CLINICAL IMAGES

Inherited Patterned Lentiginosis: A Diagnosis of Exclusion

Nadia Hasan, DO,[1] Mari M. Batta, DO,[2] & Tamara B. Fedec, DO[3]

[1] PGY 3 Family Medicine Co-chief Resident, Lankenau Family Medicine Residency - City Line Family Medicine
[2] Milstein Batta Dermatology, LLC - Teaching Faculty, Lankenau Family Medicine Residency
[3] Associate Program Director, Lankenau Family Medicine Residency City Line Family Medicine

A 55-year-old female presented to her family physician with multiple dermatological complaints. She reported a skin lesion on her left thigh. It had been present for many years, but was enlarging and darkening over the past few months. The patient also reported a pruritic rash on her torso that was present for one week. She noticed it randomly and denied any recent outdoor camping or hiking activity, new lotions or detergents, or ingestion of new medication or food. She stated that she had multiple tan "spots" on her face and arms that she was never concerned about as they had been present her "whole life" and was a feature most of her family members had. The spots were not pruritic, and she had not noticed a change in appearance for as long as she could remember.

The patient's past medical history was significant for hypothyroidism, eczema, and chronic irritable bowel syndrome. She had no allergies. Her medications included levothyroxine 25 mcg daily and over-the-counter psyllium fiber daily. She revealed a family history of a father who died of an esophageal carcinoma at an unknown age, a living brother with myeloma, a living sister with systemic lupus erythematosus and a living mother with coronary artery disease. She reported that her mother, all four sisters, daughter, and son had the same tan macules on their face along their nose and cheeks, while sparing the oral mucosa.

The patient had a minimal smoking history of a few cigarettes per day for 5 years – she quit 32 years ago. She consumed alcohol socially and denied drug use.

Review of systems was positive for skin lesions, dry itchy skin, and irritable bowel with intermittent loose stool and constipation. Pertinent negatives included absence of fever, chills, hot or cold flashes, sudden weight gain or loss, hearing loss, chest pain at rest or on exertion, shortness of breath, and blood in her stool. All other review of systems was negative.

On physical exam, there was a violaceous red papule with one focal area of brown pigmentation on the left anterior proximal thigh. Biopsy revealed a benign hemangioma. There were pink hyperpigmented macules with fine scale located diffusely on the anterior trunk consistent with tinea versicolor, which was treated with a topical antifungal cream. There was a single 3 mm blue macule consistent with a blue nevus located on the right frontal scalp. The patient also had numerous 1-3 mm light tan macules in a photo distribution over her face, including eyelid margin and lips, consistent with lentigines [Figure 1]. These lentigines were also noted on the arms [Figure 2]. There were no lentigines seen on her bilateral palms or soles or her feet. There were grouped speckled brown macules with a solitary lighter tan patch located on the right posterior thigh indicating nevus spilus. Finally, there was a well marginated oval light tan macule under the right breast consistent with a café-au-lait macule.

Pertinent negatives on exam included the absence of lentigines on the buccal mucosa, palms of her hand and soles of her feet. She had a normal cardiac and abdominal exam, and there was no thyromegaly detected.

The patient had a normal colonoscopy with no evidence of polyps. A thyroid ultrasound was normal, as was the patient's electrocardiogram. The patient received an echocardiogram that was negative for structural or wall motion abnormalities and notably absent of cardiac myxomas. Pertinent lab values included hemoglobin 13.3 g/dl, fasting glucose 82 mg/dl, and a thyroid stimulating hormone of 3.86 mIU/L – all within normal limits.

