Original paper

A retrospective analysis of secondary malignancy development in nevus sebaceus

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Nevus sebaceous (NS) is a benign hamartomatous lesion; however, benign proliferative lesions are less frequently associated with secondary neoplasms. The aim of this study is to evaluate the prevalence of secondary benign and malignant tumours seen in NS lesions, and to reveal the histopathological features of these lesions.

Eighty-six NS cases were retrospectively evaluated for gender, age, lesion location, and accompanying lesions, as well as secondary benign and malignant tumours. The data obtained using descriptive statistics were analysed.

66.3% of cases were male, 33.7% were female, and the mean age was 37.8 years. 61.6% of lesions were localised on the face, 37.2% on the scalp, and 1.2% on the back. Secondary lesion development was observed in 39.5% of cases. The most common malignancy, as reported in the literature, was basal cell carcinoma.

Although secondary lesions, secondary tumours, and malignancy development are rare in NS lesions, careful follow-up and surgical excision if necessary are recommended, especially in adulthood. This study contributes to the literature by revealing the pathological characteristics of secondary lesions accompanying NS, emphasising the need for careful histological evaluation of NS excisions in the differential diagnosis and raising awareness that malignancies may be present.

Key words: nevus sebaceous, secondary malignancy development, basal cell carcinoma.

Introduction

Nevus sebaceous (NS) is a rare, non-hereditary congenital hamartoma arising from hyperplasia of the epidermis, hair follicles, sebaceous glands, and apocrine structures. It is also known as an organoid nevus, Jadassohn nevus, or pilosyringosebaceous nevus [1] with a prevalence of approximately 0.3%. Nevus sebaceous is found at similar rates among all races, ethnicities, and in both male and female patients [2]. These lesions, usually recognised at birth or in early childhood, are most commonly localised on the scalp and face. The clinical appearance is a smooth, yellow-orange, typically oval or linear, hairless patch or plaque. It may be flat or verruciform. The clinical appearance of NS may change over time, particularly during adolescence, when hormonal effects may cause histological differentiation of the sebaceous glands, leading to the lesions becoming more prominent and transforming into a verrucous form, with an increased risk of secondary tumour development [3]. Patients usually seek medical attention due to the clinical appearance, requesting evaluation and removal.

Histologically, NS contains immature, abnormally formed pilosebaceous units in early childhood. In the early period, epidermal changes are characterised by mild acanthosis papillomatosis, while in adolescence, these histological changes become more pronounced. Sebaceous lobules become much more prominent and hyperplastic. Some lesions may show ectopic

apocrine glands or eccrine hyperplasia. The direct union of numerous large sebaceous glands with the epidermis showing acanthosis is one of the key findings that constitute the typical histological appearance of NS [4].

These structural features indicate the hamartomatous nature of the lesion, while also creating a suitable environment for the development of secondary neoplasms. In addition to epidermal changes, basal cell proliferation and irregular distribution of keratin structures are also frequently observed within the lesion [5].

Secondary tumours associated with NS are mostly benign in nature and include benign skin appendage tumours such as trichoblastoma and syringocystadenoma papilliferum. However, malignant transformations have also been reported, albeit rarely. In the literature, the most common malignancy associated with NS is basal cell carcinoma (BCC). In a retrospective study of 450 cases by Hsu *et al*., the rate of malignant tumours related to NS was reported to be 1.6%. Similarly, in a series of 707 cases by Idriss *et al*., the rate of secondary neoplasms accompanying NS was 18.9%, of which 2.5% were malignant tumours [6, 7].

The mechanisms underlying NS development are based on the interaction of multiple factors, primarily genetic mutations, embryonic development processes, and hormonal effects.

Although the pathogenesis of malignant transformation in NS is not fully understood, mutations in *HRAS* and *KRAS* which affect the *RAS*/*MAPK* pathways are thought to play a role in this process. These genetic alterations cause irregularities in the development of epidermal and sebaceous structures by providing mitogen activation that increases cell proliferation. The fact that *HRAS* and *KRAS* constitute the fundamental molecular elements of conditions referred to as "RASopathies" is one of the main reasons for heterogeneous tissue development in the lesion [8]. In the study by Groesser *et al*., *HRAS* mutations were detected in 95% of 65 NS cases, while *KRAS* mutations were detected in 5% [9]. Kim *et al*. found that secondary tumours arising from NS had known *RAS* hotspot mutations and additional genomic alterations, such as potential driver mutations and *PTCH1* copy number loss. These findings may help identify high-risk groups for tumour development in NS patients and provide evidence for prophylactic resection [10].

