Dermatology Practical & Conceptual

Dermoscopic and Histopathological Features of Melanocytic Lesions in Melanoma Patients Undergoing Adjuvant Systemic Therapy

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ABSTRACT

Introduction: Melanoma accounts for around 1% of all skin tumors yet is responsible for 80% of deaths related to skin cancer. Although adjuvant therapies improve survival, their effects on nevi remain unclear.

Objectives: This study aimed to investigate the dermoscopic and histopathological features of melanocytic nevi in melanoma patients receiving adjuvant systemic therapy.

Methods: Dermoscopic images of 1,299 melanocytic nevi from 25 melanoma patients undergoing adjuvant therapy (targeted therapy, immunotherapy, or IFN-α) were analyzed before and after treatment. The histopathological features of 129 excised nevi from 67 melanoma patients were compared between patients who received adjuvant therapy and those who did not.

Results: Melanoma patients on targeted therapy showed a greater reduction in global pigmentation and disappearance of the pigment network than those on IFN-α and immunotherapy (p=0.001 and P=0.017, respectively). IFN-α therapy was associated with more atypical pigment network changes than targeted therapy and immunotherapy (P=0.027). Histopathologically, structural atypia, cytological atypia, inflammation, and fibroplasia were more prevalent in excised nevi from patients receiving adjuvant therapy (P=0.003, P=0.004, P<0.001, P=0.020, respectively).

Conclusions: Adjuvant systemic therapy induces dermoscopic and histopathological changes in melanocytic nevi. Clinicians and pathologists should carefully consider these alterations during melanoma follow-up to inform treatment decisions.

Introduction

Cutaneous melanoma is a malignant tumor that originates in melanocytes in the skin. Although it accounts for only around 1% of all skin tumors, melanoma is responsible for almost 80% of skin cancer-related deaths [1].

Interferon-alpha (IFN-α) has been used as an adjuvant therapy in melanoma treatment for many years; however, targeted therapies and immunotherapies have replaced it in recent years [2]. Targeted therapies aim to inhibit the uncontrolled activation of the mitogen-activated protein kinase (MAPK) pathway, which plays a crucial role in melanoma pathogenesis. In targeted therapy, MAPK pathway elements such as BRAF and MEK inhibitors are used in combination. This reduces the likelihood of resistance to the drugs developing and prevents hyperproliferative skin lesions, which can occur as a result of using isolated BRAF inhibitors. Specific combinations of agents are employed in this therapeutic approach, including dabrafenib with trametinib, vemurafenib with cobimetinib, and encorafenib with binimetinib[3-4]. On the other hand, immunotherapies target the inhibitory mechanisms employed by tumor cells to evade immune system checkpoints that regulate uncontrolled cell proliferation. Immunotherapeutic agents used in melanoma treatment include PD-1 inhibitors such as nivolumab and pembrolizumab, the PD-L1 inhibitor atezolizumab, and ipilimumab, which enhances T cell activity by blocking the interaction between CTLA-4 and B7, thereby modulating the immune response [2]. However, these novel therapeutic agents are associated with various systemic and cutaneous side effects, including melanocytic lesion evolution [5].

Objectives

In this study, we aimed to investigate the dermoscopic and histopathological features of melanocytic nevi in melanoma patients undergoing adjuvant systemic therapy.

Methods

The study included melanoma patients aged 18 years and over who were under the care of our dermatology clinic between January 2013 and December 2022. This group comprised patients who had received adjuvant systemic therapy and those who had not. Those receiving adjuvant therapy were categorized into three groups: i) interferon-alpha (IFN-α) therapy, ii) targeted therapy with BRAF-MEK inhibitors, and iii) immunotherapy. Those receiving targeted therapy were given either dabrafenib with trametinib or vemurafenib with cobimetinib, while those receiving immunotherapy were given nivolumab. Serial dermoscopic evaluations were only performed in patients receiving adjuvant systemic therapy.

The images taken by video dermatoscope in melanoma patients before and after adjuvant therapy were examined and compared by two dermatologists. The first dermoscopic images taken at least three months after starting the adjuvant therapy were evaluated as posttreatment images. For patients still undergoing the adjuvant systemic therapy, the last image taken during the treatment was considered as the posttreatment image, provided it was conducted at least three months after the start of treatment. Mucosal nevi, palmoplantar nevi, dermal nevi, non-melanocytic lesions, and nevi with poor quality dermoscopic images were excluded from the study. Changes in dermoscopic features such as size, global pigmentation, regular pigment network, atypical pigment network, dots, and globules were evaluated for each nevus on pretreatment and posttreatment images.

For the histopathological analysis, two dermatopathologists retrospectively retrieved and re-evaluated archived surgical tissue specimens of melanocytic lesions from melanoma patients. The histopathological assessment included diagnosis as well as evaluation of structural atypia, cytological atypia, inflammation, and fibroplasia. The study included all excised melanocytic lesions, regardless of the reason for their removal. Lesions diagnosed as second primary melanoma were excluded from the study. Histopathological analysis was made up of two groups: i) melanocytic lesions of melanoma patients who had received at least three months of systemic adjuvant therapy, and ii) melanocytic lesions of melanoma patients who had not received any systemic adjuvant therapy. The study protocol was approved by the University Ethics Committee. (GO 23/482, 2023/10-17).