QUESTIONS:

1. After a thorough imaging and lab work up that was negative for abnormality, what is the diagnosis?
   a. Carney Complex
   b. Inherited Patterned Lentiginosis
   c. LEOPARD syndrome
   d. Peutz Jeghers syndrome
   e. Squamous cell carcinoma

2. What differentiates the lentigines of Inherited Patterned Lentiginosis from Peutz Jeghers syndrome (PJS)?
   a. Lentigines can be present on buccal mucosa in PJS, whereas the buccal mucosa is spared in Inherited Patterned Lentiginosis.
   b. Lentigines of PJS histologically resemble ephelides (freckles)
   c. The lentigines seen in Inherited Patterned Lentiginosis are autosomal dominant.
   d. The lentigines seen in PJS get darker in adulthood
   e. There are no differences; the two conditions cannot be differentiated based on physical appearance alone.

3. The most serious and potentially fatal manifestation of Carney Complex syndrome is:
   a. Ovarian carcinoma
   b. Metastic melanoma
   c. Thyroid storm
   d. Cardiac myxoma
   e. Thrombotic thrombocytopenia purpura (TTP)

4. Differences between lentigines and ephelides include all of the following EXCEPT:
   a. Ephelides do not generally indicate systemic disease
   b. Lentigines will darken with sun exposure, whereas ephelides are not affected by UV light
   c. Ephelides histologically show increased melanin and a normal amount of melanocyte, whereas lentigines present histologically with increased melanocytes
   d. Lentigines are seen predominately in people of African descent, whereas ephelides are most common in northern and western European descent
   e. Lentigines appear on non-sun exposed skin, ephelides are typically are confined to sun-exposed skin

FIGURE 1:
Facial lentigines

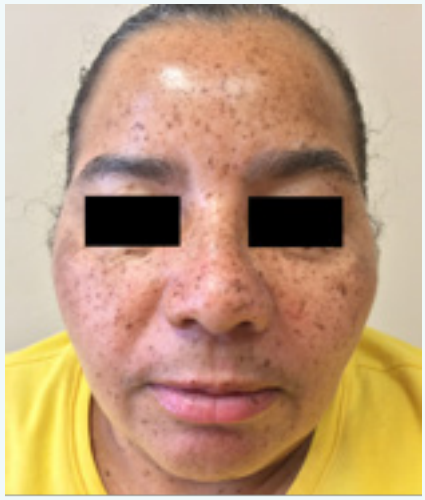
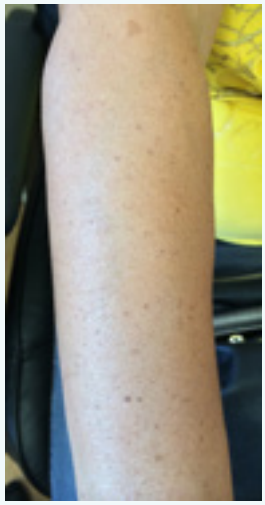


FIGURE 2:
Lentigines on forearms



ANSWERS

1. After a thorough imaging and lab work up that was negative for abnormality, what is the diagnosis?

The correct Answer is:

B) Inherited Patterned Lentiginosis

2. What differentiates the lentigines of Inherited Patterned Lentiginosis from Peutz Jeghers syndrome (PJS)?

The correct Answer is:

A) Lentigines can be present on buccal mucosa in PJS, whereas the buccal mucosa is spared in Inherited Patterned Lentiginosis.

3. The most serious and potentially fatal manifestation of Carney Complex syndrome is:

The correct Answer is:

D) Cardiac myxoma

4. Differences between lentigines and ephelides include all of the following EXCEPT:

The correct Answer is:

B) Lentigines will darken with sun exposure, whereas ephelides are not affected by UV light

DISCUSSION

The distribution and characteristics of the macules on the face and arms appeared consistent with lentigines. However, because the patient also presented with nevus spilus, blue nevus, and a café-au-lait macule, as well as gastrointestinal (GI) complaints, a family history of GI malignancy, and endocrine abnormality of hypothyroidism, further studies were obtained to rule out familial lentiginosis syndromes such as Carney complex and Peutz Jeghers syndrome.

