Cutaneous Hyperpigmentation: A Rare Extra-Intestinal Manifestation of Celiac Disease

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Abstract

Celiac disease has many manifestations. In paediatric population, it is usually presented as malabsorption with chronic diarrhea and poor growth. This female child of 3.5 year old from Shabwa governorate was presented to us with anemia required frequent blood transfusions and black discoloration of skin particularly of hands and feet. There was no gastrointestinal symptoms. Her growth parameters and rest of clinical picture was normal apart from paleness and skin black discoloration. Her initial investigations showed low Hb, normal WBC and Plat count, blood film showed leukoerthoblastic picture with increased number of atypical lymphocyte, and Bone Marrow Aspiration was inconclusive, but no blast cells. No definite diagnosis was made. Because of the long standing suffering, the family decided to take her abroad (Egypt). She was investigated there and found to have megaloblastic anemia secondary to celiac disease. She was put on vitamin B12 injection, folic acid and gluten free diet. Her condition was dramatically improved and when we saw her few weeks later in Mukalla she was complete normal with normalization of her CBC and disappearance of the skin discoloration.

Keywords: Celiac disease, megaloblastic anemia, cutaneous hyperpigmentation

Background:

Celiac disease is an immune mediated enteropathy triggered by gluten in genetically susceptible individual. Genetic, environment and immunological factors play an essential role in its pathogenesis [6,9]. The disease has a wide range of manifestations. In children the most common is intestinal while in adult mainly extra-intestinal [7].The hallmark pathophysiologic mechanism of megaloblastic anemia is an impairment of DNA synthesis in all nucleated cells secondary to vitamin B_{12} (B_{12}) and/or folate deficiency, resulting in nuclear-cytoplasmic asynchrony; distinctive megaloblastic changes, increased apoptosis, and ineffective hematopoiesis in the bone marrow[6,4]. The manifestations of megaloblastic anemia are diverse and may range from nonspecific signs and symptoms of anemia to gastrointestinal disturbances and potentially fatal neuropsychiatric and cardiovascular disorders [10] . Anemia is a common finding in celiac disease due to the malabsorption of iron and other elements such as folic acid and vitamin B12 (cobalamin) causing megaloblastic anemia.

Cutaneous hyperpigmentation which has been sporadically reported in the literature, is an often missed or overlooked clinical sign in megaloblastic anemia. They are most marked on the hand and feet (see pictrure).

The exact mechanism causing hyperpigmentation is complex and poorly understood, although is believed that vitamin B12 deprivation in the melanocyte associated with low methylcobalamin and reduced glutathione which in turn leading to increased tyrosinase activity in melanin synthesis pathway [5,8].

Case report:

A 3.5 year old female child from Shabwa governorate/Yemen, presented to us at Mukalla Maternity & Children history with history of severe anemia required multiple blood transfusions, and black discoloration of both hand and feet over the last few months. Her systemic review revealed no gastrointestinal such as diarrhea, vomiting, pain, or respiratory symptoms such as cough, dyspnea, chest pain and rest of system review was nil of note. Her nutritional history: she was breastfed for the first couple of months then artificial milk with mixed diet including cereals, introduced at the end of the first year of life.

She was a product of full term spontaneous vaginal delivery for a second degree relatives and had normal neonatal period. She had other 3 siblings whom they were well and alive. Her vaccination was up-to-date. Her examination was normal apart from pale conjunctivae and diffuse black discoloration of the palms and feet (see Figures No 1&2), in addition to the soft systolic murmur of anemia.

