

Localised Skin Hyperpigmentation as a Presenting Symptom of Vitamin B₁₂ Deficiency Complicating Chronic Atrophic Gastritis

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تغيير موضعي لصبغة الجلد إلى اللون الداكن نتيجة لنقص فيتامين ب₁₂ بسبب التهاب مزمن بالمعدة

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ABSTRACT: Vitamin B₁₂ deficiency is common in developing countries and should be suspected in patients with unexplained anaemia or neurological symptoms. Dermatological manifestations associated with this deficiency include skin hyper- or hypopigmentation, angular stomatitis and hair changes. We report a case of a 28-year-old man who presented to the Sultan Qaboos University Hospital in Muscat, Oman, in November 2013 with localised hyperpigmentation of the palmar and dorsal aspects of both hands of two months' duration. Other symptoms included numbness of the hands, anorexia, weight loss, dizziness, fatigability and a sore mouth and tongue. There was no evidence of hypocortisolaemia and a literature search revealed a possible B₁₂ deficiency. The patient had low serum B₁₂ levels and megaloblastic anaemia. An intrinsic factor antibody test was negative. A gastric biopsy revealed chronic gastritis. After B₁₂ supplementation, the patient's symptoms resolved. Family physicians should familiarise themselves with atypical presentations of B₁₂ deficiency. Many symptoms of this deficiency are reversible if detected and treated early.

Keywords: Vitamin B12 Deficiency; Hyperpigmentation; Atrophic Gastritis; Case Report; Oman.

المخلص: نقص فيتامين ب₁₂ شائع في البلدان النامية وينبغي الاشتباه به عند المرضى الذين يعانون من فقر الدم مجهول السبب أو أعراض ترتبط بالجهاز العصبي. المظاهر الجلدية المرتبطة بهذا النقص تشمل زيادة أو نقصان صبغة الجلد، التهاب جوارب الفم وتغيير في الشعر. نعرض حالة لرجل يبلغ 28 سنة قدم إلى مستشفى جامعة السلطان قابوس في نوفمبر 2013 وهو يشكو من زيادة صبغة الجلد في راحة وظهر يديه لمدة شهرين. كما كان يشكو من خدر في اليدين، فقدان الشهية والوزن، الدوخة، إعياء وألم بالفم واللسان، وكشف الفحص أنه لا يوجد لدى هذا المريض نقص في الكورتيزون ولكن البحث في الأدبيات الطبية كشف احتمال نقص فيتامين ب₁₂. وأثبتت نتيجة الفحص نقص هذا الفيتامين وفقر الدم ضخ الخلايا عند المريض. ولم يكن لديه نقص في العامل المساعد على امتصاص فيتامين ب₁₂. كما أثبت فحص خزعة المعدة التهاب مزمن بالمعدة. اختفت كل أعراض المريض بعد إعطائه فيتامين ب₁₂. لذلك ننصح بأن يتعرف أطباء الأسرة على الأعراض النادرة لنقص فيتامين ب₁₂. الكثير من أعراض نقصان فيتامين ب₁₂ قابلة للتراجع إذا شخص هذا النقص وعولج مبكراً.

مفتاح الكلمات: نقص فيتامين ب₁₂; زيادة صبغة الجلد؛ التهاب المعدة الضموري؛ تقرير حالة؛ عمان.

VITAMIN B₁₂ DEFICIENCY IS COMMON among individuals in developing countries.¹ Its prevalence is often underestimated as it is believed to occur only in strict vegetarians and patients with pernicious anaemia.¹ However, vitamin B₁₂ deficiency should be suspected in all patients with unexplained anaemia or neurological symptoms.² Various dermatological manifestations associated with B₁₂ deficiency are skin hyper- or hypopigmentation, angular stomatitis and hair changes.³ Hyperpigmentation as the primary presenting symptom of B₁₂ deficiency is rarely reported in the literature.⁴ The case reported below describes

a 28-year-old Omani man who presented with brownish-black hyperpigmentation on both hands, which proved to be due to a B₁₂ deficiency caused by chronic atrophic gastritis.

Case Report

A 28-year-old Omani male presented to Sultan Qaboos University Hospital (SQUH) in Muscat, Oman, in November 2013 with hyperpigmentation of both hands. Two months later he developed severe numbness in both hands to the extent that he could no

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Figure 1A–D: Diffuse brownish-black hyperpigmentation on the (A) dorsal and (B) palmar aspects of both hands at presentation. Improved (C) dorsal and (D) palmar hyperpigmentation was noted after vitamin B₁₂ supplementation.

longer carry objects. On further enquiry, he reported symptoms of glossitis and angular stomatitis for the preceding two weeks. He had lost 10 kg within one month (with an initial weight of 86 kg) and was experiencing anorexia, feelings of excessive fatigability and dizziness. His past medical, medication and dietary history was unremarkable. There was no previous history of fever, epigastric pain, diarrhoea, steatorrhea, diabetes mellitus, tuberculosis or use of any over-the-counter medications.