Through a diagnosis of exclusion, the patient was determined to have Inherited Patterned Lentiginosis. Inherited patterned lentiginosis is an uncommonly described benign cutaneous condition originally described by John F O'Neill and William D James in 1989 in the Archives of Dermatology.[1] Although rarely studied or noted in research articles, this condition appears to be inherited in an autosomal dominant fashion and is most commonly seen in lighter-pigmented African Americans, particularly those with mixed American Indian heritage.[2] Cutaneous findings include lentigines, which are small hyperpigmented macules that present in early childhood[1] and often increase in amount as a child ages and enters puberty.[2] These lentigines are commonly found on the central face, lips, as well as hands, elbows, and buttocks. There is sparing of the mucous membranes. In contrast to other lentiginosis syndromes, there are no associated systemic diseases and it is therefore a benign condition.[3]

While lentigines often clinically resemble ephelides (freckles), lentigines typically do not darken with sun exposure and can appear on non-sun-exposed skin. Histologically, a lentigo will show basal cell layer hyperpigmentation with increased number and hyperplasia of melanocytes.[4] In contrast, ephelides generally present with increased melanin within basal keratinocytes and a normal number of melanocytes.

The differential diagnosis for facial lentigines are familial lentigines syndromes, including Peutz-Jeghers syndrome (PJS), Carney Complex (CNC), LEOPARD syndrome, and Cronkhite-Canada syndrome, as well as more rare disorders, such as Laugier-Hunziker syndrome. Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder that usually presents in early teenage years. It is a mutation of the STK11 gene on chromosome 19p13.3.[5] Cells overgrow characteristically in the GI tract and manifest as multiple hamartomatous polyps. Rarely, polyps have been reported in ureters, nasal and respiratory tracts, and the gallbladder.[6]

The hamartomatous polyps of PJS have a high risk of turning into malignant carcinoma, and patients have a greater likelihood of developing other cancers including breast, cervical, GI, pancreatic, and endometrial carcinoma. One meta-analysis has cited a 93% cumulative risk of developing cancer.[6] It is therefore imperative that this condition be diagnosed early with colonoscopy and endoscopy so cancer screening can be implemented immediately.[5,6]

Cutaneous manifestations of PJS that are similar to inherited patterned lentiginosis include multiple 1-5 cm blue-gray to brown macules found around the eyes, nostrils, mouth, and occasionally on hands, feet and anal region.[6] The lentigines are seen in 95% of patients affected with PJS, and tend to be most visible in childhood, fading by adulthood.[7] A key difference between PJS and inherited patterned lentiginosis is the presence of lentigines on buccal mucosa in PJS.

Diagnostic criteria for PJS require at least one of the following: 1) 2 or more polyps histologically confirmed to be PJS, 2) any number of polyps plus a family history of PJS, 3) mucocutaneous pigmentation plus a family history, 4) Peutz Jegher polyps and mucocutaneous pigmentation.[8]

Carney Complex (CNC) is an autosomal dominant disorder associated with a mutation of the PRKAR1A gene on chromosome 17q22-24.[7] Cardiac myxomas are the most serious manifestation of CNC with a 16% sudden cardiac death rate.[9] Endocrine tumors and therefore endocrine hypo-and hyper-activity are also a common finding. Primary pigmented nodular adrenocortical disease, growth hormone-secreting pituitary adenomas, thyroid carcinomas, testicular tumors and ovarian cysts have all been associated with CNC.[9]

Cutaneous manifestations of CNC include lentigines located on the conjunctiva and vermilion border of lips that are most noticeable in adolescence and fade with age. Blue nevi of less than 5 mm have been reported on the face, trunk and limbs. Café-au-lait macules, nevus spilus, and cutaneous myxomas are also present, with the myxomas seen on the face, ears and trunk in 30-55% of patients.[4]