In this study, we aimed to evaluate the frequency of secondary proliferative lesions, including benign and malignant tumour development in NS cases diagnosed at our clinic, and to reveal the pathological, clinical, and demographic characteristics of these lesions.

Material and methods

Between 2010 and 2025, pathology reports and specimens from patients diagnosed with nevus sebaceus in the archives of the Department of Pathology at Celal Bayar University in Manisa were retrieved and re-evaluated. The gender, age, presence of the lesion since birth, location, presence of lesions accompanying NS, and malignancies were recorded for all cases. In the analysis of the data, descriptive statistics were used to evaluate demographic and clinical data. For this purpose, IBM SPSS Statistics (version 25.0) software was used, and frequencies (n) and percentages (%) were calculated for categorical variables. For the continuous variable of age, the mean, minimum, and maximum values were presented. Logistic regression analysis was performed to determine the factors predicting the development of secondary malignancy. The level of statistical significance was $p < 0.05$. The analysis results were organised in an SPSS-compatible format.

Results

In a 15-year retrospective study, a total of 86 patients diagnosed with NS were re-evaluated. Of these patients, 29 were female (33.7%) and 57 were male (66.3%). The youngest patient was 4 years old, and the oldest was 86 years old, with an average age of 37.7 years. In our study, there were 6 individuals (7%) in the 0–11 age range (children), 22 individuals (25.6%) in the 12–18 age range (adolescents), and 58 individuals (67.4%) aged 19 years and older (adults). The distribution of lesions according to location was 53 (61.6%) on the face, 32 (37.2%) on the scalp, and 1 (1.2%) on the back. Seventeen lesions (19.7%) were present from birth. In 52 cases (60.5%), only NS was present, while in 34 cases (39.5%), secondary proliferative lesions, benign and malignant tumours, were present alongside NS (Table I). Of these secondary lesions, 18 were benign tumours of the skin appendages. These were distributed as follows: 5 syringocystadenomas papilliferum, 7 trichilemmomas, 3 trichoblastomas, 2 sebaceomas, and 1 apocrine hydrocystoma. The most common malignant skin tumour seen in NS was BCC. Basal cell carcinoma developed on the NS background in 12 (13.9%) of all NS cases. One case (1.1%) had squamous cell carcinoma, and one sebaceous carcinoma (1.1%) in conjunction with NS. In 9 cases, benign skin lesions (intradermal nevus, seborrheic keratosis, verruca vulgaris) were repeatedly detected in association with NS and other benign and malignant lesions. In 7 cases, more than 2 benign and malignant proliferative lesions were present together. Among these, the association of BCC and syringocystadenoma papilliferum was prominent (Figures 1–8). Logistic regression analysis was performed using variables such as age, gender, congenital or non-congenital nature of the lesion, and localization, to predict the development of secondary malignancy. The model was generally found to be significant (likelihood ratio $p < 0.001$, Pseudo $R^2 = 0.37$). The age variable was associated with an approximate 2%

increase in malignancy risk for each additional year (OR = 1.02; 95% CI: 0.99–1.05), although this finding was not statistically significant ($p = 0.129$). In terms of lesion location, cases located on the scalp and back showed approximately twice the risk of malignancy compared to cases located on the face (OR = 2.07; 95% CI: 0.64–6.73), but this difference was also not statistically significant ($p = 0.226$) (Figs. 1, 2).

Discussion

Nevus sebaceous is a hamartomatous lesion that usually appears during the congenital period and may show morphological changes during adolescence. Phakomatosis pigmentokeratotica, SCALP syndrome (sebaceous nevus syndrome, central nervous system symptoms, aplasia cutis, limbal dermoid, and neurocutaneous melanosis with pigmented nevus), and linear sebaceous nevus syndrome (Schimmelpenning-Feuerstein-Mims syndrome) are known to accompany specific syndromes in which central nervous system and eye abnormalities, oral lesions, and skeletal defects may be seen [4].

The malignant transformation potential of NS has been recognised for a long time, and this study evaluated the distribution of secondary tumours accompanying NS using retrospective data spanning 15 years.

Our study included 6 individuals aged 0–11 years (children) (7%), 22 individuals aged 12–18 years (adolescents) (25.6%), and 58 individuals aged 19 years and older (adults) (67.4%). All benign and malignant secondary malignancies were observed in the adult age group.

