"), and continued to the dorsum of the left hand, where grafted skin due to the previous operation was found (Figure *2F* arrows, labeled "1A" and "1B"). The

patient underwent excision of a black papule on the upper arm (Figure 2D, labeled "3A"); the lesion was diagnosed as BCC (Figure 3A and Table 1).

The patient was transferred to another clinic eight years earlier, where she underwent excision of a total of 13 papules at the clinic over the following eight years. The pathological examination reports documented diagnoses of BCC, as in the previous specimen (Figure 3B-3D and Table 1). Occasional papillomatous projections were observed, suggesting the presence of an epidermal nevus, as indicated by the arrow in Figure 3D. Three years earlier, the appearance of two new black papules was recorded (asterisks in Figure 2G and Figure 2H), and both lesions were excised (arrows in Figure 2G and Figure 2H). Histologically, the tumor consisted of irregularly shaped small tumor nests of basaloid cells (Figure 3E) with artificial clefts (Figure 3E inset), leading to a diagnosis of BCC.

However, upon reviewing the available previous histological slides, including those shown in Figure 1 and Figure 3, we found that some specimens exhibited peripheral palisading of the tumor nests without apparent artificial clefts (Figure 3B-3D). Instead, abundant fibrous stroma was present around the nest, and immature follicular bulb-like structures were observed within and around the tumor nests, suggesting follicular differentiation (insets in Figures 3B-3D). Therefore, trichoblastomas were suspected in these specimens. Sellheyer et al. reported the usefulness of PHLDA1 immunostaining for distinguishing trichoblastoma from BCC [7]. We attempted to perform immunostaining with this antibody; however, unfortunately, we were unable to reproduce their results in our system.

Therefore, we relied on conventional hematoxylin and eosin (H&E) staining to distinguish between the two tumors. We re-evaluated the histological features of the specimens based on the distinguishing features described in the Introduction [10,11]. These features are summarized in Table 2. Based on the overall histological features, five specimens were considered more consistent with trichoblastoma than with BCC. Therefore, these specimens were re-diagnosed as trichoblastoma.

Elements	Trichoblastoma	BCC
Tumor border	Smooth	Irregular
Fibrous stroma around the tumor	Abundant	Scant
Cleft	Around the tumor nest	Within surrounding stroma
Follicular germ/papillae structure	Yes	No
Massive necrosis	No	Possible

TABLE 2: Histological features distinguishing trichoblastoma from basal cell carcinoma

Of the 17 tumors previously diagnosed as BCC, 11 were available for histological re-examination, and 5 were re-diagnosed as trichoblastoma. The previous and revised diagnoses, together with those of the other specimens, are summarized in Table 1 and Table 3.

Lesions	Initial diagnosis	Revised diagnosis
BCC	17	12
Trichoblastoma	0	5
Epidermal nevus	3	3
Seborrheic keratosis	3	3
Hyperpigmentation	1	1

TABLE 3: Summary of excised lesions

BCC: basal cell carcinoma

In the first year of her visit to our hospital, papules on the left shoulder (Figure 2B, broken rectangle, labeled "3F") were excised at the previous clinic in September. Histopathological examination of the excised

specimen revealed irregularly shaped tumor nests composed of basaloid cells with cytological atypia and a high nucleus/cytoplasmic ratio (Figure *3F*). Peripheral palisading was observed (Figure *3F*, arrow in inset), and prominent artificial clefts were present around the tumor nest (Figure *3F*, asterisk in inset). The lesion was diagnosed as BCC.

The patient was transferred to our clinic in the same month because the surgical wound in the previous clinic had become infected. On examination, a sutured wound of about 10 cm in length with fresh red erythema was present on the left shoulder (yellow arrows in Figure *4A* and Figure *4B*). A similar pigmented plaque, extending to the left side of the back and from the left shoulder to the left little finger, remained as it had been 10 years earlier (Figure *4A*-*4E*). In the left upper extremity, the color and sizes of the papules were less prominent (Figure *4C*-*4E*). Compared with 10 years earlier, however, many new black papules had developed or preexisting papules had enlarged (asterisks in Figure *4F* and Figure *4G*). Dermoscopic examinations of the larger black papules (Figure *4F*, labeled "5A,C" and Figure *4A*, labeled "5B,D") demonstrated large blue-gray ovoid nests, several leaf-like structures, and loss of pigment network (Figure *5A* and Figure *5B*).

