Imerslund-Grasbeck syndrome in a Chinese family with distinct skin lesions refractory to vitamin B$_{12}$

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**Abstract**

Two brothers in a Chinese family with selective malabsorption of vitamin B$_{12}$ associated with proteinuria (Imerslund-Grasbeck syndrome) presented with widespread mottled skin pigmentation, termed poikiloderma. In contrast to anaemia, this pigmented disturbance remained unresponsive to vitamin B$_{12}$ replacement. This is different from the reported hyperpigmentation sometimes seen in vitamin B$_{12}$ deficiency which is reversible following treatment. As far as is known, an irreversible and persistent skin disorder has not been reported in this syndrome before.

not. The refractoriness of the skin lesions to vitamin B₁₂ treatment has not been reported before.

Case reports
A 21 year old Chinese man was admitted because of proneness to fatigue and dyspnoea on exertion, and for evaluation of a skin disorder. The latter was initially noted at the age of 4 years and was characterised as a generalised symptomless pigmentation. At the age of 5, he sought medical attention because of dizziness and fainting spells and was found to have megaloblastic anaemia. Routine blood picture showed haemoglobin of 51 g/l, mean corpuscular volume (MCV) of 121 fl, leucocyte count of 2.8 × 10⁹/l, and a platelet count of 122 × 10⁹/l. He improved with cyanocobalamin 1000 µg monthly given intramuscularly and has continued this treatment since then. However, the skin disorder remained. His dietary history was normal. Both parents, who are not consanguineous, and his two sisters appear normal and have no anaemia. His younger brother (case 2) had megaloblastic anaemia as a result of vitamin B₁₂ deficiency and similar skin lesions.

On admission, the patient appeared to be a well developed and well nourished man. Clubbing, koilonychia, organomegaly, and neurological deficits were absent. The results of a xylose tolerance test and biopsy specimens of stomach and small intestine were normal. Cytopathological studies were normal. Cortisol concentrations were within normal ranges. Other studies, including a dual isotope (Dicopac) vitamin B₁₂ absorption test, and pentagastrin test taken two months after discontinuing vitamin B₁₂ replacement, are shown in the table. His skin lesions presented as widespread mottled pigmentation over the whole body, especially over both groins (fig 1), back, neck, and both flanks. These lesions were exaggerated by exposure to the sun and were identified as poikiloderma. The skin biopsy specimen showed flattened epidermis, hydropic degeneration of basal cells, and pigmentary incontinence (fig 2).

The 19 year old younger brother presented with a similar clinical course. Skin manifestations appeared when he was 3 years old and megaloblastic anaemia was noted a year later. His original blood count showed a haemoglobin of 63 g/l, an MCV of 114 fl, a leucocyte count of 4.5 × 10⁹/l, and a platelet count of 141 × 10⁹/l. Despite regular intramuscular cyanocobalamin treatment, the skin lesions remain unchanged. His haematological investigations (table) were also taken two months after discontinuing vitamin B₁₂ replacement.

Discussion
The diagnosis of Imerslund-Grasbeck syndrome in our patients was confirmed by isolated vitamin B₁₂ deficiency; malabsorption of vitamin B₁₂, as demonstrated by a dual isotope vitamin B₁₂ absorption test; intact intrinsic factor and gastric secretion; absent intrinsic factor antibody in serum; normal serum transcobalamin I, II, and III; no morphologically identifiable lesion in the stomach and
small intestine; and persistent proteinuria with normal renal function.

The pathogenesis of vitamin B$_{12}$ malabsorption in this syndrome remains unknown. In one study, the uptake of IF-B$_{12}$ complex in vitro by homogenised ileal biopsy specimens from one patient was found to be normal and it was therefore postulated that the defect lay at a later stage after the attachment of the IF-B$_{12}$ complex to the surface of the ileal cell. In another detailed study of two brothers with the syndrome, IF-B$_{12}$ uptake in the ileum in vivo was examined by subcellular fractionation of ileal biopsy specimens. No uptake of vitamin B$_{12}$ was detected in the ileal tissue.

Reversible cutaneous pigmentation sometimes occurs in vitamin B$_{12}$ deficiency. In 1963 Baker et al described hyperpigmentation as a sign of vitamin B$_{12}$ deficiency, and noted its frequency in dark-skinned peoples. Indeed, almost all reports of this association have involved people from Africa or India. The importance of the association between hyperpigmentation and vitamin B$_{12}$ deficiency rests in its reversibility after vitamin B$_{12}$ replacement. The mechanism for this reversible change is unclear. It has been postulated that vitamin B$_{12}$ deficiency lowers the intracellular reduction potential, with a concomitant decrease in the reduced glutathione:oxidised glutathione (GSH:GSSG) ratio. Once the tyrosinase inhibiting effect of GSH has been diminished, the epidermal melanocytes are then stimulated to produce melanin. At the same time, the lowered GSH concentration results in retardation of mitosis, as well as diminished DNA synthesis. This could result in epidermal atrophy and hyperpigmentation. The exaggeration of hyperpigmentation by exposure to sunlight in vitamin B$_{12}$ deficiency, as observed in our patients, may be due to a further lowering of intracellular GSH content by ultraviolet light.

In vitamin B$_{12}$ deficiency, brown skin pigmentation usually occurs over the dorsal aspects of fingers and toes, around the nails, and also on the finger pulp. These dermatological signs usually disappear after treatment. In our patients the skin manifestation was widespread mottled hyperpigmentation, especially over both groins, lateral abdomen and neck, termed poikiloderma. This peculiar pigmentary disturbance is similar to that of the patients with this syndrome described by Gillian et al and Watson-Williams et al. Of interest, was the persistence of the skin lesions which also persists despite vitamin B$_{12}$ treatment. The reason for this refractoriness to vitamin B$_{12}$ in our patients is unclear but may have been related to racial or genetic differences and may in part explains the heterogeneous nature of this syndrome, which may be polygenic in origin.

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