Cutaneous Manifestations of Cobalamin Deficiency in Bowel Resection Patient with Thalassemia Trait

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ABSTRACT:
A 32-year-old male patient with a history of ileum dissection due to blunt abdominal injury, a history of bacterial overgrowth, and beta thalassemia traits, presented with hyperpigmentation at palms, gingivae, nails, and premature greying of hair. His hematologic conditions included megaloblastic anemia. Peripheral blood smear revealed hypersegmented neutrophils. The bone marrow biopsy showed neucleocytoplasmic asynchrony. Neurological examination was completed without significant finding of proprioception loss or ataxia. The cobalamin level was confirmed as low level. One mg of B12 was intramuscularly injected daily for a week and 1 mg intramuscular injection weekly. One month following, the hair showed repigmentation.
Key words: Vitamin B12, Bowel Resection, Hyperpigmentation, Depigmented Hair, Grey Hair

A 32-year-old Thai male patient presented with diarrhea and steatorrhea for 9 months. He had loss of appetite, and weight loss for 10 kilograms. He was admitted and dermatologist was consulted for hyperpigmentation. His medical history included colonic perforation due to blunt abdominal injury. He underwent right hemicolectomy with ileocecal valve resection for 10 cm at the age of 18. He had beta thalassemia trait with baseline at hemoglobin 9-10 mg/dL and history of small intestinal bacterial overgrowth. His current medications were vitamin D2 60000 IU/week, $CaCO_3$ 3000 mg/day, folic acid 5 mg/day, double-dose of vitamin B1-6-12 (100 mg-5 mg-50 µg), and double-dose of multivitamin.

Physical examination revealed moderately pale, no sensation nor proprioception loss. Dermatological manifestations included multiple well-defined hyperpigmented linear patches along upper and lower attached gingivae (Figure 1), hyperpigmented bands and patches at 1^{st}-4^{th} fingernails of both hands (Figure 2), increased hyperpigmentation of palmar creases (Figure 3), and depigmented hair (Figure 4).

The initial laboratory test showed hemoglobin 10 g/dL with MCV 77.8 fl (baseline 67 fl, 76.5-94.2 fl) RDW 32% (12.2-14.5%). Peripheral blood smear was noted as hypochromic, poikilocytosis 2+, anisocytosis 2+, macroovalocyte, microcytic RBC, few pencil cells, hypersegemented neutrophils, large platelet with dysplastic features. Bone marrow biopsy was performed and revealed hypercellular marrow, erythroid hyperplasia, giant myeloid cells, hypersegmented neutrophils, and neucleocytoplasmic asynchrony. Vitamin B12 level was confirmed as low at 65.3 pg/ml (199-771 pg/ml) and the patient was diagnosed with vitamin B12 deficiency.

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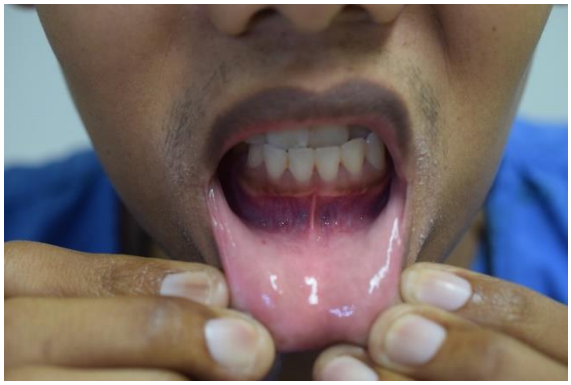

