

Hair Repigmentation as a Melanoma Warning Sign

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PRACTICE POINTS

- Localized repigmentation of the hair is a rare phenomenon that may indicate underlying melanoma.
- Careful clinicopathologic correlation is necessary to appropriately diagnose and manage this unusual presentation of melanoma.

To the Editor:

An 85-year-old man with a history of hypertension and chronic kidney disease presented with a localized darkening patch of hair on the left parietal scalp that had progressed over the last 7 years (Figure 1A). He had no prior history of skin cancer. Physical examination revealed the remainder of the hair was gray. There was an irregularly pigmented plaque on the skin underlying the darkened hair measuring 5.0 cm in diameter that was confirmed to be melanoma (Figure 1B). He underwent a staged excision to remove the lesion. The surgical defect was closed via a 5.0×6.0-cm full-thickness skin graft.

The initial biopsy showed melanoma in situ. However, the final pathology report following the excision revealed an invasive melanoma with a Breslow depth of 1.0 mm (Clark level IV; American Joint Committee on Cancer T1b).¹ Histopathology showed pigment deposition with surrounding deep follicular extension of melanoma (Figure 2).

The patient declined a sentinel lymph node biopsy and agreed to a genetic profile assessment.² The results of the test identified the patient had a low probability of a positive sentinel lymph node and the lowest risk of melanoma recurrence within 5 years. The patient was clear of disease at 12-month follow-up.

Based on a PubMed search of articles indexed for MEDLINE using the terms *hair repigmentation* and *melanoma*, there have been 11 other reported cases of hair repigmentation associated with melanoma (Table).³⁻¹³ It initially was suspected that this rare phenomenon primarily existed in the female population, as the first 5 cases were reported solely in females,³⁻⁷ possibly due to the prevalence of androgenetic alopecia in males.¹¹ However, 6 cases of repigmentation associated with melanoma were later reported in males⁸⁻¹³; our patient represents an additional reported case in a male. It is unknown if there is a higher prevalence of this phenomenon among males or females.

Most previously reported cases of repigmentation were associated with melanoma in situ, lentigo maligna type. Repigmentation also has been reported in malignant melanoma, as documented in our patient, as well as desmoplastic and amelanotic melanoma.^{5,6} In every case, the color of the repigmentation was darker than the rest of the patient's hair; however, the repigmentation color can be different from the patient's original hair color from their youth.^{4,5,11}

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The authors report no conflict of interest.

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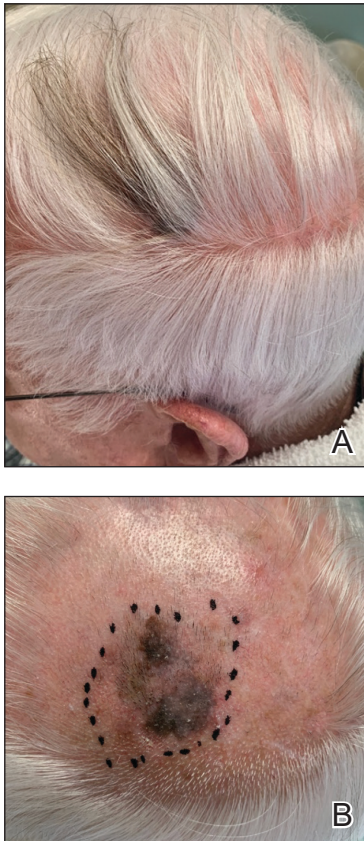


FIGURE 1. A, Localized darkening of hair on the left parietal scalp. B, An irregularly pigmented plaque measuring 5.0 cm in diameter was noted underlying the darkened hair.