Secondary tumour development was detected in 39.5% of the 86 NS cases in our study. This rate is higher than the 18–32% range reported in the literature [2–5]. The vast majority of secondary lesions were benign skin appendage tumours, the most common being syringocystadenoma papilliferum, trichoepithelioma-like tumours (trichoblastoma, trichilemmoma), and sebaceoma. In the meta-analysis by Ye *et al*. and Pang *et al*., syringocystadenoma papilliferum stands out as the most common benign tumour, similar to the study by Hsu *et al*. and Idriss *et al*. [6, 7, 11, 12]. In our series, trichilemmoma (8.1%) was the most common benign tumour associated with NS, followed by syringocystadenoma papilliferum.

The most common secondary malignancy in our study was BCC, which developed in 12 cases (13.9%) based on NS. This rate is higher than the rates reported

Table I. Distribution of demographic characteristics of patients with nevus sebaceus

Characteristic	Number of patients (n)	Percentage
Gender		
Female	29	33.7
Male	57	66.3
Age (years)		
0–11 (children)	6	7.0
12–18 (adolescent)	22	25.6
≥ 19 (adult)	58	67.4
Location		
Face	53	61.6
Scalp	32	37.2
Back	1	1.2
Presence of secondary lesions		
Only NS	52	60.5
NS + secondary lesion	34	39.5
Total	86	10

NS – nevus sebaceous

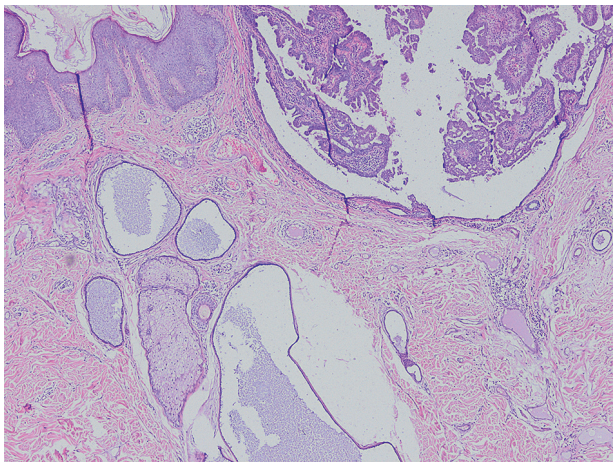

Figure 1. Syringocystadenoma papilliferum with acanthosis in the epidermis, eccrine gland hyperplasia, and disorganised sebaceous glands in the dermis (HE10×)*

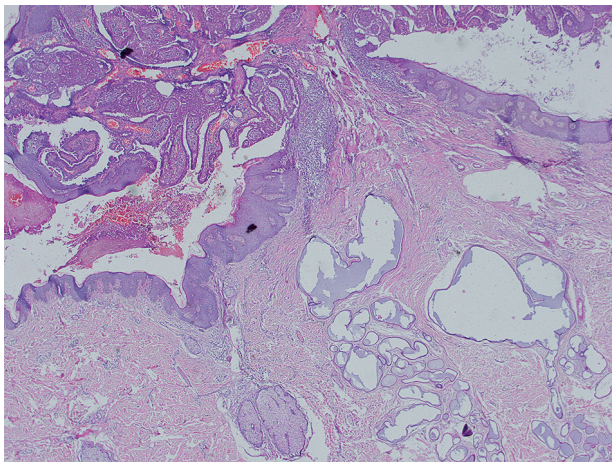

Figure 2. Syringocystadenoma papilliferum on the basis of nevus sebaceus (HE 4×)*

