Large, linear pigmentation anomaly: an unusual case of dyspigmentation

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Abstract

Segmental pigmentation anomalies can be further divided into segmental pigmentation disorder (SPD) complex and café-au-lait macules (CALMs). Both are congenital skin conditions characterized by hyper- or hypopigmentation. Segmental pigmentation disorder is a rare entity, whereas CALMs are common skin lesions that may be associated with various genetic conditions, especially when several are present and the patient has other indicators of a genetic abnormality. When the CALM is segmental, segmental neurofibromatosis (type V) may be considered in the differential diagnosis. Herein we present a 48-year-old woman with a history of malignant melanoma who presented with a large, linear, hyperpigmented patch on her shoulder and arm, present since around birth. The differential diagnosis consisted of CALM versus hypermelanosis (a subtype of SPD). Given a family history of a similar lesion, in addition to a personal and family history of melanoma and internal cancers, a hereditary cancer panel was completed demonstrating genetic variance of uncertain significance. This case brings attention to a rare dyspigmentation disorder and questions a possible association with melanoma.

Keywords: café-au-lait, CHEK2, hypermelanosis, neurofibromatosis, pigmentation disorder, segmental

Introduction

A hyper- or hypopigmented, segmental patch can be classified as a segmental pigment anomaly, which may be further subdivided into segmental pigmentation disorder (SPD) simplex or a café-au-lait macule (CALM). These two entities may be easily confused given their similar histopathologic presentation—melanin macroglobules found in melanocytes and basal keratinocytes. The difference lies clinically. Both CALMs and SPDs describe light-to-dark-brown ("coffee-colored"), round or oval macules with either smooth or irregular borders. However, SPD has sharp midline demarcation, whereas CALMs may cross the midline [1,2].

When CALMs are segmental in nature, an important entity in the differential diagnosis to consider is segmental neurofibromatosis (SNF; type V). Segmental neurofibromatosis is a rare form of neurofibromatosis (NF) in which the classic signs of NF such as neurofibromas, freckling, and CALMs appear in a restricted, mosaic distribution related to a late mutation in the *NF1* gene during embryogenesis [3,4]. Prevalence of SNF is approximately 0.0014–0.002% [5]. The diagnosis of SNF can be made when an area is affected with café-au-lait lesions alone. An NF mutation may be present in other tissues as well; therefore, patients with SNF are usually followed regularly by a physician.

Herein, we report a patient with SPD associated with a personal and family history of melanoma and other internal malignancies. This case presents an interesting differential diagnosis. Our literature search did not show a similar presentation.

Case Synopsis

A woman in her mid-40s with past medical history of malignant melanoma presented to the outpatient dermatology clinic for a total body skin examination.

During the skin exam, a well-circumscribed, linear, brown patch was discovered which extended from her right scapula, laterally down her arm, to just past the antecubital fossa (**Figure 1**). A similar large, brown patch was found on her posterior neck. She stated that these two patches had been present and unchanged since she was young. She did not have any other similar brown patches, axillary freckling, or neurofibromas. The patient was negative for skeletal abnormalities, macrocephaly, or abnormal facies. She did not appear to have any cognitive defects or hyperactivity. Slit-lamp testing for Lisch nodules was not preformed. Additionally, her skin examination revealed dozens of scattered tan-brown verrucous lesions on her trunk and extremities with benign features, consistent with seborrheic keratoses.

The patient's malignant melanoma had been diagnosed in Columbia several years prior and subsequently removed there. It was located on her mid-back and was not emanating from her SPD. She was unsure of its Breslow depth and no records were available to review. She did not take any medication regularly and was a lifelong nonsmoker. She was otherwise well.

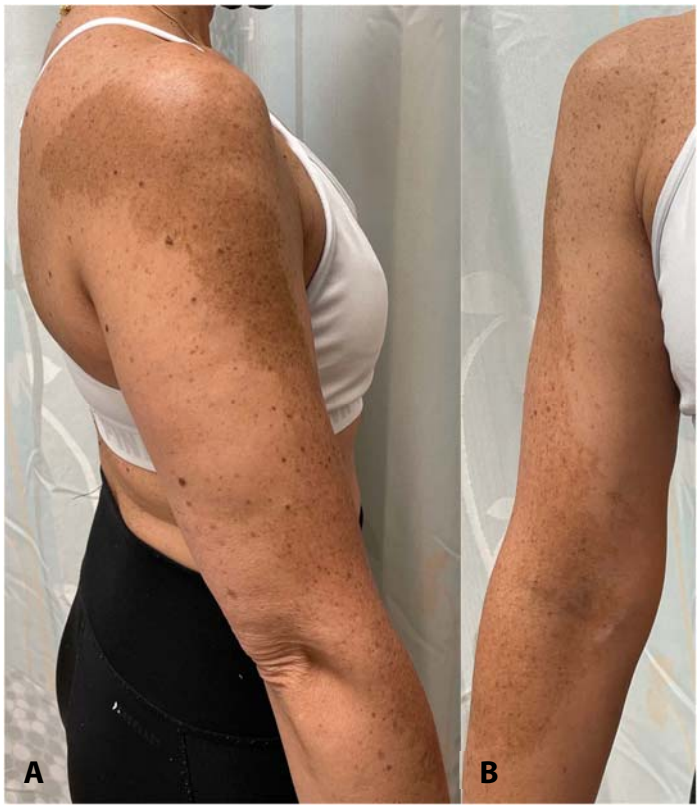

Figure 1. ***A)*** *Lateral view of a large, well-demarcated, hyperpigmented patch beginning on the patient's right shoulder and extending laterally down the patient's right arm.* ***B)*** *Anterior view of a large, well-demarcated, hyperpigmented patch on the patient's right arm.*