Statistical Analyses

Statistical analyses were performed using IBM SPSS for version 23.0. Numerical variables were summarized as mean ± standard deviation or median (minimum-maximum), while categorical variables are presented as frequency and

percentage. The chi-square test was used to assess differences in sex distribution between treatment groups, an independent t-test was used to evaluate differences in imaging age, and the Kruskal-Wallis test was employed to investigate differences in follow-up duration. The effects of sex, imaging age, follow-up duration, nevus localization, and treatment groups on changes in size, pigmentation, network disappearance, network accentuation, atypical changes, new dots/globules, and disappearing dots/globules in nevi were determined using generalized estimating equations (GEE). Statistical significance was set at $P<0.05$.

Results

A total of 67 patients who had been diagnosed with histopathologically confirmed melanoma were included in the study. Of these patients, 30 (44.8%) were male and 37 (55.2%) were female. The mean age at diagnosis was 49.0 ± 13.9 years (range 22–82). Of the 67 patients, 25 (37.3%) received adjuvant systemic melanoma therapy, while 42 (62.7%) were followed up without adjuvant systemic therapy. Of those receiving adjuvant systemic therapy, six (24.0%) were treated with IFN-α, 11 (44.0%) received targeted therapy, and eight (32.0%) underwent immunotherapy. The mean age of patients taking adjuvant systemic therapy was 46.4 ± 13.4 years (range 22–67); the mean age of the group not taking adjuvant systemic therapy was 50.6 ± 14.1 years (range 25–82). There was no statistically significant difference in age between the two groups ($P=0.232$).

The clinical features of melanoma patients are summarized in Table 1 according to whether or not they received adjuvant systemic therapy.

Dermoscopic Evaluation

A total of 2,558 lesions from 25 patients undergoing adjuvant systemic therapy were imaged using a video dermatoscope. Following evaluation of the pre- and posttreatment images, 1,259 lesions were excluded from the study as they

Table 1. Clinical characteristics of melanoma patients.

	Patients with adjuvant systemic therapy (N=25) N (%)	Patients without adjuvant systemic therapy (N=42) N (%)	Total number of patients (N=67) N (%)
Melanoma Subtypes			
SSM	3 (12.0)	20 (47.6)	23 (34.3)
Nodular	9 (36.0)	3 (7.1)	12 (17.9)
LMM	2 (8.0)	6 (14.3)	8 (11.9)
ALM	0	7 (16.7)	7 (10.4)
Nevoid	4 (16.0)	5 (11.9)	9 (13.4)
Spitzoid	1 (4.0)	0 (0.0)	1 (1.5)
Dermal	0 (0.0)	1 (2.4)	1 (1.5)
Unknown	2 (8.0)	0 (0.0)	2 (3.0)
Unknown primary origin	4 (16.0)	0 (0.0)	4 (6.0)
Localization			
Head and neck	8 (32.0)	5 (11.9)	13 (19.4)
Trunk	10 (40.0)	8 (19.0)	18 (26.9)
Upper extremity	2 (8.0)	13 (31.0)	15 (22.4)
Lower extremity	1 (4.0)	10 (23.8)	11 (16.4)
Palmar	0 (0.0)	2 (4.8)	2 (3.0)
Plantar	0 (0.0)	4 (9.5)	4 (6.0)
Unknown primary origin	4 (16.0)	0 (0.0)	4 (6.0)
Clinical Stage at first diagnosis			
1A	0 (0.0)	14 (33.3)	14 (20.9)
1B	3 (12.0)	19 (45.2)	22 (32.8)
2A	0 (0.0)	3 (7.1)	3 (4.5)
2B	4 (16.0)	6 (14.3)	10 (14.9)
2C	2 (8.0)	0 (0.0)	2 (3.0)
3	15 (60.0)	0 (0.0)	15 (22.4)
4	1 (4.0)	0 (0.0)	1 (1.5)

Abbreviations: SSM: superficial spreading melanoma; LMM: lentiginous malignant melanoma; ALM: acral malignant melanoma; SD: standard deviation.

Table 2. Demographic and clinical features of patients receiving adjuvant systemic therapy.

	IFN-α Therapy (N=6)	Targeted Therapy (N =11)	Immunotherapy (N=8)	Total patient (N=25)	p-value
Sex, N (%)					
Female	3 (50.0)	4 (36.4)	5 (62.5)	12 (48.0)	0.524
Male	3 (50.0)	7 (63.6)	3 (37.5)	13 (52.0)	
Age at imaging, year					
Mean±SD	51.0± 1.0	47.5±14.0	44.0±12.9	47.2±12.7	0.611
Range	35-68	22-67	25-60	22-68	
Follow-up duration, month					
Mean±SD	14.8±6.0	26.8±21.1	18.5±10.1	21.0±15.5	0.510
Range	8-25	9-72	4-31	4-72	

did not meet our criteria. A total of 1,299 melanocytic nevi were assessed and compared in the pre- and posttreatment dermoscopic images. The median number of melanocytic nevi evaluated per patient was 42.00 (range 4–220). Of the 1,299 nevi evaluated, 400 (30.8%) belonged to patients who received IFN-α, 622 (47.9%) to those who underwent targeted therapy, and 277 (21.3%) to those treated with immunotherapy.