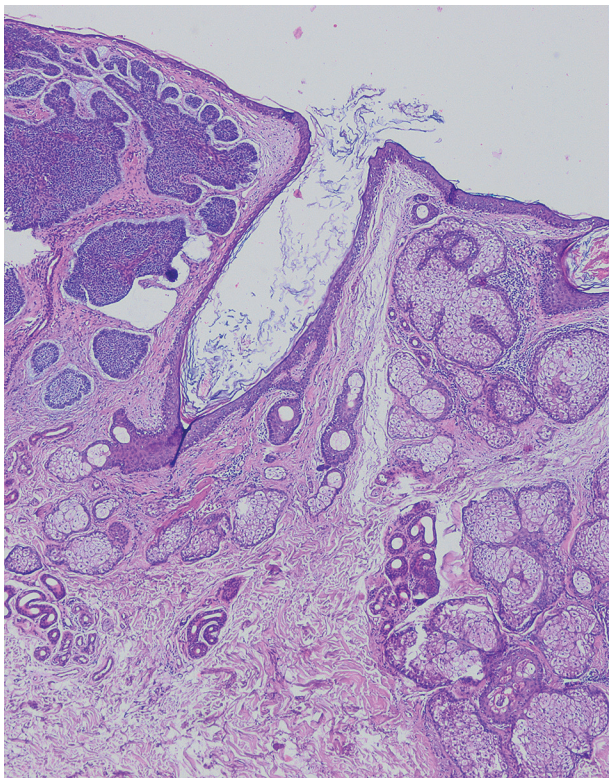

Figure 3. Basal cell carcinoma developed on the basis of nevus sebaceous, left side basal cell carcinoma, right side nevus sebaceous consisting of disorganised sebaceous glands (HE 4×)

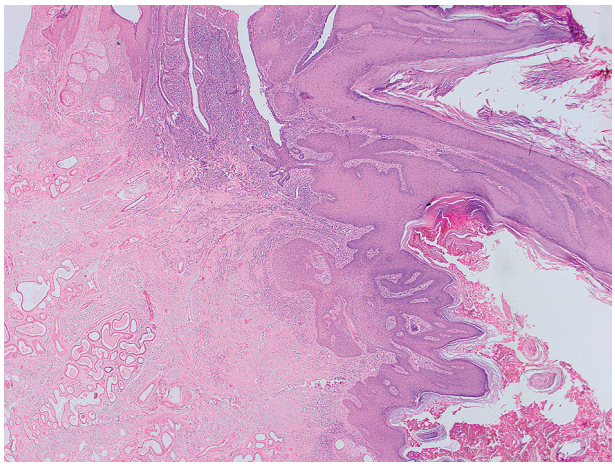

Figure 5. Trichilemmoma and syringocystadenoma papilliferum associated with nevus sebaceus (HE 4×)

by Pang *et al*. (1.7%), Hsu *et al*. (0.9%), and Idriss *et al*. (1.1%). This may be because patients referred to our centre were selected based on clinically suspicious or progressive lesions. Furthermore, the detection of sebaceous carcinoma and squamous cell carcinoma in one case each indicates that NS may rarely predispose to other malignant tumours. Multiple tumour associations were detected in 7 cases (8.1%). This rate also supports the study by Idriss *et al*., which indicated that multiple tumour types can occur simultaneously [7].

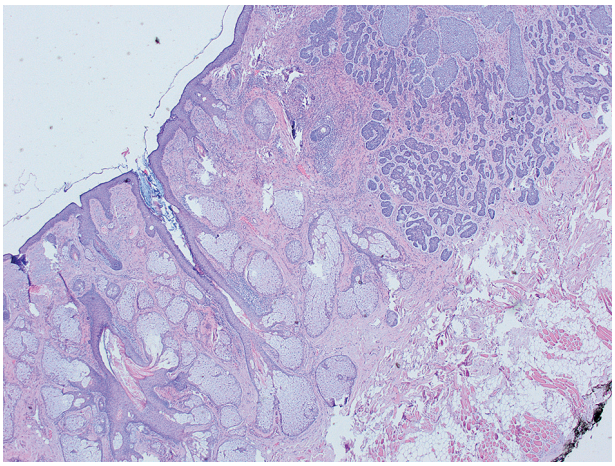

Figure 4. Another case of basal cell carcinoma and nevus sebaceus together. Right side basal cell carcinoma, left side nevus sebaceous consisting of disorganised sebaceous glands (HE 4×)

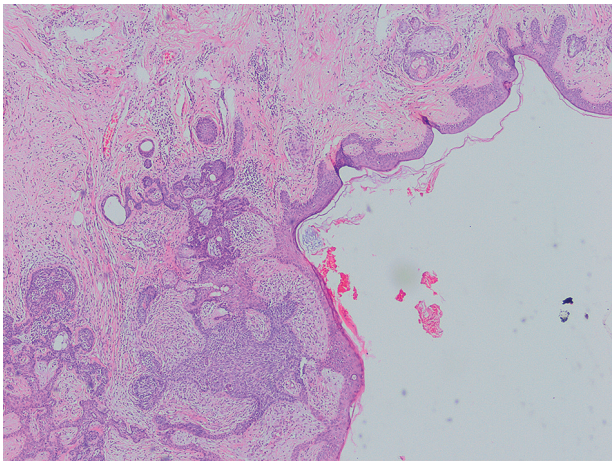

Figure 6. Trichoblastoma associated with nevus sebaceus (HE 4×)