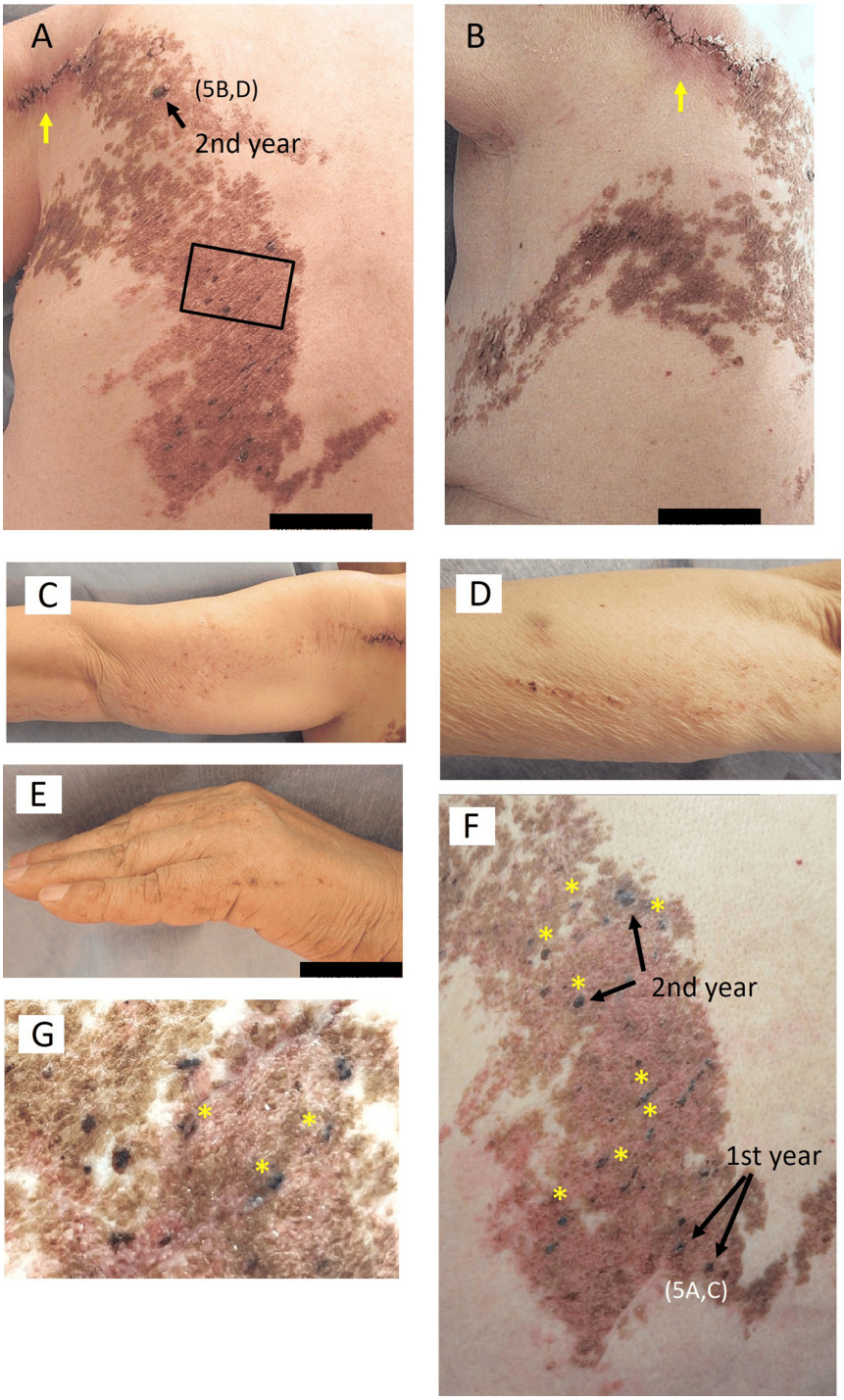


FIGURE 4: Clinical appearances of the lesions at first visit to our hospital

A-E: Photographs taken during the first year of her visit to our hospital. Yellow arrows in A and B indicate an inflamed sutured wound. In panel A, an excised papule is indicated by a black arrow, and the year of excision is also indicated. A label “5B,D” corresponds to Figure 5B and 5D. F and G: Photographs taken in the following year (second year). F: Close-up view of the caudal aspect of the lesion in panel A. Excised papules are indicated by black arrows, and the years of excision are also indicated. G: Close-up views of the area enclosed by the box in panel A. In F and G, yellow asterisks indicate newly appeared lesions as compared to those present 10 years earlier. In F, a label “5A,C” corresponds to Figure 5A and Figure 5C.