The demographic and clinical features of the patients receiving adjuvant systemic therapy are shown in Table 2 for each therapy group.

A total of 1,299 melanocytic nevi were analyzed, with the results presented in Table 3. Following adjuvant systemic therapy, a reduction in size was observed in 170 (13.1%) of the nevi, while an increase in size was noted in 138 (10.6%) of them. No size change was observed in 991 (76.3%) of the nevi. There was no significant difference in size changes among the three treatment groups.

Following adjuvant systemic therapy, comparison with pretreatment images revealed decreased pigmentation in 573 (44.1%) nevi and increased pigmentation in 46 (3.5%) nevi. According to the results of the multivariate analysis, patients receiving targeted therapy were 3.74 times more likely to exhibit global pigmentation changes than those receiving immunotherapy (95% confidence interval (CI): 1.70–8.24, *P*=0.001).

Following adjuvant systemic therapy, 200 nevi (15.4%) showed disappearance of the pigment network without atypical changes, as observed in pretreatment imaging. According to the results of the multivariate analysis, patients receiving targeted therapy were 2.4 times more likely to experience pigment network disappearance than those receiving immunotherapy (*P*=0.035). Following adjuvant treatment, 167 melanocytic nevi (12.9%) showed an accentuation of the pigment network without any atypical changes when compared to baseline dermoscopic images.

Atypical changes in the pigment network, defined as variations in network thickness, color, distribution, and network diameter, were observed in 35 (2.7%) of the nevi. According to the results of the multivariate analysis, patients receiving IFN-α therapy were 3.0 times (95% CI: 1.15–7.72) more likely to develop atypical pigment network changes compared to those undergoing immunotherapy (*P*=0.025).

When posttreatment images were compared with pretreatment images, new dot or globule formation was observed in 97 (7.5%) nevi. Conversely, 209 (16.1%) nevi showed a loss in the number of dots or globules. No significant difference was observed between the treatment groups in terms of dot or globule numbers. Multivariate analysis of dot and globule loss revealed that the duration of treatment was a significant predictor. For each additional month of treatment, the likelihood of dot or globule loss increased by 1.9% (odds ratio (OR): 1.019, 95% CI: 1.009–1.029, *P*=0.000). Additionally, older age at the time of imaging was associated with a reduced likelihood of dot or globule loss (OR: 0.967, 95% CI: 0.953–0.981, *P*=0.000).

Dermoscopic changes related to each adjuvant systemic therapy were shown in Figures 1–3.

Histopathological Evaluation

A total of 134 excised melanocytic lesions from 67 patients were included in the study for histopathological evaluation. Of these, 39 lesions (29.1%) were from patients who had received adjuvant systemic therapy and 95 (70.9%) were from patients with melanoma who had not. Three of the lesions in the adjuvant therapy group and two of the lesions in the non-adjuvant group were diagnosed as melanoma. Of the remaining melanocytic nevi in the adjuvant therapy group, 21 were from patients treated with interferon-alpha (IFN-α), seven were from patients receiving targeted therapy, and eight were from patients undergoing immunotherapy. In the adjuvant systemic therapy group, the localizations were the head and neck in one lesion (2.8%), the lower extremities in four lesions (11.1%), the upper extremities in nine lesions (25.0%), and the trunk in 22 lesions (61.1%). By contrast, of the 93 excised melanocytic

Table 3. Clinical and dermoscopic features of melanocytic nevi in therapy groups.

	IFN-α Therapy N= 400 N (%)	Targeted Therapy N=622 N (%)	Immunotherapy N= 277 N (%)
Nevus localization			
Head and neck	15 (3.7)	34 (5.4)	32 (11.5)
Trunk	153 (38.2)	234 (37.6)	70 (25.2)
Upper extremity	122 (30.5)	219 (35.2)	116 (41.8)
Lower extremity	110 (27.5)	135 (21.7)	59 (21.2)
p-value		0.774	
Size			
Reduced	44 (11.0)	99 (15.9)	27 (9.7)
No change	333 (83.3)	427 (68.6)	231 (83.4)
Increased	23 (5.8)	96 (15.4)	19 (6.9)
p-value	0.994	0.092	*
Odds ratio (95% CI)	0.99 (0.38-2.58)	2.32 (0.87-6.19)	*
Pigmentation			
Decrease	88 (22.0)	413 (66.4)	72 (26.0)
No change	290 (72.5)	193 (31.0)	197 (71.1)
Increased	22 (5.5)	16 (2.6)	8 (2.9)
p-value	0.947	**0.001**	*
Odds ratio (95 CI%)	0.97 (0.39-2.37)	4.80 (1.92-11.99)	*
Pigment network			
Disappearance	26 (6.5)	157 (25.2)	17 (6.1)
No change	318 (79.5)	382 (61.4)	232 (83.8)
Accentuation	56 (14.0)	83 (13.3)	28 (10.1)
p-value	0.458	0.017	*
Odds ratio (95% CI)	1.37 (0.60 – 3.1)	2.87 (1.21 – 6.8)	*
Development of atypical pigment network			
Yes	23 (5.8)	7 (1.1)	5 (1.8)
No	377 (94.3)	615 (98.9)	272 (98.2)
p-value	**0.027**	0.298	*
Odds ratio (95% CI)	3.31 (1.14-9.62)	0.61 (0.25-1.52)	*
Number of dots/globules			
Reduced	27 (6.8)	159 (25.6)	21 (7.6)
No change	336 (84)	422 (67.8)	238 (85.9)
Increased	37 (9.3)	41 (6.6)	18 (6.5)
p-value	0.546	0.028	*
Odds ratio (95% CI)	1.194 (0.672-2.123)	2.650 (1.108-6.339)	*

