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DERMATOLOGY CLINIC
What's Your Diagnosis?

FACIAL LESIONS in a PRE-TEEN

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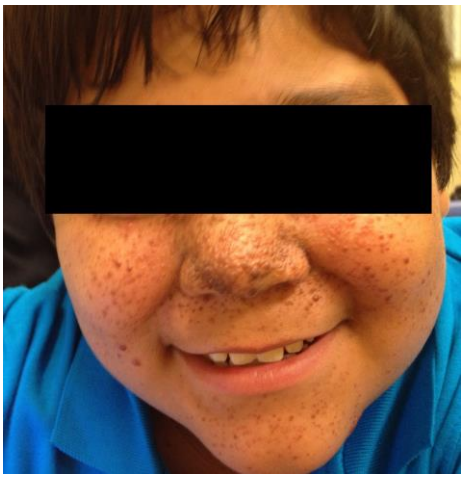
An 11-year-old Hispanic male with moderate mental retardation and a very happy disposition presents to your clinic for management of worsening pink-tan bumps on his cheeks, nose, chin and perinasal skin. He has had them for over 5 years. On history, mom reports that he has a fairly well-controlled seizure disorder. On examination, he also has many oval-shaped hypopigmented macules on his trunk, a few larger and indurated plaques on his back, as well as discrete café au lait macules. Mom is unsure if he has a heart murmur and he has no history of renal disease. There are no immediate family members with similar skin findings. Assuming a genetic condition, which of these skin findings was likely the first to develop?

A) Shagreen patch (collagenoma)
B) Café au Lait macules
C) Hypopigmented 'Ash Leaf' spots
D) Sebaceous Adenomas (angiofibromas)



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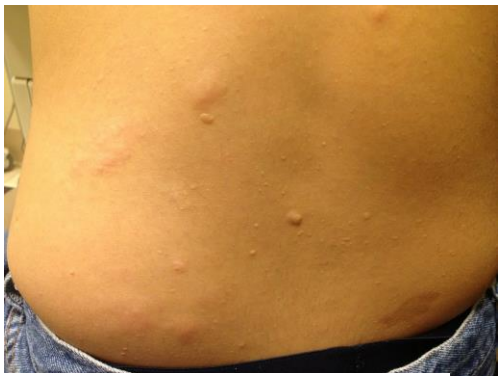

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ANSWER: C) Hypopigmented Macules

DISCUSSION

This patient has Tuberous Sclerosis Complex (TSC), a neurocutaneous syndrome that is characterized by classic features, including benign hamartomas of the skin, brain, heart, eyes, lungs, liver and kidneys. Up to 80% of cases are associated with de novo mutations in one of two genes, TSC1 (chromosome 9q; encodes for hamartin; 20% of cases) and TSC2 (chromosome 16p; encodes for tuberin; 60% of cases). Together, functional tuberin and hamartin form a complex that inhibits cell growth by regulating the mTOR signaling pathway (the complex switches Rheb from the active GTP-bound state to the inactive GDP-bound state). TSC1 mutations are associated with a milder phenotype than TSC2 mutations. Approximately 20% of cases are inherited (TSC1 and TSC2 mutations are about equal in this population), and may present with a family history. Diagnosis is made clinically. Genetics can be used to aid in diagnosis, but as gene mutations have not been discovered in 20% of cases, molecular testing is not dependable for ruling out the diagnosis. Since penetrance can be variable, it can be helpful to examine family members when the diagnosis is equivocal in a child.

Definitive diagnosis requires 2 major features (*) or 1 major and 2 minor features. Probable diagnosis if 1 major and 1 minor feature. Possible diagnosis if only 1 major feature or only 2+ minor features.

Skin Findings

- HYPOPIGMENTED MACULES* – These white patches are seen in 97% of patients at birth or soon after. They are usually on the trunk, but can be seen on the scalp and extremities (confetti lesions on shins, develop in adolescence or adulthood). They range in size from a few millimeters to a few centimeters, and tend to be persistent and stable in shape in size. Classic lesions are ash-leaf shaped, but they can be round, oval, linear or confetti-like. In fair-skinned children, they are best viewed in a darkened room with a Wood's lamp. At least 3 lesions are required for diagnosis.
- FIBROUS FOREHEAD PLAQUE* – Usually present at birth, single or multiple thickened plaques with follicular depressions can be seen on the forehead, cheeks or scalp in 25% of patients with TSC.
- FACIAL ANGIOFIBROMAS* (ADENOMA SEBACEUM) – These firm, pinkish, 1-4mm, dome-shaped papules are seen in 75% of patients with TSC. They usually develop between 2-6 years of age, but can develop earlier or as late as teens/20s. They are found around and under the nose, cheeks and chin. They can be mistaken for acne in preteens.
- SHAGREEN PATCH* (COLLAGENOMA, CONNECTIVE TISSUE NEVUS) – Characteristically found on the lower back, this thickened patch with peau d'orange-like texture is seen in 14-20% of patients in later childhood.
- PERIUNGUAL/SUBUNGUAL FIBROMAS ($\geq$2)* – These fibrous, indurated bumps develop around and under the fingernails and toenails (and sometimes the gingiva) are seen in 80% of post-pubertal patients. Early lesions may appear only as a longitudinal ridge in the nail plate.