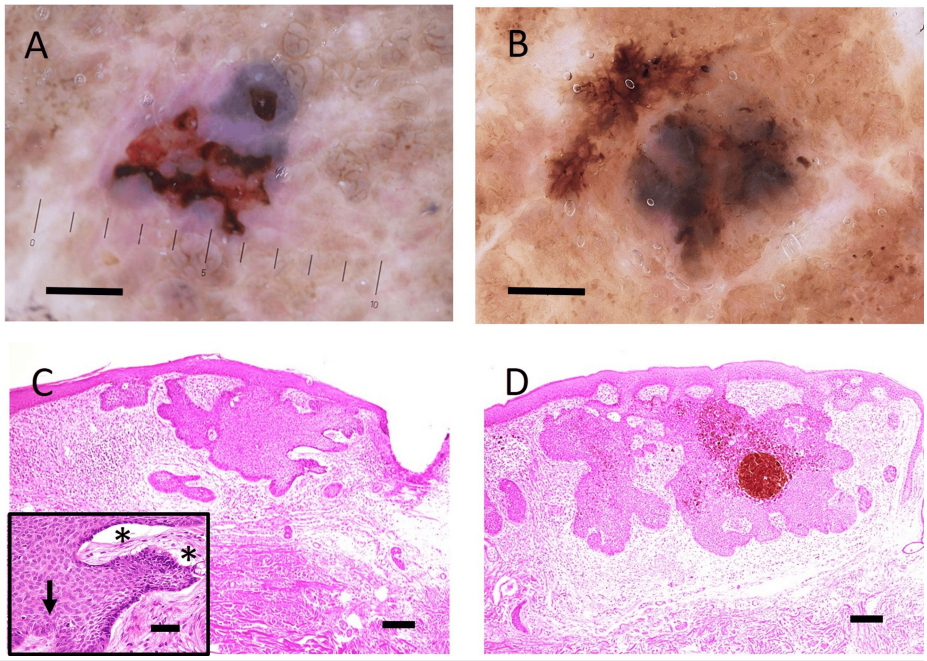


FIGURE 5: Dermoscopic and histological images of recently excised lesions

Dermoscopic (A and B) and histological (C and D) images of two lesions in Figure 4 excised in the first year (Figure 4F, labeled "5A,C") and second year (Figure 4A, labeled "5B,D"). Panels A and C correspond to the papule labeled "5A,C" in Figure 4F, and panels B and D correspond to the papule labeled "5B,D" in Figure 4A. In C, the inset shows palisading (arrow) and artificial cleft (asterisk). In A and B, scale bars indicate 2 mm. In C and D, scale bars indicate 200 μm, and scale bars in the insets indicate 50 μm.

The patient was admitted, and antibiotic treatment was initiated, resulting in the healing of the infected wound. She subsequently requested excision of black papules on her back, and two of them (Figure *4F*, arrows labeled "1st year") were excised. One of the excised specimens (Figure *4F*, labeled "5A,C") was diagnosed as BCC (Figure *5C*), whereas another was diagnosed as seborrheic keratosis (Table *1*). In March of the second year, the patient was re-admitted, and three pigmented lesions on the back (Figure *4A*, black arrow, labeled "5B,D", and Figure *4F*, arrows) were excised. The larger papule (Figure *4A*, labeled "5B,D") was also diagnosed as BCC (Figure *5D* and Table *1*), whereas the other two papules were diagnosed as seborrheic keratosis (Table *1*). The patient was subsequently transferred to another clinic in the second year, where she is currently being followed up. The entire clinical course is summarized in Figure *6*.

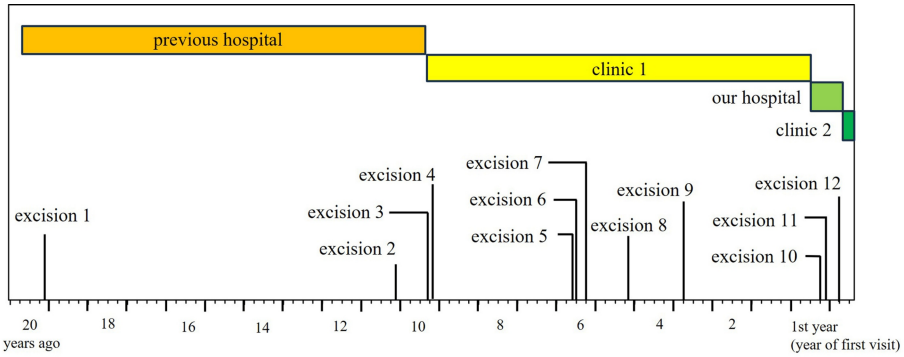


FIGURE 6: Clinical course of the patient

The year of the patient's first visit to our hospital was designated as the first year. Numerals along the horizontal bar indicate the number of years before the first visit. Periods during which the patient was treated at hospitals and clinics are shown in colored boxes. All excision events are indicated.