The patient reported that her father had multiple melanomas first diagnosed when he was 40 years old, and a similar hyperpigmented patch on his anterior neck. No other member of her family—including her two children—had such patches, NF, or known genetic abnormalities. Her family history was also significant for colon cancer (paternal aunt, age 50), breast cancer (paternal grandmother, age 55), gastric cancer (maternal aunt, age 53), and pancreatic cancer (maternal grandmother, age 77).

She was referred to the clinical genetics department owing to her personal and family history of cancer. Around the time of her visit, she was diagnosed with invasive ductal carcinoma of the breast (pending treatment). An Invitae common hereditary cancer panel was ordered by her surgical oncologist. This panel tests 47 genes associated with cancers including *NF1* (neurofibromatosis 1) and *CDKN2A* (melanoma). Her test demonstrated two genetic variants of uncertain significance in the *CHEK2* gene (497A>G) and the *SMAD4* gene (671A>T). Her pap tests and colonscopies thus far have been negative.

Case Discussion

This patient presented with a segmental pigmentation anomaly; more specifically, a linear café-au-lait macule versus segmental hypermelanosis in conjunction with multiple seborrheic keratoses and a history of malignant melanoma and breast cancer.

If the linear hyperpigmented patch represents a CALM, then the question of whether it is isolated, familial, or part of a syndrome is important. One or two CALMs are present in roughly 10% of the population; if familial, they follow an autosomal dominant inheritance pattern. When part of a syndrome, CALMs are usually small and numerous. In contrast, large, solitary patches are more likely to be segmental lentigines not associated with a syndrome. Though her two large patches do not fit the clinical presentation of a syndrome, the question of a genetic association should be explored given her

father's similar café-au-lait patch and melanoma diagnosis.

Localized café-au-lait patches may represent mosaic presentations of neurofibromatosis. Though she did not demonstrate axillary freckling or neurofibromas in these areas, SNF should still be considered in the differential diagnosis. Segmental neurofibromatosis is generally considered a non-inheritable disorder given that it is a somatic mutation. However, a few cases have been reported of children inheriting NF from parents with SNF, thus leading to the conclusion that SNF may indicate increased susceptibility to somatic mutation at the NF locus [6,7]. Segmental neurofibromatosis has also been associated with increased risk of malignancies such as malignant melanoma. Most malignancies are of neural crest cell origin and the risk of internal malignancies and systemic involvement has not been determined [5]. In these patients, regular follow up with primary care, ophthalmology, and dermatology physicians is warranted to evaluate for manifestations of systemic involvement.

The patient's genetic results showed mutations in the *CHEK2* and *SMAD4* genes. *CHEK2* is associated with autosomal dominant predisposition to breast, colon, prostate, and thyroid cancer and has some correlation with ovarian, renal, and urinary tract cancer. There are conflicting studies on whether *CHEK2* is associated with increased risk of skin cancer [8]. Insufficient evidence is available to determine whether the patient's particular genetic variant results in functional abnormalities. However, algorithms indicate that the missense change is likely to be disruptive. This genetic defect may perhaps explain the patient's personal and family history of internal malignancies and melanoma, but the relation to the segmental pigmentation anomaly is undetermined. The *SMAD4* gene is associated with autosomal dominant juvenile polyposis syndrome, hereditary hemorrhagic telangiectasia, and Myhre syndrome, though her particular genetic anomaly was determined by algorithm to unlikely result in functional alterations. It should be noted that genetic variants of uncertain significance are rarely pathogenic when later reassessed [9].

This case is interesting both in the diagnosis and in the potential for newly discovered syndromes. No significant research so far has indicated associations between large, linear SPD or of heritable SNF associated with multigenerational skin malignancies. If such associations are indeed present and inheritable, patients affected with these lesions should be educated on the risks of passing the trait to biological children and the importance of skin cancer screening.

Conclusion

Segmental pigmentation anomalies present a diagnostic challenge and whether they are associated with cutaneous malignancies has not been elucidated. Given various possible genetic etiologies underlying café-au-lait macules and segmental neurofibromatosis and given our patient's lesional presentation associated with personal and family history of similar lesions and cancer, genetic causes may warrant further exploration, particularly regarding the *CHEK2* gene.

Potential conflicts of interest

G Yosipovitch conducted clinical trials or received honoraria for serving as a member of the Scientific Advisory Board and consultant of Pfizer, TREVI, Regeneron, Sanofi, Galderma, Novartis, Bellus, Kiniksa, and Eli Lilly, and received research funds from Pfizer, Leo, Sanofi, Regeneron, Eli Lilly, and Novartis. The remaining authors declare no conflicts of interest regarding the content of this report.

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