Abbreviations: IFN-α: interferon-alpha; CI: confidence interval. *While calculating the odds ratio, the selected reference group.

lesions from patients not receiving adjuvant systemic therapy, 13 (14%) were on the head and neck, 13 (14%) on the lower extremities, 25 (27%) on the upper extremities, and 42 (45%) on the trunk. A statistically significant difference in the localization of excised melanocytic lesions was found between patients who received and did not receive adjuvant systemic therapy (P=0.003). Analysis showed that truncal lesions were more frequently excised in patients receiving adjuvant systemic therapy, whereas lesions on the head and neck and on the upper and lower extremities were more commonly excised in patients who did not receive adjuvant systemic therapy (Table 4).

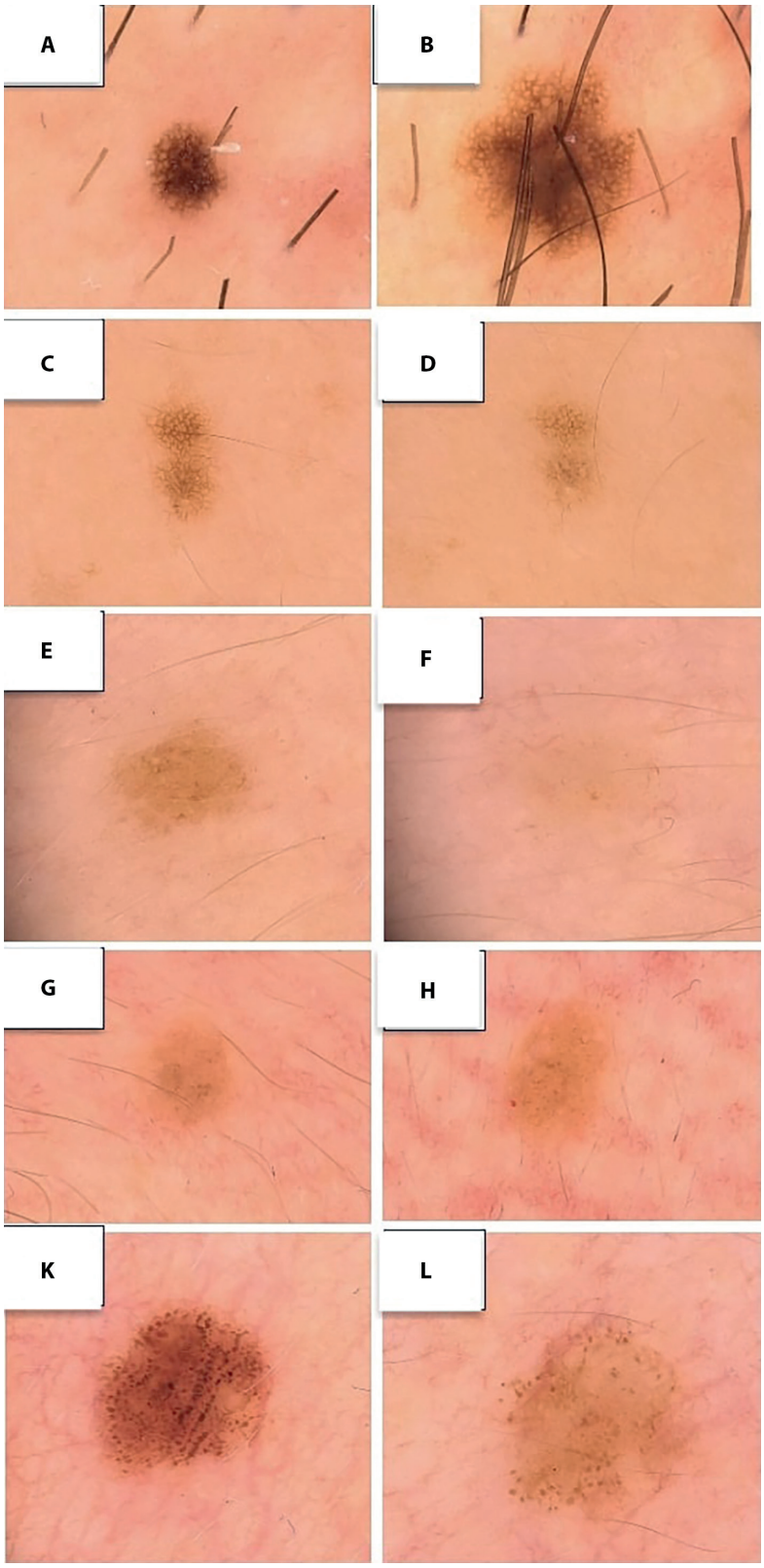

Figure 1. Targeted therapy-related dermoscopic changes; nevus showing growth and accentuation of the pigment network at the 24th month of follow-up with targeted therapy (1A-1B); nevus exhibiting decrease in pigmentation during the 9th month of follow-up with targeted therapy (1C-1D); nevus with shrinkage, decreased pigmentation, 30-month follow-up after targeted therapy (1E-1F); Nevus showing growth and formation of new dots/globules, 30-month follow-up under targeted therapy (1G-1H); Nevus with decreased pigmentation and loss of dots/globules targeted therapy, 25-month follow-up (1K-1L).