In summary, the patient underwent 12 excisions, and a total of 23 lesions were excised. Of the 23 lesions, 17 had initially been diagnosed as BCCs. Upon retrospective review of the available specimens, 5 of the 17

lesions were re-diagnosed as trichoblastomas, while the remaining 12 retained the diagnosis of BCC. The final number and classification of the excised lesions are summarized in Table *3*. In the present case, black papules appeared within the epidermal nevus, and one of these lesions was diagnosed as BCC at an earlier visit. The number of black papules subsequently increased, and some of the newly appeared papules were diagnosed as trichoblastoma or BCC. Thus, the appearance of new papules within the epidermal nevus suggests the presence of secondary tumors, although rare.

Discussion

Epidermal nevus is a hamartoma that usually arises at birth [1]. It is characterized by an accumulation of papillomatous or hyperkeratotic papules, often arranged linearly, along the lines of Blaschko [1]. Histologically, it is characterized by benign papillomatous proliferation with varying degrees of hyperkeratosis and acanthosis, resembling seborrheic keratosis [8]. In our case, the lesion clinically presented as a large plaque composed of papillomatous hyperkeratotic papules, with partial linear arrangement. Histological examinations of the initially excised specimens showed hyperkeratotic papillomatosis, while occasional papillomatous lesions were observed in subsequently excised specimens. These clinical and histological findings support the diagnosis of linear epidermal nevus.

In the present case, many of the excised lesions were initially diagnosed as BCC at a previous hospital and clinic. However, upon retrospective review of the 11 available histological specimens, 6 were considered consistent with BCC, whereas the remaining 5 were re-diagnosed as trichoblastoma (Table *1* and Table *3*). PHLDA1, a follicular stem cell marker, has been reported to be useful for distinguishing trichoblastoma from BCC [7]. However, in our system, immunostaining for PHLDA1 did not allow reliable differentiation between these tumors. Therefore, we relied on conventional H&E staining, and we re-evaluated the diagnoses based on the histological features of trichoblastoma described in the Introduction [10,11] and summarized in Table *2*. This represents a limitation of the diagnostic approach in the present report.

The most widely recognized hamartoma associated with the development of the secondary tumors is sebaceous nevus (discussed below), whereas secondary tumors are much less commonly associated with epidermal nevus [2]. Regarding BCC, only 11 cases have been reported over the past 5 decades [2]. Moreover, regarding trichogenic tumors, only two cases of trichilemmomas and two cases of trichoepitheliomas have been reported to date [2-4]. Therefore, to the best of our knowledge, the present case represents the first reported case of trichoblastoma associated with an epidermal nevus. Table *4* summarizes the previously published cases of BCC and trichogenic tumors associated with epidermal nevus. Middle-aged patients were predominantly affected, and many epidermal nevi were small in size, or BCC was solitary. In contrast, large lesions exceeding the size of a palm tended to be associated with multiple tumors, with up to 51 tumors reported in a single patient [12]. Consistent with these reports, our case had a relatively large epidermal nevus, from which a total of 17 BCCs and trichoblastomas were identified.