Figure 1 Gingival hyperpigmentation

Figure 2 Nail changes - hyperpigmentation

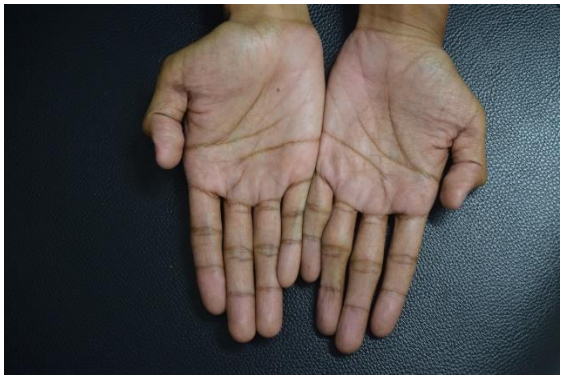

Figure 3 Palmar crease hyperpigmentation

Vitamin B12 or cobalamin is an essential water-soluble vitamin that plays roles in methionine and tricarboxylic acid cycle and both processes are vital for DNA synthesis[1]. Cobalamin is a coenzyme to form methionine which needs to turn folate cycle and produce thymidine required in DNA synthesis. Otherwise, cobalamin as adenosylcobalamin is a cofactor involved in tricarboxylic acid cycle and heme biosynthesis[1,2]. According to all relevance, cobalamin deficiency precedes the clinical signs in dermatologic, hematologic, and neurologic conditions.

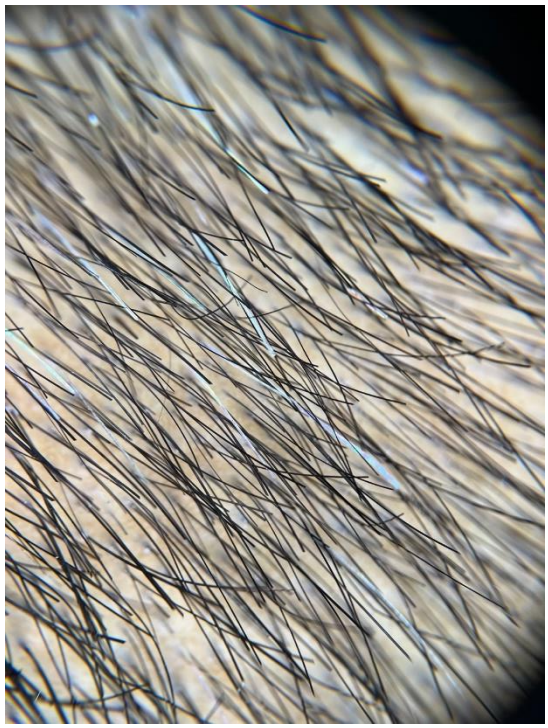

Figure 4 Premature greying of hair

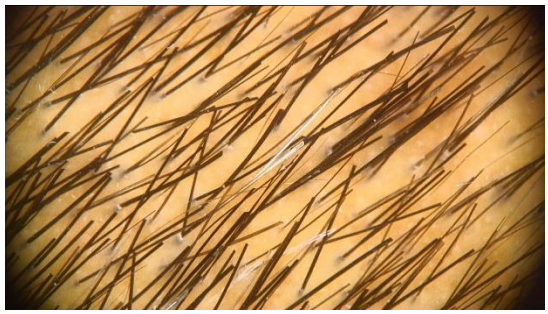

Figure 5 Repigmentation of hair after 1 month of treatment

Vitamin B12 is abundant in animal food sources such as meat, liver, eggs, fish, and dairy products. B12 compound in food is unbounded by acid in stomach and cobalamin binds with haptocorrin, produced by salivary gland, to protect cobalamin from acid degradation. Afterward, the compound is conducted to the duodenum. In the proper environmental pH, cobalamin is shifted to bind with intrinsic factor, produced by the gastric parietal cell, and proceeds to distal ileum for absorption[1]. B12 is absorbed into the bloodstream and distributed to cells that have dominant storage in the liver.

The etiology of vitamin B12 deficiency has 3 main mechanisms. First, inadequate intake of high B12 dietary such as poor intake, strict vegetarian, and exclusive breastfed infants from low vitamin B12 mothers. Second, malabsorption could be sorted into 4 groups including 1) decrease gastric acidity which inadequately unbounded the B12 compound in food e.g., long-term use of proton pump inhibitor or histamine 2 receptor antagonist 2) decrease intrinsic factor e.g., pernicious anemia, chronic atrophic gastritis, postgastrectomy, bariatric surgery 3) imbalance and interfere of gut microbiota e.g., bacterial overgrowth, *Diphyllobothrium latum*, and *Giardia lamblia* infestation 4) impaired absorption e.g., inflammatory bowel disease such as Crohn disease, Zollinger-Ellison syndrome, celiac disease, short-bowel syndrome, metformin. Finally, inborn error diseases related to transporters or interfering in cobalamin metabolism[1].