Systemic Findings

- CNS – Seizures (seen in 80-90% of patients; may begin as infantile spasms that develop into focal or generalized seizures by age 2-3 years); Mental retardation (62% of patients; severity correlates with age of seizure onset); Cortical tubers* (50-75% of patients); Subependymal nodules*; Subependymal giant cell astrocytoma*; Cerebral white matter radial migration lines
- EYE – Retinal nodular hamartomas* (glioma/phakoma; present in 50% of patients); Retinal achromic patch
- CARDIAC – Rhabdomyomas* (usually asymptomatic and tend to regress spontaneously, but can result in CHF, murmur, cyanosis and sudden death in 1st year of life)
- LUNG – Lymphangioleiomyomatosis* (3% of adult women with TSC); Lung cysts
- RENAL – Angiomyolipomas (≥2)* (70% of patients); Multiple renal cysts (20-30% of patients; the TSC2 gene is contiguous with the polycystic kidney disease PKD1 gene, so cysts develop in patients with mutations in both TSC2 and PKD1)
- MSK – Dental pits (≥3); Osseous lytic lesions and periosteal thickening (85% of patients, esp hands/feet).

Ddx

Hypomelanotic macules in newborns and infants can be confused for nevus depigmentosus (usually single), nevus anemicus (not truly hypopigmented) or vitiligo (depigmented). Facial angiofibromas, collagenomas and confetti-like macules are also seen in MEN1 (up to 88%, 72% and 6%, respectively). Collagenomas can be mistaken for smooth muscle hamartomas, lipomas or plexiform neurofibromas (seen in Neurofibromatosis, together with café au lait macules).

Work-Up and Monitoring

The Tuberous Sclerosis Consensus Conference Guidelines for the Evaluation of Newly Diagnosed Children recommend:

- Head CT or MRI
- EEG, if patient has seizures
- Ophthalmologic (Fundoscopic) exam
- EKG, and follow up Echocardiogram, if needed
- Renal ultrasound
- Neurodevelopmental testing
- Oral exam (baseline)

The Tuberous Sclerosis Consensus Conference Guidelines for the Evaluation of Established TSC Patients recommend:

- Head CT or MRI every 1-3 years
- EEG, as needed for seizure management
- Renal ultrasound every 1-3 years
- Neurodevelopmental testing when child enters school, and again, if any educational or behavioral concerns
- Oral exam every 6 months
- Jaw X-ray by age 6-7 years to look for bone cysts

- Dermatology exam yearly, if patient has treatable skin lesions
- Chest CT in adult women only

Management

The prognosis of patients with TSC depends on the severity of their clinical phenotype, as well as their degree of neurologic involvement. The leading cause of premature death is status epilepticus and bronchopneumonia, secondary to neurologic issues.

- Seizure management – Anticonvulsant medications should be used to control seizure activity. Early treatment and early and consistent seizure prevention can reduce the risk of retardation and neurocognitive and developmental delay.
- Neurosurgical intervention – While the brain tumors associated with TSC are generally benign, they can become space-occupying, as well as increase intracranial pressure, leading to loss of vision, headaches, papilledema and nausea/vomiting. Routine imaging can diagnose lesions that may require removal or debulking.
- Facial angiofibromas – A cosmetic issue, these have classically been treated with cryotherapy, electrodessication, curettage, surgery or laser ablation.

New Therapies

mTOR (mammalian target of rapamycin) inhibitors have been successful in managing and/or reducing the severity of both the extracutaneous and skin manifestations of TSC. Oral rapamycin has demonstrated regression of brain astrocytomas, renal angiolipomas and lung lymphangioleiomyomas, as well as facial angiofibromas. Topical rapamycin 0.2% gel has demonstrated some efficacy in repigmenting hypomelanotic macules, as well as improving the appearance of facial angiofibromas, potentially reducing the need for long term systemic medications and/or surgical intervention. More studies are needed to determine optimum safety, dosing, formulation and treatment duration.

References

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