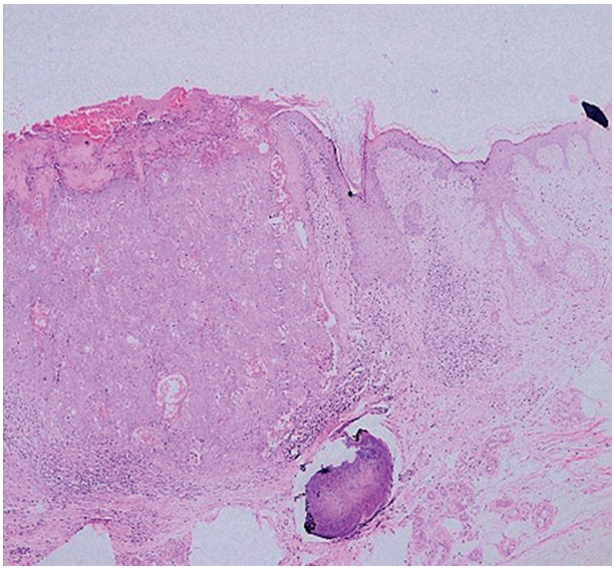

Figure 7. Sebaceous carcinoma associated with nevus sebaceus. Diagnosis supported by immunohistochemistry (HE 4×)

A significant relationship between secondary tumour development and age is noteworthy. Malignant tumours were particularly observed in the older age group, consistent with the findings of Ye *et al*. showing an increased risk of malignant transformation with advancing age [11]. Furthermore, the rate of secondary tumours was lower in the 17 cases where NS was present from birth, suggesting that lesions with a long-term stable course may carry a lower risk.

The fact that NS alone was detected in 60.5% of cases shows that not every NS lesion necessarily results in tumour development, but that careful clinical and histological follow-up is necessary. Clinically silent or stable NS lesions can be monitored conservatively; however, biopsy and excision should be considered for lesions that show rapid growth, ulceration, or colour change. However, there is no consensus on the timing of NS excision [1, 13]. Kong *et al*. suggested that surgical removal of NS in the scalp could be postponed until after childhood due to the higher likelihood of complications in children compared to adults following surgical excision [14]. In our study, no malignancy was detected in the under-18 age group. Given the various neoplastic potentials of NS and the ability of this hamartoma to transform into a malignant tumour, there is an ongoing debate about whether NS should be removed during childhood. To avoid a more complex procedure, Moody *et al.* recommend prophylactic excision of NS in all children before it becomes malignant and while the lesion is still small [15]. However, excision may not be necessary since malignancy does not develop in most NS [16].

The *RAS* gene family plays a key role in the pathogenesis of nevus sebaceus. *HRAS* mutations are detected in 90–95% of cases, while *KRAS* mutations are reported less frequently. These mutations activate the *RAS/MAPK* pathway, leading to cellular proliferation and differentiation disorders, thus explaining both the hamartomatous structure of NS and the potential for secondary tumour development.

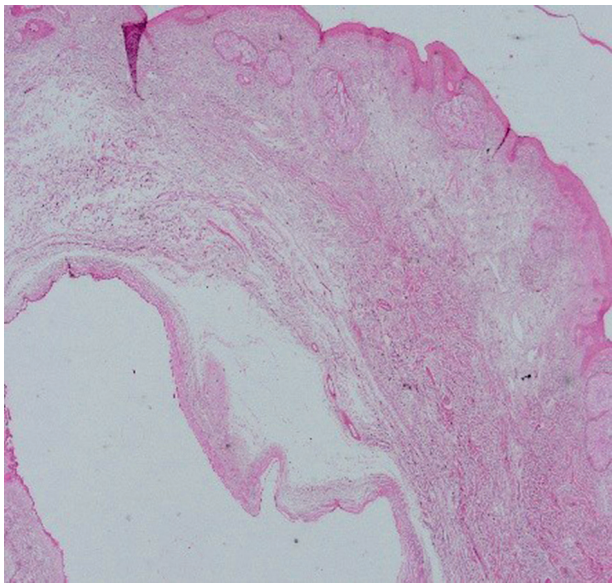

Figure 8. Coexistence of apocrine hydrocystoma and nevus sebaceus (HE 4×)

Studies by Groesser *et al*. and Pepi *et al*. have demonstrated that postzygotic *HRAS/KRAS* mutations are the primary determinant in NS and related syndromes. Pepi *et al*. provided the first evidence of the c.35G > T *KRAS* genetic variant in both skin lesions and brain samples from a patient with focal cortical dysplasia type Ia, hippocampal sclerosis, and nevus sebaceous syndrome [9, 17]. Happle introduced the concept of NS as a "mosaic RASopathy" into the literature [18]. Recent literature has emphasised that *KRAS* variants and rare *HRAS* sequence alterations may also be associated with NS [19, 20]. The review by Silva *et al*. comprehensively addressed NS at the clinical, histopathological, and molecular levels [13].