Diagnosis usually begins with findings suggestive of CNC based on the cutaneous manifestations and family history. Testing for endocrine abnormalities initially include thyroid panels, blood glucose, and urinary cortisol. If abnormal, plasma adrenocorticotropic hormone (ACTH), growth hormone (GH), insulin-like growth factor and dexamethasone suppression testing can be performed. Patients should be evaluated with echocardiogram to rule out a cardiac myxoma. Other imaging may be performed based on lab values and clinical suspicion, including adrenal CT scans, thyroid US, testicular US, ovarian US, and pituitary MRI.[7]

LEOPARD syndrome is a rare autosomal dominant disorder caused by a mutation of the PTPN11 gene on chromosome 12q24.1.[10] Its name is an acronym for the various manifestations of this syndrome: Lentigines, Electrocardiogram abnormalities, Ocular hypertolerism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness. The lentigines of LEOPARD syndrome are found primarily on the upper trunk and face, but not oral mucosa – a feature that distinguishes it from PJS but is similar to inherited patterned lentiginosis. Unlike PJS and CNC, the lentigines start in infancy and then increase in number with age. Often, lentigines are the first clinical clue to diagnosis,[10] and it is made if lentigines plus two of the other features are present. If lentigines are absent (only 10% of cases), diagnosis is established if a first degree relative is affected and three of the aforementioned features are present.[7]

Cronkhite–Canada syndrome (CCS) is a rare, non-familial syndrome that presents around the 6th decade. It is characterized by hamartomatous polyps throughout the GI tract that are phenotypically similar to those seen in PJS. These polyps are associated with other mucosal changes and protein losing enteropathy that lead to severe malabsorption.[11] A patient will present with sudden onset severe malnutrition, as well as alopecia, onycholysis and lentigines of the palms and dorsal hands. Lentigines have not been reported on the face or buccal mucosa.[12]

Laugier-Hunziker syndrome (LHS) is a benign acquired syndrome where 2-5 mm blue-black and brown macules appear as either solitary or multiple lesions commonly on the tongue and gingiva. They are seen after puberty and histologically look more like ephelides than lentigines, with increased melanin and normal melanocytes. Additionally, buccal mucosa and nails can be involved 60% of the time.[13]

CONCLUSION

A 55 year old African American female presented with lentigines and other cutaneous and systemic abnormalities that raised suspicion for systemic disease. A full work up was obtained and all results were benign, ruling out familial lentiginosis syndromes. The lentigines on her face were not bothersome, and the patient opted to conservatively manage with monthly self-skin checks, daily sunscreen application and strict photo protection, and routine follow up with her dermatologist. If the patient had opted for skin treatment, her PCP could refer her to dermatology for intense pulsed light source (IPL) therapy, which has been shown to completely clear facial lentigines caused by PJS.[14] There are multiple other types of lasers that have also been shown to lighten or completely remove lentigines.[15] There are skin-lightening agents that can be prescribed that have been shown to lighten lentigines, but a prescriber should be experienced in such agents and use with caution, especially if they are to be applied to face. Agents used alone, in combination therapy or as an adjuvant to cryotherapy include fluocinolone acetonide 0.01%, hydroquinone 4% and tretinoin 0.05%.[16]

Inherited patterned lentiginosis, a diagnosis of exclusion, is highly prevalent in the African American community, but has gained minimal attention in medical research and literature due to its benign nature. It poses no harm to patients, does not progress, and usually does not get formally diagnosed.[1,3] However, if a patient presents with the cutaneous presentation of inherited lentigines along with any of the signs and symptoms of an underlying systemic disease, it is imperative to be aggressive in ruling out other conditions, as lentigines may be the first indication of a more serious issue.