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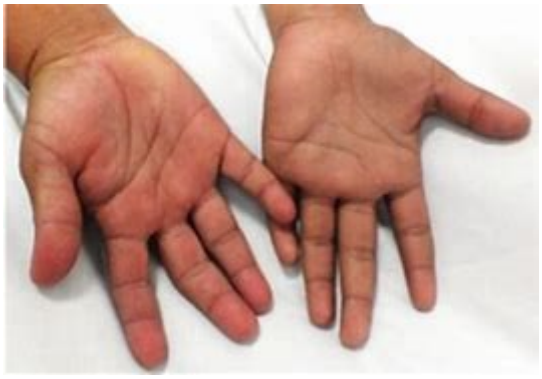

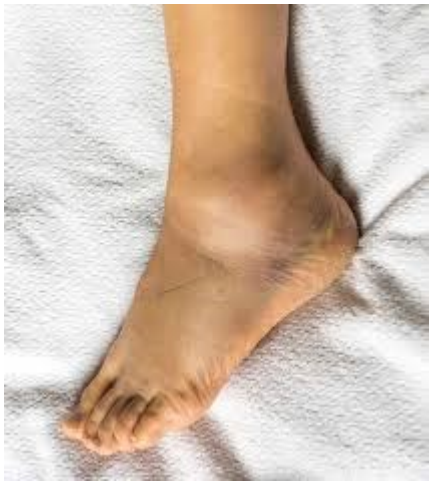

Figure (1) and Figure (2) shows diffuse black discoloration of the palms and feet of the patient

Patient's investigations showed complete blood count CBC): total WBC: 12.1x10^9/L, Neutrophil 11.4%, lymphocyte 88.1% and Hb: 4.7gm/dl, MCV: 89.1 fl, Plat: 139x10^9/L blood film showed leukoerythoblastic, normocytic macrocytic anemia picture with atypical lymphocytes of 15%, no blast was seen, liver and renal profiles were normal. Stool examination was normal and no occult blood. Bone marrow aspiration was done and the result was inconclusive with no blast seen, and suggestive of hemolytic anemia.

In view of the apparent black discoloration of the feet, Ultrasound was asked to evaluate the patency of the blood vessels, and was reported to be normal. She had been seen by dermatologist at Ibn-Sina hospital in Mukalla and no diagnosis was made for her black discoloration.There was no explanation of the black discoloration hands and feet, and no definite cause of her anemia.

The family decided to take her abroad (Egypt). She was investigated there. Her investigations revealed: complete blood count (CBC): Hb: 5.3 gm/dl, total leucocyte count: 10,100 mm^3 with lymphocyte of 93% and segmented leukocyte of 5%, platelet: 53,000 mm^3 , MCV: 89.7 fl, reticulocyte count: 0.05%, and blood film showed marked normochoromic normocytic anemia, marked absolute neutropenia and moderate thrombocytopeni. Bone marrow showed a picture of Megaloblastic anemia.

She was diagnosed as a case of megaloblastic anemia and the family was told that the black discoloration is secondary to vitamin B12 deficiency. She was sent to Paediatric gastroenterologist & nutritionist who asked for celiac disease screening which revealed tissue Transglutaminase IgA positive of 110 unit (Normal < 20), transglutaminase IgG negative and serum IgA was normal for her age (93,0 mg/dl). Intestinal biopsy was not done. (These were the only investigations brought by the father). The hematologist put her on vitamin B12 injection, folic acid and gluten free diet (a list of diet which contained gluten was given to the family). Her condition was dramatically improved and when we saw her few weeks later at our hospital (Maternity & children hospital) in Mukalla she was completely normal with normalization of her CBC and disappearance of the skin discoloration.

Discussion:

Celiac disease has extremely varied clinical presentation which may occur singly or in combination, and the age at onset can be anytime from infancy to late in adult life [2]. Anemia is one of its most associated finding and it may be found without associated intestinal symptom as in our case. The anemia could be due to any of the hematinic (iron, vitamin B12 or folate) deficiency. In megaloblastic type that is due to vitamin B12 or folate deficiency other cytopenia could be resulted (leukopenia and/ or thrombocytopenia) [3].

Megaloblastic anemia associates with different skin manifestations such as hyperpigmentation, vitiligo and hair changes. In our case hyperpigmentation was present which is consistent with finding of Somanath Padhi et al. who reported Twenty-one (84%) of 25 megaloblastic anemia had skin hyperpigmentation [8]. Celiac disease could be presented without intestinal symptoms as in our case [2]. Skin manifestation could be the only

presenting feature of vitamin B12 deficiency as reported by Kannan & Ming Ng [7].