Number	Age	Sex	Location of epidermal nevus	Size of epidermal nevus	Tumor diagnosis	Number of tumor lesions	Number of excised tumors	Associated tumor	Reference
BCC	-	-	-	-	-	-	-	-	-
1	42	M	Abdomen	2~3 × palm	BCC	Several	Several	-	2
2	40	F	Cheek	5 × 1 cm	BCC	1	1	-	2
3	24	M	Chest, arm	1.5× palm	BCC	1	1	-	2
4	58	-	Head	Hen-egg	BCC	1	1	-	2
5	53	M	Chest, back, arm	3× palm	BCC	2	1	-	2
6	48	F	Neck, face	Hen-egg	BCC	3	3	-	2
7	61	M	Back	~12 × 1 cm	BCC	1	1	-	2
8	32	M	Upper arm	2× palm	BCC	4~5	1	-	2
9	73	F	Leg, foot	1× palm	BCC	51	4	MM	12
10	79	M	Neck	Hen-egg	BCC	1	1	Eccrine sweat gland tumor	2
11	40	F	Lower abdomen, upper leg	~1× palm	BCC	Unknown	1	SFA, SCAP	2
12	84	F	Back, arm	2× palm	BCC	~40	12	-	Present case
Trichogenic tumor	-	-	-	-	-	-	-	-	-
1	52	M	Parietal	-	Trichoepithelioma	1	1	-	4
2	51	F	Buttock, lower limb	2× palm	Trichoepithelioma	4~5	1	-	3
3	31	M	Axilla, trunk, buttock, elbow	1.5× palm	Trichilemmoma	Several	3	Poroma, SCAP	2
4	29	F	Groin, knee	Unknown	Trichilemmoma	1	1	-	2
5	84	F	Back, arm	2× palm	Trichoblastoma	~40	5	-	Present case

TABLE 4: Basal cell carcinomas and trichogenic tumors associated with epidermal nevus

The upper part summarizes cases of BCC associated with epidermal nevus reported over the past five decades, whereas the lower part summarizes trichogenic tumors associated with epidermal nevus reported to date.

BCC: basal cell carcinoma, M: male, F: female, MM: malignant melanoma, SFA: syringofibroadenoma, SCAP: syringocystadenoma papilliferum

Sebaceous nevus is a common hamartoma from which secondary tumors may arise [5]. A meta-analysis demonstrated an overall rate of secondary tumor development of 12.8% [5]. Syringocystadenoma papilliferum and trichoblastoma are common benign tumors arising in sebaceous nevus, whereas BCC and SCC are the major malignant tumors, accounting for 2.4% of cases [5]. However, the distinction between BCC and trichoblastoma is often controversial [6,7]. The frequent development of neoplasms in sebaceous nevus has been attributed to the presence of hotspot mutations in HRAS and, occasionally, KRAS in a mosaic fashion [13,14]. More recently, additional non-RAS mutations, including driver mutations and copy-loss, have been reported [15]. The hotspot mutations are detected in more than 90% of sebaceous nevus [16,17] and have also been identified in tumors arising within sebaceous nevus. Therefore, these tumors are considered to be clonally derived from cells harboring the hotspot mutations within the background sebaceous nevus.

On the other hand, in epidermal nevus, SCC is the most commonly associated tumor, followed by BCC and other tumors [2]. Hotspot mutations in RAS, similar to those found in sebaceous nevus, have also been identified in epidermal nevus. However, in contrast to the sebaceous nevus, the RAS mutations are detected

in only approximately 40% of epidermal nevus, while mutations in PIK3CA and FGFR3, which have not been reported in sebaceous nevus, are detected in approximately 40% of cases [18]. Thus, the genetic mutation profiles differ between sebaceous nevus and epidermal nevus; however, the reason for the marked difference in frequency of tumor development between these two hamartomas remains unknown. One study demonstrated different genetic mutations in BCC and the background epidermal nevus using a microdissection-based approach in a single case, suggesting that the tumor and the epidermal nevus had distinct clonal origins [19]. Thus, the mechanisms underlying tumor development in epidermal nevus are poorly understood.

Conclusions

The present case demonstrated a large epidermal nevus associated with multiple BCCs and trichoblastomas. In this report, we did not investigate the biological or clonal relationships between the epidermal nevus and the secondary tumors. Therefore, it remains unclear whether the epidermal nevus itself served as a background for the development of these secondary tumors. However, the association of secondary tumors within epidermal nevi is quite rare; thus, unlike sebaceous nevi, epidermal nevi are not generally recognized as hamartomas that are frequently associated with secondary tumors. Nevertheless, when new lesions appear within a preexisting epidermal nevus, they may represent either benign or malignant secondary tumors, and appropriate histological evaluation is warranted.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Osamu Okamoto, Maako Kudo, Kazushi Ishikawa, Junpei Wada, Toshihiro Sato

Acquisition, analysis, or interpretation of data: Osamu Okamoto, Maako Kudo, Kazushi Ishikawa, Junpei Wada, Toshihiro Sato

Drafting of the manuscript: Osamu Okamoto, Maako Kudo, Kazushi Ishikawa

Critical review of the manuscript for important intellectual content: Osamu Okamoto, Maako Kudo, Kazushi Ishikawa, Junpei Wada, Toshihiro Sato

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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