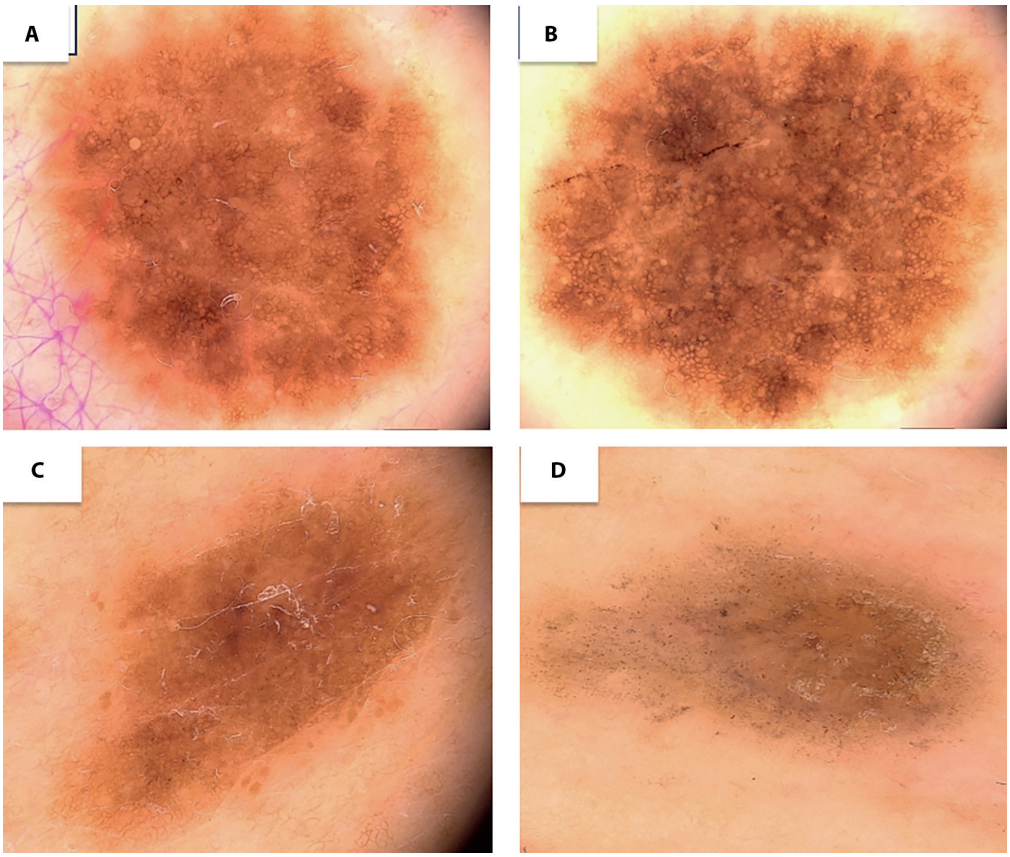

Figure 2. Interferon-alpha treatment related dermoscopic changes; Nevus showing increased pigmentation and atypical changes in the pigment network during follow-up with interferon-alpha at 12 months (2A-2B); Nevus showing reduced pigmentation and formation of new dots/globules, 10-month follow-up under interferon alpha treatment (2C-2D).