REFERENCES

1. O'neill, J. F., and W. D. James. "Inherited Patterned Lentiginosis in Blacks." Archives of Dermatology 125.9 (1989): 1231-235. Web < http://archderm.jamanetwork.com/article.aspx?articleid=550865>.
2. Bolognia, Jean, Joseph L. Jorizzo, and Julie V. Schaffer. "Neoplasms of the Skin." Dermatology. 3rd ed. Philadelphia: Elsevier Saunders, 2012. 1854-855. Print.
3. James, William D., Dirk M. Elston, Timothy G. Berger, and George Clinton Andrews. "Melanocytic Nevi and Neoplasms." Andrews' Diseases of the Skin: Clinical Dermatology. 11th ed. London: Saunders/ Elsevier, 2011. 677. Print
4. Horvath, Anelia, and Constantine A. Stratakis. "Carney Complex and Lentiginosis." Pigment Cell & Melanoma Research 22.5 (2009): 580-87. Web < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136757/>.
5. Li, Yonggjian, Qinghai Zeng, Zhiling Liao, Rong Xiao, Guiying Zhang, and Haiquan Wen. "Peutz-Jeghers Syndrome and Family Survey: A Case Report." International Journal of Clinical and Experimental Pathology 6.5 (2013): 982-84. Web < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3638114/>.
6. Kopacova, Marcela. "Peutz-Jeghers Syndrome: Diagnostic and Therapeutic Approach." World Journal of Gastroenterology 15.43 (2009): 5397. Web < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2778095/>.
7. Lodish, Maya B., and Constantine A. Stratakis. "The Differential Diagnosis of Familial Lentiginosis Syndromes." Familial Cancer 10.3 (2011): 481-90. Web < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3417307/>.
8. Lim W, Hearle N, Shah B, et al. Further observations on LKB1/STK11 status and cancer risk in Peutz-Jeghers syndrome. Br J Cancer 2003; 89:308. Web < http://www.nature.com/bjc/journal/v89/n2/full/6601030a.html>
9. Bertherat, Jerome. "Carney Complex (CNC)." Orphanet Journal of Rare Diseases. BioMed Central, 06 June 2006. Web< http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1513551/>.
10. Sarkozy A, Digilio MC, Dallapiccola B. Leopard syndrome. Orphanet J Rare Dis 2008; 3:13. Web < http://www.ojrd.com/content/3/1/13>.
11. Samoha, Smadar, and Nadir Arber. "Cronkhite-Canada Syndrome." Digestion 71.4 (2005): 199-200. Web < http://www.karger.com/Article/PDF/86134>.
12. Provost, Thomas T., and John A. Flynn. Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease. Hamilton, Ont.: B.C. Decker, 2001. Print.

13. Wang, Wen-Mei, Xiang Wang, Ning Duan, Hong-Liu Jiang, and Xiao-Feng Huang. "Laugier–Hunziker Syndrome: A Report of Three Cases and Literature Review." International Journal of Oral Science. Nature Publishing Group, n.d. Web. 14 July 2015. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3633062/>.

14. Remington, B. Kent, and Todd K. Remington. "Treatment of Facial Lentigines in Peutz-Jeghers Syndrome With an Intense Pulsed Light Source." Dermatologic Surgery Dermatol Surg 28.11 (2002): 1079-081. Web. http://journals.lww.com/dermatologicsurgery/pages/articleviewer.aspx?year=2002&issue=11000&article=00021&type=abstract

15. Todd, Michael M., Tena M. Rallis, John W. Gerwels, and Tissa R. Hata. "A Comparison of 3 Lasers and Liquid Nitrogen in the Treatment of Solar Lentigines." Arch Dermatol Archives of Dermatology 136.7 (2000): n. pag. Web. <http://archderm.jamanetwork.com/article.aspx?articleid=190439>.

16. Hexsel, D., C. Hexsel, M.d. Porto, and C. Siega. "Triple Combination as Adjuvant to Cryotherapy in the Treatment of Solar Lentigines: Investigator-blinded, Randomized Clinical Trial." Journal of the European Academy of Dermatology and Venereology J Eur Acad Dermatol Venereol 29.1 (2014): 128-33. Web. <http://www.ncbi.nlm.nih.gov/pubmed/24684165>.