The exact mechanism responsible for hair repigmentation in the setting of melanoma is unclear. It has been speculated from prior cases that repigmentation may be caused by paracrine stimulation from melanoma cells activating adjacent benign hair follicle melanocytes to produce melanin.^{7,14,15} This process likely is due to cytokines or growth factors, such as c-kit ligand.^{14,15} Several neural and immune networks and mediators activate the receptor tyrosine kinase KIT, which is thought to play a role in activating melanogenesis within the hair bulb.¹⁴ These signals also could originate from changes in the microenvironment instead of the melanoma cells themselves.⁶ Another possible mechanism is that repigmentation was caused by melanin-producing malignant melanocytes.⁴

Because this phenomenon typically occurs in older patients, the cause of repigmentation also could be related to chronic sun damage, which may result in upregulation of stem cell factor and α -melanocyte-stimulating hormone, as well as other molecules associated with melanogenesis, such as c-KIT receptor and tyrosinase.^{15,16} Upregulation of these molecules can lead to an increased number of melanocytes within the hair bulb. In addition, UVA and narrowband UVB have been recognized as

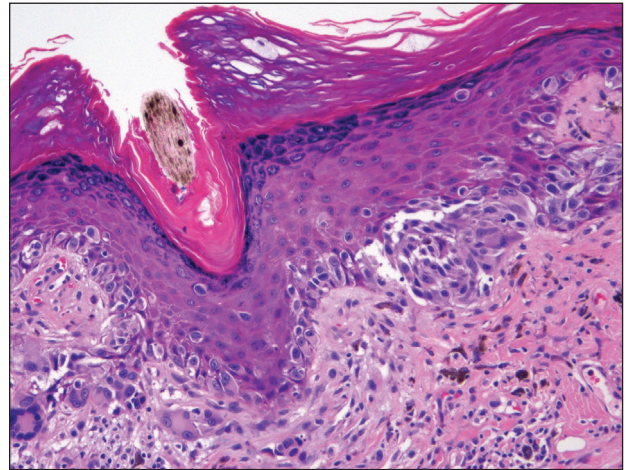


FIGURE 2. Staged excision of the pigmented area of the left parietal scalp revealed an emerging hair shaft with dark, variably chunky pigment deposition seen in association with surrounding melanoma (H&E, original magnification $\times 100$).

major players in melanocyte stimulation. Phototherapy with UVA or narrowband UVB has been used for repigmentation in vitiligo patients.¹⁷

In cases without invasion of hair follicles by malignant cells, repigmentation more likely results from external signals stimulating benign bulbar melanocytes to produce melanin rather than melanoma cell growth extending into the hair bulb.⁶ In these cases, there is an increase in the number of hair bulbar melanocytes with a lack of malignant morphology in the hair bulb.⁸ If the signals are directly from melanoma cells in the hair bulb, it is unknown how the malignant cells upregulated melanogenesis in adjacent benign melanocytes or which specific signals required for normal pigmentation were involved in these repigmentation cases.⁶

Use of medications was ruled out as an underlying cause of the repigmentation in our patient. Drug-related repigmentation of the hair typically is observed in a diffuse generalized pattern. In our case, the repigmentation was localized to the area of the underlying dark patch, and the patient was not on any medications that could cause hair hyperpigmentation. Hyperpigmentation has been associated with acitretin, lenalidomide, corticosteroids, erlotinib, latanoprost, verapamil, tamoxifen, levodopa, thalidomide, PD-1 inhibitors, and tumor necrosis α inhibitors.¹⁸⁻³⁰ Repigmentation also has been reported after local radiotherapy and herpes zoster infection.^{31,32}

The underlying melanoma in our patient was removed by staged square excision. Excision was the treatment of choice for most similar reported cases. Radiotherapy was utilized in two different cases.^{3,4} In one case, radiotherapy was successfully used to treat melanoma in situ, lentigo maligna type; the patient's hair grew back to its original color, which suggests that normal hair physiology was restored once melanoma cells were eliminated.³

Summary of Reported Cases of Hair Repigmentation in Association With Melanoma³⁻¹³