A clinical examination revealed a diffuse brownish-black discolouration on both the palmar and dorsal aspects of both hands which was more pronounced at the distal and proximal interphalangeal joints [Figure 1A & B]. There was ulceration on both sides of the tongue with angular stomatitis. No abnormal pigmentation was found on any other site of the skin or on the buccal mucosa. On neurological examination, the patient was unable to feel a 10 g monofilament on either hand; however, he could feel vibration on the hands and his proprioception was intact. The patient had brisk reflexes in the upper limbs but diminished reflexes in the lower limbs. The plantar reflexes were equivocal and Romberg's test results were negative. The rest of the physical examination was normal. Serum cortisol and adrenocorticotropic hormone levels were normal, ruling out Addison's disease. A

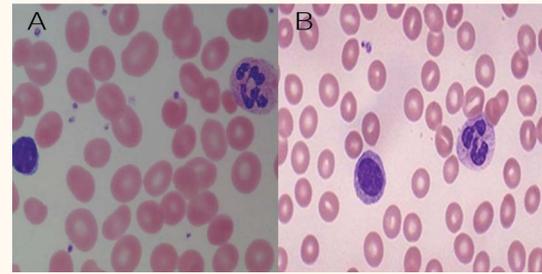


Figure 2A & B: May-Grünwald-Giemsa stain at x40 magnification showing blood cell morphology (A) before and (B) after treatment with vitamin B₁₂.

complete blood count showed macrocytosis with megaloblastic features, although his haemoglobin level was normal [Figure 2].

The patient's B₁₂ and folate levels were subsequently assessed; his B₁₂ level was found to be significantly low [Table 1]. As B₁₂ plays a pivotal role in many metabolic pathways, further metabolic work-up showed high levels of both methylmalonic acid and homocysteine. Multiple biopsies from an endoscopy were consistent with a fungal infection at the lower end of the oesophagus and chronic gastritis including focal intestinal metaplasia without any evidence of

Table 1: Summary of haematological, biochemical and other investigation results for the current patient with localised skin hyperpigmentation

| Investigation | Value | Normal range |
|---|---------------|-----------------|
| Haemoglobin | 12.2 g/dL | 11.5–15.5 g/dL |
| Mean corpuscular volume | 115 fL ↑↑ | 78–96 fL |
| Red cell distribution width | 17.2% ↑ | 11.5–16.5% |
| C-reactive protein | 2 mg/L | 0–8 mg/L |
| Vitamin B ₁₂ | 75 pmol/L ↓↓ | 133–675 pmol/L |
| Folate | 20.4 mmol/L | 7.0–45.1 mmol/L |
| Cortisol at 10 am | 422 nmol/L | 185–624 nmol/L |
| Adrenocorticotropic hormone at 8 am | 98 ug/L | 24–336 ug/L |
| Homocysteine plasma | 36 µmol/L ↑↑ | <15 µmol/L |
| Methylmalonic acid | 3.4 µmol/L ↑↑ | <0.5 µmol/L |
| Anti-deamidated gliadin antibody IgA and immunoglobulin G | 1 µ/mL | 0–25 µ/mL |
| Transglutaminase antibody immunoglobulin A | 1 µ/mL | 0–20 µ/mL |
| Human immunodeficiency virus serology | Negative | Negative |

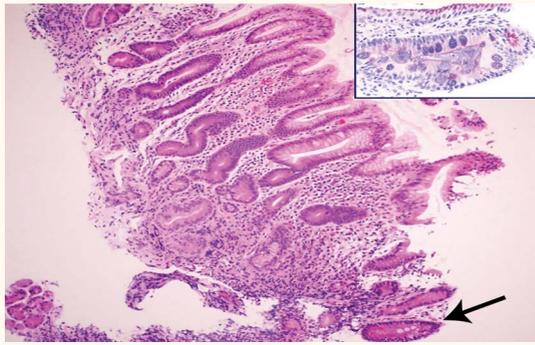


Figure 3: Haematoxylin and eosin stain of a gastric biopsy sample from the antrum showing crypt disarray and moderate chronic inflammation of the lamina propria with foci of intestinal metaplasia (arrow) at x100 magnification. **Inset:** Periodic acid-Schiff-alcian blue stain showing foci of intestinal metaplasia with alcianophilic mucinous cells at x400 magnification.