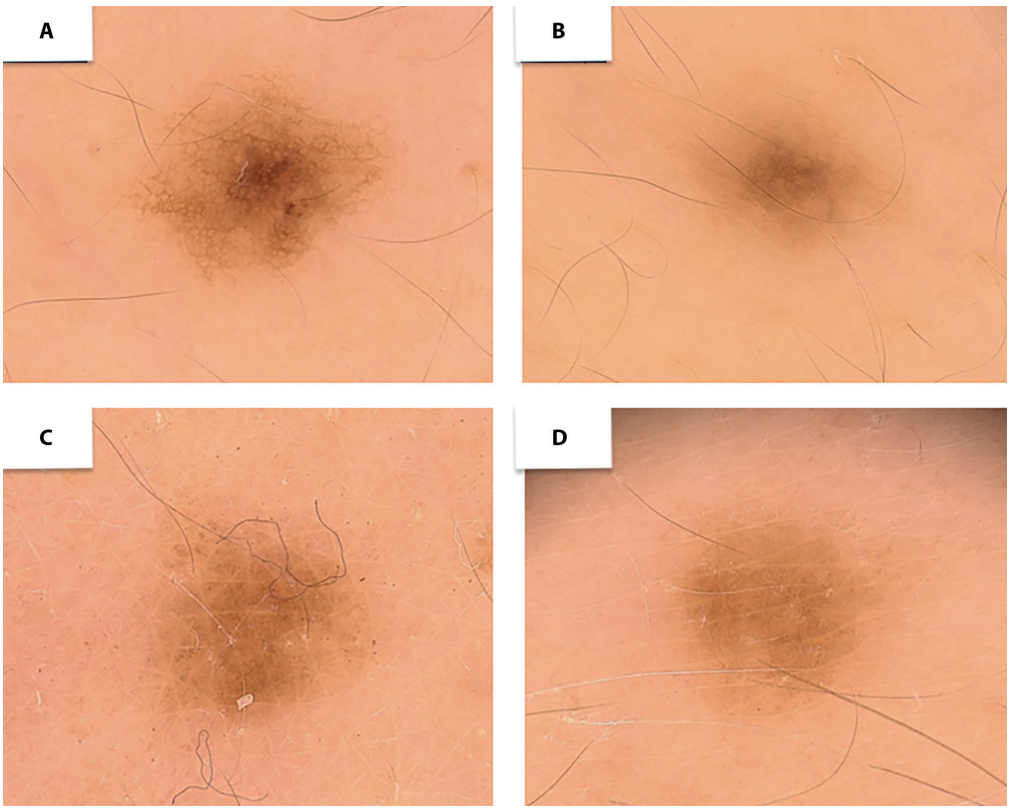

Figure 3. Immunotherapy treatment related dermoscopic changes; Nevus showing reduction, decreased pigmentation, and loss of pigment network at the 10th month of follow-up with immunotherapy (3A-3B); Nevus showing reduction, decreased pigmentation, and loss of pigment network at the 36th month of follow-up with immunotherapy (3C-3D).

Table 4. The frequency of histopathological criteria in excised melanocytic nevi.

	MN in patients receiving adjuvant systemic therapy (N=36) N (%)	MN in patients not receiving adjuvant systemic therapy (N=93) N (%)	Total MN (N=129) N (%)	p-value
Structural atypia	19 (52.8)	75 (80.6)	94 (72.9)	**0.003**
Absent	17 (47.2)	18 (19.4)	35 (27.1)	
Present				
Cytological atypia	22 (61.1)	76 (81.7)	98 (76.0)	**0.004**
Absent	11 (30.6)	14 (15.1)	25 (19.4)	
Mild cytological atypia	3 (8.3)	3 (3.2)	6 (4.7)	
Severe cytological atypia				
Inflammation	11 (30.6)	53 (57.0)	64 (49.6)	**<0.001**
Absent	12 (33.3)	24 (25.8)	36 (27.9)	
Mild inflammation	8 (22.2)	14 (15.1)	22 (17.1)	
Moderate inflammation	5 (13.9)	2 (2.2)	7 (5.4)	
Severe inflammation				
Melanophages	9 (25.0)	29 (31.2)	38 (29.5)	0.607
Absent	27 (%75.0)	64 (68.8)	91 (70.5)	
Present				
Fibroplasia	20 (55.6)	75 (80.6)	95 (73.6)	**0.020**
Absent	16 (44.4)	18 (19.4)	34 (26.4)	
Present				

MN: melanocytic nevi

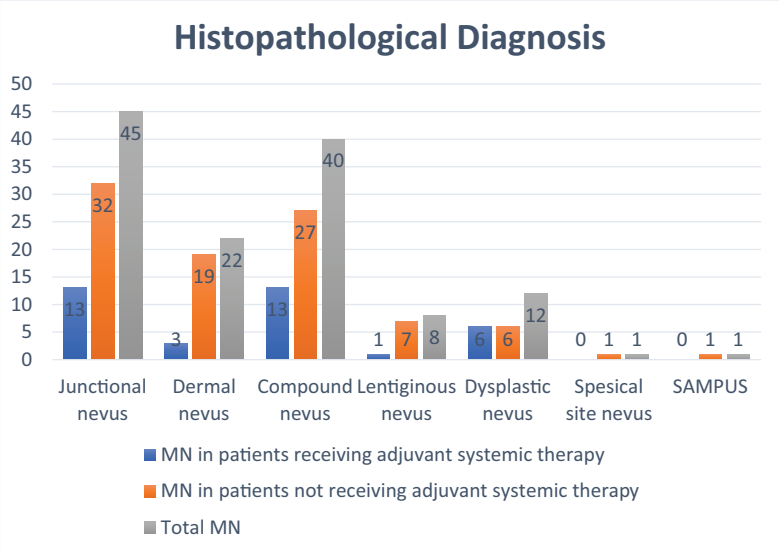

Figure 4. Histopathological subtypes of excised nevi in patients diagnosed with melanoma. Abbreviations: MN: melanocytic nevus, SAMPUS: superficial atypical melanocytic proliferations of uncertain significance

When melanocytic lesions were evaluated in detail in terms of histopathological diagnosis, junctional nevi were the most common diagnosis in both groups. Histopathological diagnosis of excised melanocytic lesions are shown in Figure 4. When comparing melanocytic lesions of melanoma patients who received adjuvant systemic therapy to those who did not, structural atypia, cytological atypia, inflammation, and fibroplasia were more frequently observed in melanocytic lesions of melanoma patients who received adjuvant therapy (P=0.003, P=0.004, P<0.001, and P=0.020, respectively). Figures 5–6 show some histopathological parameters in nevi of melanoma patients taking adjuvant systemic therapy.