An early sign of vitamin B12 deficiency is linear glossitis[3]. However, angular cheilitis and Hunter's glossitis or atrophic glossitis are more common for mucositis in vitamin B12 deficiency. The character of atrophic glossitis includes atrophic, red, and painful tongue with atrophy of the filiform papillae.

Abnormal pigmentation is the key feature of vitamin B12 deficiency. Physical examination shows localized hyperpigmentation at the knuckle, as an early sign[12], the palmoplantar creases, flexural areas, generalized hyperpigmentation[5], nail changes, and depigmentation of hair[6]. Vitamin B12 plays a part in 3 main mechanisms in hyperpigmentation. Firstly, vitamin B12 maintains glutathione levels which act in inhibiting tyrosinase enzyme and melanin synthesis pathway. Secondly, micro-ophthalmia-associated transcription factor (MITF) is activated and simultaneously activates tyrosinase enzyme and melanin synthesis. Lastly, methylcobalamin takes part in turning homocysteine into methionine. Therefore, homocysteine level is accumulated and leads to turn dopaquinone into melanin in cobalamin depletion[5].

For extracutaneous manifestations of vitamin B12 deficiency, hematologic manifestations have been reported as megaloblastic anemia, hypersegmented neutrophils, neutropenia, thrombocytopenia, and pancytopenia. Moreover, a previous study has described a significant association between megaloblastic anemia and the presence of hyperpigmentation[5]. To summarize, complete physical examination including dermatologic examination will reveal the nutritional underlying diseases. Besides, neurological manifestations have been recognized as peripheral neuropathy, cognitive impairment[1,] and subacute combined degeneration of the spinal cord which is related to demyelination affecting the dorsal column and lateral corticospinal tracts resulting in proprioception defect and ataxia[7].

In diagnostic markers for B12 deficiency, serum B12 level is the first line. In symptomatic patients with obvious risks of inadequate intake or malabsorption, cut-off point of serum B12 level is < 200 pg/mL (<148 pmol/L)[9]. In asymptomatic population, cut-off point for diagnosis vitamin B12 deficiency is <150 pg/mL (<111 pmol/L). In case of cobalamin level between 150-200 pg/mL in non-specific

suspicions, serum cobalamin should be repeated in 1-2 months and second line marker such as serum methylmalonic acid should be performed.[9] In addition, all markers have limitation.[10] False low level of serum cobalamin could be detected in multiple myeloma, haptocorrin deficiency, folate deficiency, and oral contraception. Serum methylmalonic acid may be false elevation in renal dysfunction. Therefore, there is no gold standard diagnostic test in vitamin B12 deficiency and clinical correlation are obligatory.

For treatment, cobalamin should be considered as daily 1 mg intramuscular route for 1 week for patients with severe neurologic symptoms or malabsorption. In non-urgent patients with mild form of malabsorptive function, cobalamin loading dose should be initiated with 1-2 mg oral daily dose which shows equivalent efficacy to parenteral route in patients without malabsorption. In case of dietary deficiency, oral daily high dose at least 6 µg of B12 should be replaced the deficit over 3-4 months.[1] For maintenance phase, 100-300 mcg of cobalamin is required monthly to preserve tissue storage which equals 2.4 mcg daily. Since the bioavailability of cobalamin is 0.5-4%, oral doses of cobalamin 1 mg/day are suggested for maintenance in normal absorption group[1]. However, patients with malabsorption must be supplemented with parenteral route and cost-effectiveness is considered in the setting where intramuscular injection is inexpensive for oral cobalamin use[8].

After treatment, hematological conditions could be responded to in approximately 5 days, but neurological response is slower[1]. Regarding literature reviews, mucocutaneous changes and hyperpigmentation usually respond within 8-12 weeks[5].