Helicobacter pylori [Figure 3]. The duodenal biopsy also revealed mild chronic inflammation and focal villous blunting. An autoimmune work-up was negative, including antiparietal cell, intrinsic factor antibody (IFA), transglutaminase and anti-gliadin antibody tests. A skin biopsy of the hyperpigmented lesions showed dermal vessels with mild lymphocytic cuffing and ectatic capillaries.

The patient was prescribed 1,000 µg of intramuscular B₁₂ every day for one week, followed by the same dose once a week for four weeks and then once a month for two months. Following the treatment, the patient underwent remarkable symptomatic improvement. His skin pigmentation completely normalised within eight weeks of treatment with B₁₂ [Figure 1C & D].

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Discussion

Vitamin B₁₂ deficiency was considered to be the cause of localised hyperpigmentation in the reported patient, due to the fact that the hyperpigmentation disappeared following the normalisation of serum B₁₂ levels with treatment. The most common causes of B₁₂ deficiency are either a strict vegetarian diet or malabsorption of B₁₂ due to inadequate gastric production or defective functioning of IFA.^{1,2} Other causes include a gastrectomy, surgical resection of the terminal ileum, bacterial overgrowth of the small intestine, diverticulitis, coeliac disease, Crohn's disease, chronic alcoholism, human immunodeficiency virus, *Diphyllobothrium* infestation, giardiasis and medications such as metformin and colchicine.^{1,2}

In addition, malabsorption of B₁₂ has been associated with long-term (>4 years) use of histamine type 2 receptor antagonists and proton-pump inhibitors.⁵ Of these potential causes of B₁₂ deficiency, the only one applicable to this patient was the possibility of inadequate IFA production by the stomach due to histologically-proven chronic atrophic gastritis.

Amarapurkar *et al.* reported that there was no statistically significant difference in haematological, biochemical and histological parameters in IFA-positive and IFA-negative gastritis.⁶ These may be part of the spectrum for the same disease, with *H. pylori* as the agent responsible for initiating the process. It has been reported that patients who are IFA-negative are classified as chronic atrophic gastritis cases.⁶ In the current patient, the associated *Candida* infection at the lower part of the oesophagus may also be explained by a B₁₂ deficiency, as vitamin B group deficiencies have been reported as one of the causes for a *Candida albicans* infection.⁷

Pigmentation in B₁₂ deficiency can also masquerade as pigmentation due to Addison's disease.^{4,8-12} There are few reported cases of vitamin B₁₂ deficiency in which mucocutaneous lesions predate other manifestations.^{4,8-12} In these cases, the skin changes were characterised by Addisonian brownish-black hyperpigmentation which affected more than one area of the body, including sun-exposed sites, such as the palmar and dorsal aspects of the hands and feet and the knuckles, flexures, tongue, oral mucosa, palmar creases, nails and gluteal region.^{4,8-12} The pigmentation observed in the current patient differs from these reported cases in that it was localised only to the hands, which may possibly be due to an early diagnosis of the condition. Kannan *et al.* described a similar case of B₁₂ deficiency where the patient presented over a short period of time (1.5 months) with localised hyperpigmented macular lesions on the dorsum of the middle phalanges of both feet.³

From the current case, it is obvious that skin signs and symptoms, specifically hyperpigmentation, can precede the typical neurological signs and symptoms of B₁₂ deficiency. Mori *et al.* proposed that skin hyperpigmentation can be an important clue in diagnosing B₁₂ deficiency and that dermatologists need to be familiar with the clinical appearance of this disorder.¹⁰ The mechanism of hyperpigmentation is not well understood. It has been suggested that the lack of B₁₂ causes depletion in intracellular glutathione levels which normally inhibit tyrosinase activity in melanogenesis; the lack of this inhibitor would lead to an increase in melanogenesis.¹³ Mori *et al.* reported

that the dominant mechanism of hyperpigmentation due to B₁₂ deficiency is not a defect in melanin transport but rather an increase in melanin synthesis.¹⁰

Conclusion

B₁₂ deficiency should be considered as an underlying cause of unexplained hyperpigmentation. In the current case, a patient presented with localised hyperpigmentation of the palmar and dorsal aspects of both hands which resolved rapidly after B₁₂ supplementation. It is essential for family physicians to familiarise themselves with atypical presentations of B₁₂ deficiency, as early detection and adequate treatment of the condition can prevent neurological complications.

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