Hyperpigmented patch of the left hemithorax

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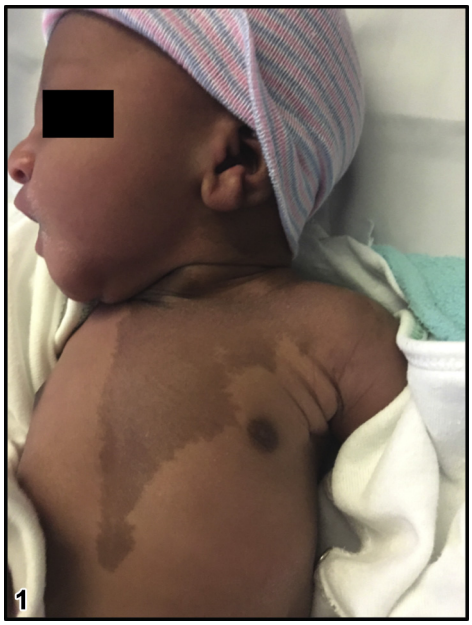
Key words: café-au-lait; coast of Maine; hyperpigmented patch; McCune-Albright.



A 6-hour-old infant was found to have large irregularly bordered brown patches on the trunk, neck (Fig 1), and buttocks. The infant otherwise had a normal-term delivery without any concerning findings.

Question 1: Which of the following syndromes typically presents with lesions featuring the morphology seen here?

A. McCune-Albright syndrome

B. LEOPARD syndrome

C. Neurofibromatosis type 1

D. Peutz-Jeghers syndrome

E. Legius syndrome

Answers:

A. McCune-Albright syndrome — Correct. McCune-Albright syndrome is characterized by abnormalities in endocrine function, polyostotic fibrous dysplasia, and café-au-lait spots. The café-au-lait spots are generally large, respect the midline, and often have irregular, jagged borders, resembling

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Funding sources: None.
Conflicts of interest: None disclosed.
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JAAD Case Reports 2019;5:280-2.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.01.028

the coast of Maine. These spots are the presenting finding.[1]

B. LEOPARD syndrome – Incorrect. LEOPARD syndrome is a rare inherited disorder associated with multiple congenital anomalies also known as multiple lentigines syndrome. LEOPARD is an acronym for the major findings in this disease: multiple Lentigines, EKG (electrocardiogram) conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness.

C. Neurofibromatosis type 1 – Incorrect. The café-au-lait spots found in patients with neurofibromatosis type 1 typically have regular borders resembling the coast of California, are often smaller, and do not respect the midline. Although linear segmental variants of neurofibromatosis type 1 can present with larger, segmental café-au-lait spots, these lesions also typically have more regular borders.

D. Peutz-Jeghers syndrome – Incorrect. Patients with Peutz-Jeghers syndrome have multiple perioral lentigines and intestinal polyps and a predisposition for gastrointestinal tract and other malignancies. These patients do not typically have café-au-lait spots.

E. Legius syndrome – Incorrect. Almost all patients with Legius syndrome present with 6 or more café-au-lait spots. These café-au-lait spots are similar to those present in neurofibromatosis type 1, with their regular borders, smaller size, and crossing of the midline.

Question 2: Which of the following is NOT an endocrine abnormality associated with the syndrome that has this cutaneous finding?

A. Precocious puberty

B. Cushing syndrome

C. Hypophosphatemic rickets

D. Hyperthyroidism

E. Hyperparathyroidism

Answers:

A. Precocious puberty – Incorrect. Precocious puberty is reported to be associated with McCune-Albright syndrome.[1]

B. Cushing syndrome – Incorrect. Cushing syndrome is reported to be associated with McCune-Albright syndrome.[1]

C. Hypophosphatemic rickets – Incorrect. Hypophosphatemic rickets is reported to be associated with McCune-Albright syndrome.[2]

D. Hyperthyroidism – Incorrect. Hyperthyroidism is reported to be associated with McCune-Albright syndrome.[1]

E. Hyperparathyroidism – Correct. Precocious puberty, Cushing syndrome, hypophosphatemic rickets, and hyperthyroidism are all reportedly associated with McCune-Albright syndrome. Hyperparathyroidism is the only endocrinologic sequelae listed that has not been reported to be associated with McCune-Albright syndrome.[3]

Question 3: If this finding were associated with a syndromic condition, what gene mutation and mode of inheritance would be expected in this patient?

A. *SPRED1*; postzygotic mutation

B. *GNAS1*; autosomal dominant

C. *PTPN11*; autosomal dominant

D. *GNAS1*; postzygotic mutation

E. *STS*; X-linked recessive

Answers:

A. *SPRED1*; postzygotic mutation – Incorrect. Although McCune-Albright syndrome is caused by a postzygotic mutation, it is not a mutation in the *SPRED1* gene. Legius or NF1-like syndrome is caused by a postzygotic mutation in the *SPRED1* gene.

B. *GNAS1*; autosomal dominant – Incorrect. Although McCune-Albright syndrome is caused by a mutation in the *GNAS1* gene, it is not inherited in an autosomal dominant manner. Albright hereditary osteodystrophy is caused by a mutation in the *GNAS1* gene and is inherited in an autosomal dominant manner.

C. *PTPN11*; autosomal dominant – Incorrect. LEOPARD syndrome and not McCune-Albright syndrome is caused by a mutation in the *PTPN11* gene. The former is inherited in an autosomal dominant manner.

D. *GNAS1*; postzygotic mutation – Correct. McCune-Albright syndrome is caused by a nonheritable postzygotic mutation in the *GNAS1* gene. This mutation is found only in individuals demonstrating mosaicism.[4] The protein product of the *GNAS1* gene, $G_s\alpha$, is activated in excess as a result of this mutation, which overstimulates adenylyl cyclase,

leading to an overproduction of intracellular cyclic adenosine monophosphate.[5]

E. *STS*; X-linked recessive — Incorrect. X-linked ichthyosis and not McCune-Albright syndrome is caused by a mutation in the *STS* gene. The former is inherited in an X-linked recessive manner.

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