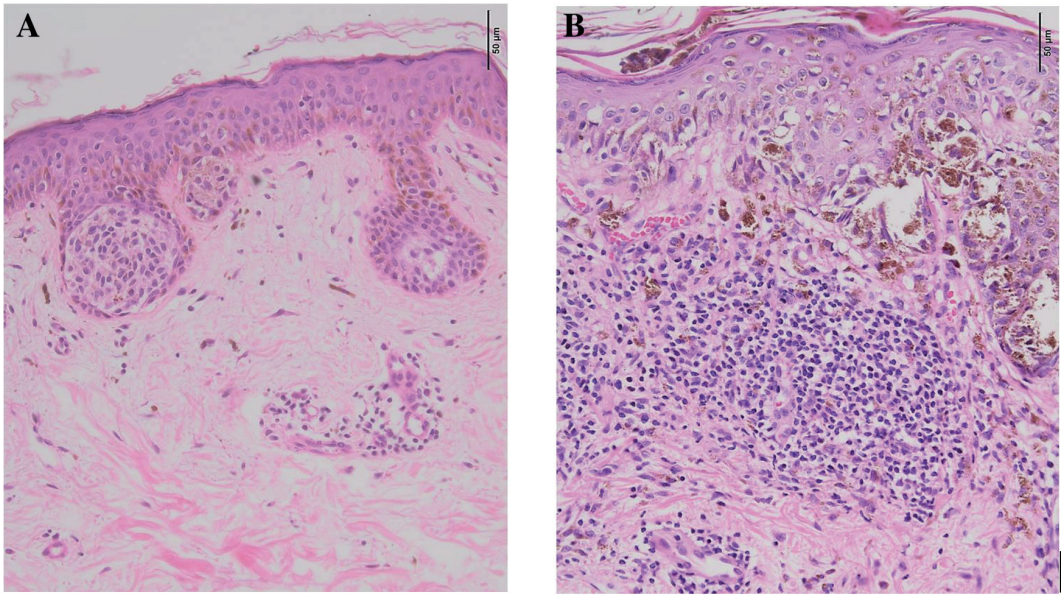

Figure 5. A) Nevus with mild inflammation under interferon-alpha (200x). B) Nevus with severe inflammation and melanophages infiltration under interferon-alpha (200x).

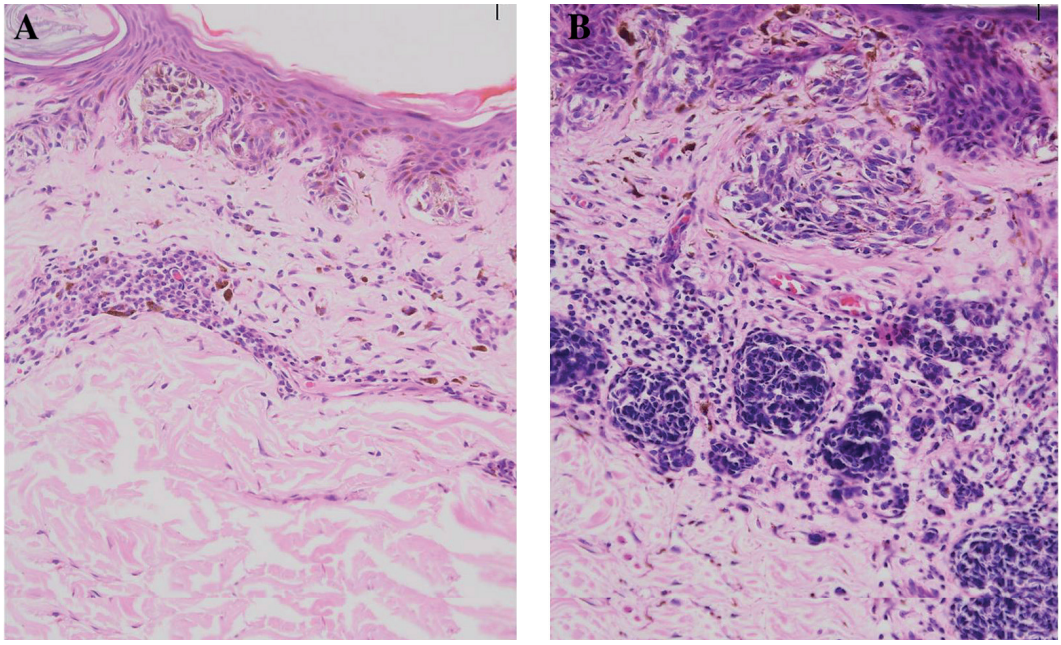

Figure 6. A) Nevus with mild cytological atypia and moderate inflammation under targeted therapy (200x). B) Nevus with severe cytological atypia under immunotherapy (x200).

Discussion

Melanoma patients have an increased risk of developing secondary melanomas [3]. However, monitoring these patients can be challenging due to the presence of multiple atypical melanocytic lesions, either clinically or dermoscopically, and exposure to radiotherapy or systemic adjuvant therapies. These factors can complicate lesion follow-up, influence excision decisions, and increase the risk of overdiagnosis. The effects of chemotherapy and immunosuppressive treatments on melanocytic lesions have been previously documented [4]. However, the potential secondary effects of systemic therapies used for primary melanoma treatment on nevi have not been clearly established. Therefore, this study was designed to evaluate the impact of adjuvant systemic treatments on melanocytic lesions in melanoma patients.