Reference (year)	Age, y	Sex	Lesion size	Lesion thickness/ extension	Repigmentation color	Biopsy diagnosis	Treatment/outcome
Dummer ³ (2001)	76	F	Not reported	Not reported	Gray to brown (original color not reported)	Melanoma in situ, lentigo maligna type	Radiotherapy/hair grew back gray
Inzinger et al ⁴ (2013)	91	F	8-mm diameter	3.5 mm/deep dermis and follicular extension	White to red to black to light brown (original color = light blonde)	Malignant melanoma	Excision/local recurrence and lymph node metastasis 10 mo later; second excision and radiotherapy/no recurrence within 4 mo
Rahim et al ⁵ (2013)	82	F	35×35 mm	Breslow thickness, 7 mm/upper hair follicle extension	Gray to strawberry blonde (original color = brown)	Desmoplastic melanoma with associated lentigo maligna	Excision/no recurrence within 6 y
Tiger et al ⁶ (2014)	88	F	6.5×3 cm	Dermoepidermal junction and follicular extension	White to dark brown (original color not reported)	Melanoma in situ, lentigo maligna type	No treatment or follow-up reported
Amman and Dummer ⁷ (2016)	91	F	4×3 cm	Perifollicular extension	Unknown to black (original color not reported)	Melanoma in situ, lentigo maligna type	Excision/no follow-up reported
Chan et al ⁸ (2019)	80	M	3.0×2.5 cm	Follicular extension	Gray to black (original color not reported)	Melanoma in situ, lentigo maligna type	Excision/no recurrence within 1 y
Lackey et al ⁹ (2019)	86	M	15×8 cm	Not reported	White to black (original color not reported)	Melanoma in situ, lentigo maligna type	Imiquimod cream 5%/no recurrence within 17 mo; repigmentation cleared
Chew et al ¹⁰ (2020)	75	M	30×30 mm	Superficial hair follicles and eccrine ducts extension	White/gray to black (original color not reported)	In situ and invasive malignant melanoma, lentigo maligna type	Excision/no follow-up reported
López-Sánchez and Collgro ¹¹ (2020)	56	M	<5-mm diameter	Follicular extension	White to black (original color = brown)	Melanoma in situ, lentigo maligna type	Excision/no recurrence within 12 mo
Gessler et al ¹² (2022)	85	M	4.5×3.0 cm	Follicular extension	White to brown (original color not reported)	Melanoma in situ, lentigo maligna type	Excision/no follow-up reported
Hasegawa et al ¹³ (2023)	80	M	13.8×5.8 mm	From the dermis to subcutis without follicular invasion/perifollicular infiltration of amelanotic melanoma cells	Gray to brown-black (original color not reported)	Malignant amelanotic melanoma	Pembrolizumab (2 mg/kg every 3 wk)/no recurrence within 1 y
Current case	85	M	5.0-cm diameter	Breslow depth, 1.0 mm/deep follicular extension	White to black (original color not reported)	Malignant melanoma	Excision/no recurrence within 12-mo follow-up

Abbreviations: F, female; M, male.

One reported case demonstrated successful treatment of lentigo maligna type–melanoma with imiquimod cream 5% applied 6 times weekly for 9 months with a positive cosmetic result.⁹ The exact mechanism of imiquimod is not fully understood. Imiquimod induces cytokines to stimulate the production of IFN- α via activation of toll-like receptor 7.³³ There was complete clearing of the lesion as well as the hair pigmentation,⁹ which suggests that the treatment also eliminated deeper cells influencing pigmentation. A case of malignant amelanotic melanoma was successfully treated with anti-PD-1 antibody pembrolizumab (2 mg/kg every 3 weeks), with no recurrence at 12 months. Pembrolizumab acts as an immune checkpoint inhibitor by binding to the PD-1 receptor and allowing the immune system to recognize and attack melanoma cells. After 5 doses of pembrolizumab, the patient was clear of disease and his hair color returned to gray.⁵

In 2022, melanoma was estimated to be the fifth most commonly diagnosed cancer among men and women in the United States.³⁴ Early melanoma detection is a critical factor in achieving positive patient outcomes. Hair repigmentation is a potentially serious phenomenon that warrants a physician visit. Melanoma lesions under the hair may be overlooked because of limited visibility. Physicians must inspect spontaneous hair repigmentation with high suspicion and interpret the change as a possible indirect result of melanoma. Overall, it is important to increase public awareness of regular skin checks and melanoma warning signs.

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