This literature reveals that the molecular profile in NS is heterogeneous, but that *RAS* mutations, in particular, play a critical role in our understanding of the risk of malignant transformation. Therefore, prospective

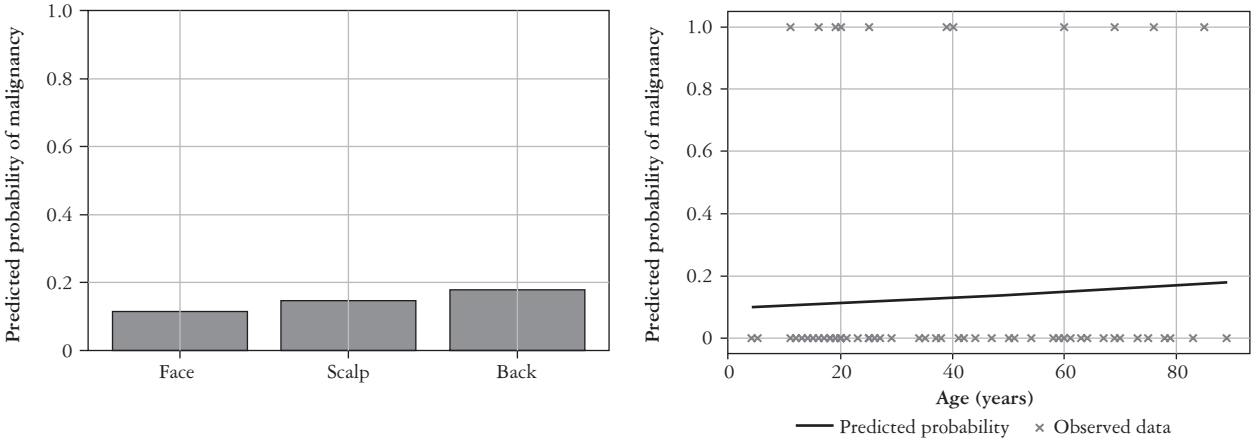

Figure 9. While scalp and back lesions showed a slightly higher predicted probability compared with facial lesions, these differences did not reach statistical significance and slight trend toward increased probability with advancing age, the relationship was not statistically significant

and molecularly supported studies in the future will enhance the reliability of clinical risk classification.

This study has some limitations. Because it is retrospective, it carries the risk of selection bias in patient groups, lesions that are clinically suspicious or show progression are more likely to be excised and sent for histopathological examination, and so malignancy rates may have been overestimated. All histopathological diagnoses were evaluated using light microscopy and, when necessary, immunohistochemistry; however, molecular analysis was not performed. The lack of molecular analysis precluded the identification of genetic markers that could predict secondary tumour development. The lack of long-term follow-up data limits the evaluation of recurrence rates and prognosis. Finally, the single-centre nature of the study limits the applicability of the findings to larger populations. Even with these constraints, the study adds novel information to the limited body of literature on NS and may help guide both clinical practice and future investigations.

Conclusions

Nevus sebaceus is a congenital lesion that requires follow-up for secondary tumour development. Our study found that secondary benign and malignant tumours, as well as proliferative lesions, were observed in approximately 40% of NS cases. The most common accompanying malignancy was basal cell carcinoma, and multiple tumour associations were found with a non-negligible frequency. It is worth noting that the risk of malignant transformation increases with age, and NS lesions, particularly in the adult age group, should be closely monitored. Histopathological examination remains the gold standard in cases of clinical suspicion.

The results of this study contribute to the literature regarding the frequency and types of secondary tumour development in NS lesions. However, the identification of molecular markers that can predict malignant transformation may make patient management more objective. Future multicentre studies, supported by molecular analysis and studies incorporating long-term clinical data, will help to more clearly define risk groups and develop effective clinical algorithms.

Disclosures

1. Institutional review board statement: The study was approved by the Ethics Committee of Manisa Celal Bayar University with approval number 20.478.486/3198, on 11 June 2025.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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