In our study, six patients received IFN-α, 11 patients received targeted therapy, and eight patients received immunotherapy. Although IFN-α is no longer included in current melanoma treatment guidelines, its impact on melanocytic lesions remains

clinically relevant. The dermoscopic monitoring of melanoma patients previously treated with IFN-α is routinely performed in our clinic as disease progression may necessitate the initiation of novel treatment agents such as targeted therapies or immunotherapies. Identifying dermoscopic changes in patients who have received IFN-α for any reason can help clinicians recognize drug-induced alterations in melanocytic lesions, potentially preventing unnecessary excisions. In our study, we observed an increased development of atypical pigment networks in patients treated with IFN-α, highlighting the importance of recognizing these changes in clinical practice to ensure appropriate management of melanocytic lesions in this patient group that has received this treatment.

Both Perier et al.[5] and Zhao et al.[6] have demonstrated that combination therapy involving BRAF and MEK is associated with a reduction in the pigmentation of melanocytic lesions. In our study, the pigmentary changes observed in the targeted therapy group were consistent with the data reported in the literature. A statistically significant difference in global pigmentation change was found between the treatment groups, with the targeted therapy group showing a significantly higher rate of pigmentation changes compared to the IFN-α and immunotherapy groups. The literature suggests that combined immunotherapy agents induce stronger immune responses, leading to more frequent depigmentation in melanocytic lesions compared to monotherapy [4]. We propose that the lower depigmentation rates in the immunotherapy group of our study may be related to the fact that all patients in this group received nivolumab monotherapy. Furthermore, a longer follow-up period was associated with a higher incidence of pigmentation changes in our study. Although the average follow-up time was not statistically significant, the longer follow-up duration in the targeted therapy group is thought to contribute to the higher incidence of depigmentation observed in this group. In our study, nevi in patients receiving targeted therapy showed reduced pigmentation and more frequent disappearance of the pigment network, which is likely to reflect the inhibitory effect of this treatment on melanocytes.

Additionally, analysis of atypical changes in the pigment network revealed a statistically significant difference between the treatment groups. Nevi in patients receiving IFN-α therapy exhibited atypical pigment network changes more frequently than those receiving targeted therapy and immunotherapy. Although no study has examined the impact of adjuvant treatments on the development of secondary primary melanomas in melanoma patients, it is noteworthy that atypical pigment network changes were less prevalent in nevi of patients receiving targeted therapy and immunotherapy.

In our study, no significant difference was observed in the change in dot and globule numbers between the treatment groups. However, multivariate analysis revealed that dot and globule loss was associated with treatment duration. As previously reported in the literature, dot and globule loss is an expected phenomenon associated with ageing. However, as the age differences between the treatment groups in our study were statistically similar, the effect of age on dot and globule loss is considered minimal.

Although case reports have described histopathological changes in melanocytic nevi following adjuvant therapy, there have been no comprehensive studies [7, 8]. In our study, nevi excised from patients receiving adjuvant systemic therapy exhibited structural and cytological atypia, inflammation and fibroplasia more frequently than those from untreated patients. These results may indicate immune-mediated effects of adjuvant agents on melanocytes, as suggested by a previous report on treatment-induced changes in other cell types [9]. However, due to the absence of baseline histopathological data, and given that atypical nevi are more prevalent in melanoma patients, these associations should be interpreted with caution.

The dermoscopic alterations observed in patients undergoing adjuvant systemic therapy may be indicative of underlying histopathological changes in melanocytic nevi. Regression-related features such as hypopigmentation, fibrosis, and inflammatory infiltrates have been described in dermoscopic and histopathological contexts. In this study, the increased frequency of dermoscopic hypopigmentation in patients undergoing treatment may be partially attributed to such microscopic alterations. Furthermore, the presence of structural atypia in histology may correspond to the atypical pigment network patterns observed in dermoscopy [10]. However, due to the limited number of excised lesions, it was not possible to analyze histopathological changes according to treatment modality. Future studies involving larger, treatment-specific cohorts are required to investigate these associations further.

This retrospective study has several limitations. Firstly, dermoscopic follow-up was not standardized, which may have influenced lesion monitoring and assessment. Secondly, serial dermoscopic evaluation was not performed in patients who did not receive adjuvant systemic therapy; therefore, the study lacked a dermoscopic control group, which limits causal inference and may affect the generalizability of our findings. Furthermore, the specific reasons for the excision of melanocytic lesions were not systematically documented, which limits the interpretation of the relationship between the observed dermoscopic changes and the decisions to excise. Future prospective studies with standardized protocols and an appropriate control group are necessary to overcome these limitations.

Conclusions

In conclusion, this study demonstrates that adjuvant therapy for melanoma patients is associated with dermoscopic changes to melanocytic lesions. These changes include a

reduction in global pigmentation, a loss of the pigment network, and alterations to atypical pigment patterns. These findings emphasize the importance of carefully monitoring these lesions using dermoscopy on an ongoing basis in this patient group. Further research is needed to clarify the clinical significance of these changes and their potential relationship with melanoma development.

Ethical Approval: Reviewed and approved by Hacettepe University Ethics Committee; approval GO 23/482 and approval number 2023/10-17.

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