According to prevention of vitamin B12 deficiency in risk patients, monitoring cobalamin level is recommended in addition to clinical assessment. Cobalamin supplement in asymptomatic patients with cobalamin level 150-200 pg/mL is considered in patients with pregnancy and breast-feeding and in patients who have persistent reduced cobalamin level at 150-200 pg/mL in following 1-2 months, oral low dose 50 µg of cobalamin supplement is suggested for 4 weeks with repeating serum cobalamin level at 3-4 months as guideline recommendation[9].

Another point to consider is that in patients with surgery affecting vitamin B12 absorption, monitoring cobalamin level and prophylactic supplementation are recommended.[9] Even though oral supplement is inadequate, there is no prospective studies about intramuscular cobalamin supplementation in patients who have surgery affecting vitamin B12 absorption.[9] In bariatric surgery, oral supplementation 1 mg/wk or 250-350 µg/day is suggested in gastric bypass, and 1 mg/month or 3 mg every 6 months intramuscularly for other surgery.[11]

There are several learning points in this patient. Firstly, serum cobalamin level should be monitored and followed up after the ileocecal resection for early detection. Secondly, because of the ileal resection where is the most active area for B12 absorption, the route of supplementation should be concerned. Lastly, cobalamin level should be repeated following the supplementation to confirmed that patient received adequate requirement and optimal for healthy function.

We report infrequent disease as vitamin B12 deficiency presented with hyperpigmentation at palms, gingivae, premature greying of hair, with hematologic conditions including megaloblastic anemia and hypersegmented neutrophils. In this patient, a gastrointestinal and nutritional specialist were consulted. Chronic diarrhea in this patient was treated as small intestinal bacterial overgrowth syndrome with metronidazole along with 1 mg B12 was intramuscularly injected daily for a week and 1 mg intramuscular injection weekly. One month following, despite of persist skin

hyperpigmentation, the hair significantly showed repigmentation (Figure 5).

References

1. Green R, Allen LH, Bjørke-Monsen AL, et al. Vitamin B_{12} deficiency. Nat Rev Dis Primers 2017;3:17040.
2. Ge Y, Zadeh M, Mohamadzadeh M. Vitamin B12 Regulates the Transcriptional, Metabolic, and Epigenetic Programing in Human Ileal Epithelial Cells. Nutrients 2022;14:2825.
3. Graells J, Ojeda RM, Muniesa C, Gonzalez J, Saavedra J. Glossitis with linear lesions: an early sign of vitamin B12 deficiency. J Am Acad Dermatol 2009;60:498-500.
4. Radochová V, Slezák R, Radocha J. Oral Manifestations of Nutritional Deficiencies: Single Centre Analysis. Acta Medica (Hradec Kralove) 2020;63:95-100.
5. Padhi S, Sarangi R, Ramdas A, et al. Cutaneous Hyperpigmentation in Megaloblastic Anemia: a Five Year Retrospective Review. Mediterr J Hematol Infect Dis 2016;8: e2016021.
6. Noppakun N, Swasdikul D. Reversible hyperpigmentation of skin and nails with white hair due to vitamin B12 deficiency. Arch Dermatol 1986;122:896-9.
7. Saji AM, De Jesus O. Spinal Cord Subacute Combined Degeneration [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2023 Sep 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560728/
8. Iacobucci G. Consider intramuscular injections for older people with vitamin B_{12} deficiency, says NICE. BMJ 2023;382:1604.
9. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 2014;166:496-513.
10. Jajoo SS, Zamwar UM, Nagrale P. Etiology, Clinical Manifestations, Diagnosis, and Treatment of Cobalamin (Vitamin B12) Deficiency. Cureus 2024;16:e52153.
11. Ziegler O, Sirveaux MA, Brunaud L, Reibel N, Quilliot D. Medical follow up after bariatric surgery: nutritional and drug issues. General recommendations for the prevention and treatment of nutritional deficiencies. Diabetes Metab 2009;35:544-57.
12. Srivastava A, Choudhary S. Knuckle Pigmentation as an Early Cutaneous Sign of Vitamin B12 Deficiency: A Case Report. JNMA J Nepal Med Assoc 2020;58:798-800.