In children unexplained cytopenia alone or in combination should raise the suspicion of celiac disease, hence detailed diet history and necessary investigations are needed. In addition the presence of unexplained skin hyperpigmentation needs the exclusion of megaloblastic anemia.

Conclusion

A high index suspicion of megaloblastic anemia should be maintained in patient with cutaneous hyperpigmentation of feet and hand and in the presence of cytopenia (s). It should prompt an investigation for celiac disease.

References:

1- Brescoll J, Daveluy S. A review of vitamin B12 in dermatology. Am J Clin Dermatol. 2015; 16:27–33.

2- Ediger TR, Hill ID. Celiac disease. Pediatrics in review. 2014; 35 (10): 409-415

3- Fisgin T, Yarali N, Duru F, Usta B, Kara A. Hematologic manifestation of childhood celiac disease. Acta Haematol. 2004;111(4):211-4

4- Hoffbrand AV. Megaloblastic anemias. In: Fauci AS, Brunwald E, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008. pp. 643–651.

5- Hoffman, C.F., Palmer, D.M., *and* Papadopoulos, D. (2003). Vitamin B12 deficiency: a case report of ongoing cutaneous hyperpigmentation. Cutis 71, 127–130.;

6- Kliegman RM, Behrman RE, Jenson HB, Stanton BF. NELSON TEXTBOOK OF PEDIATRICS, 18th ed**.** Philadelphia: Saunders Elsevier Inc, 2007; 335-2

7- Kannan R, Ming Ng MJ, Cutaneous lesions and vitamin B12 deficiency: An often-forgotten link. Can Fam Physician. 2008 Apr; 54(4): 529–532.

8- Padhi S., Sarangi R.L., Ramdas A., Ravichandran K., Varghese R.G., Alexander T., Kurian G., Mookkappan S. Cutaneous hyperpigmentation in megaloblastic anemia: a five-year retrospective review. Mediterr J Hematol Infect Dis 2016, 8(1): e2016021, DOI

9- Shamir Raanan. Advances in celiac disease. Gastroenterol Clin N Am 32 (2003) 931–947

10- Stabler SP. Vitamin B12 deficiency. N Eng J Med. 2013;368:149–160

تقرير حالة

اسوداد الجلد: عرض نمطي نادر لحالة فقر الدم ضخم الخلايا القاعدية (الارومات megaloblastic) الناتج عن مرض تحسس القمح (سيلياك)

نور عبدالعزيز بن كروم عمر عبدالرحمن باوزير

فائزه سالمين ناجي

الملخص

يظهر مرض تحسس القمح بأنماط مختلفة سوى في الجهاز الهضمي او خارجه. أو في الأطفال شائعا مايكون في الجهاز الهضمي على شكل إسهال مزمن وعوز في النمو. هذه حالة طفلة عمرها 3.5 سنة من شبوة عانت من فقر دم شديد تطلب نقل دم متكرر مع وجود سواد في جلد اليدين والقدمين. تاريخها المرضي لم يكن فيه أي أعراض للجهاز الهضي. فحوصاتها الأولية بما فيها بزل نخاع العظم لم تنتج عن أي تشخيص نهائي. ونظرا لمعاناة العائلة المزمن سافرت المريضة إلى مصر وهناك عملت لها الفحوصات اللازمة وشخصت بفقر الدم ضخم الخلايا القاعدية (الأرومات Megaloblastic anemia) ناتجا عن تحسس القمح. اعطيت لها إبر ب 12 مع حامض الفولك والامتناع عن كل المأكولات الحاوية على قلوتين القمح (gluten) تحسنت المريضة كثيرا وعند معاودتها لنا بعد عدة أسابيع كانت جميع فحوصاتها طبيعية واختفى سواد الجلد تماما.

كلمات مفتاحية: مرض تحسس القمح، فقر الدم ضخم الخلايا القاعدية، اسوداد الجلد.