Megaloblastic Anemia in a Patient with Addison's Disease: A Case Report

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Abstract
Primary adrenal insufficiency (Addison's disease) is due to adrenocortical disease. This study is about a 40 year old man who had been referred to a hematologist who assessed him for anemia. He had been affected by a periodic paresthesia one month prior to his visit to the physician. According to the clinical presentation, macrocytic anemia and hypersegmentation of PMN in PBS, BMA/B was performed, which reported "megaloblastic anemia".
In 2001, his skin became mildly hyperpigmented, on the elbows, hands, groin and knees. In 2002, he felt weakness, had the sweats, arthralgia and myalgia. The patient was refered to a clinic and then to a hospital. But, his symptoms did not abate, therefore he was refered to the Imam-khomeini Hospital located in Tehran, and was admitted. At the hospital, new signs were detected: hypotension, hyponatremia (Na=100), raised ALT and TSH levels, and macrocytic anemia.The physician suspected primary adrenal insufficiency. More tests were performed and the diagnosis of Addison's disease was confirmed. Noticing one of the rare features in Addison's disease is megaloblastic anemia.

Keywords: Primary Adrenal Insufficiency, Addison's Disease, Megaloblastic Anemia

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Introduction
Primary adrenal insufficiency (Addison's disease) is due to adrenocortical disease, while secondary and tertiary adrenal insufficiency are due to disorders of the pituitary gland (ACTH secretions) or the hypothalamus. Primary adrenal insufficiency is associated with both cortisol and mineralocorticoid deficiencies.
In contrast, secondary and tertiary adrenal insufficiency are associated with cortisol, but not mineralocorticoid deficiency.
The Clinical features of Addison's disease are multiple. One of these features is megaloblastic anemia (whose prevalence is 2%), which is a rare feature. This is a case of Addison's disease (2001-2009) with megaloblastic anemia in the clinical presentations.

Case report
The patient was a 40 year old man, Married, Muslim (Shiite), an inhabitant of Nashtaroud (in northern iran), who has 2 children. He is a cabdriver, but, from 1996 to 2000, he had been working several jobs in southern Iran, Chabahar, as a cabdriver, stonecutter, welder and an asphalt worker. His chief complaint was anemia. In October, 2009, he was referred to a hematologist to be assessed for this anemia. He had been affected with periodic paresthesia from one month before that date. It had become gradually progressive. His knees down to toes in both legswere affected, much

so that the patient could not wear his shoes during the bouts of paresthesia. This was accompanied by fatigue, weakness, a feeling of being cold, mild thyroid enlargement (grade 2), thick, coarse hair, and longitudinal brown lines on the nails (Figure-1). There was also symmetric hyperpigmentation, thickening and itching of the elbows, groin, knees and dorsal surfaces of his hands (Figure- 2). The lab data in the first visit on 19 Oct, 2009 was as follows:

RBC= 2.39, Hb= 9.5, Hct= 28.4 (↓), MCV= 118 (↑), MCH= 39.7 (↑), MCHC= 33.5, RDW= 14.5, Plt= 215,000

WBC= 5100: Neut.= 34%, Lymph.= 57%, Mono.= 4%, Eos.= 4%, Band= 1%.

PBS: Macroovalocyte= few, Macrocytosis= (+), WBC morphology= Hypersegmentation of PMN.

FBS= 71 mg/dl, U/A= 4.2 mg/dl, Cholestrol (total)= 139 mg/dl, TG= 97 mg/dl

SGOT= 19 U/L, SGPT= 16 U/L, ALKP= 112 U/L

His past medical history was considerable:

In 2001, his skin became mildly hyperpigmented, on his elbows, hands, groin and knees. In 2002, he felt weakness, sweats, arthralgia and myalgia. he was refered to a clinic. A general physician, suggested brucellosis and the patient underwent anti-brucelosis therapy. He was not cured. Two months later, more symptoms appeared: fever, monotonous headache in the frontal and occipital areas which led to insomnia, vertigo, decreased consciousness levels, paresthesia in his lower limbs, icter, dark urine (occasionally), weight loss (from 71 kg down to 63 kg). Then, he was referred to a hospital. His lab data was in normal range. His first blood pressure (BP) measured 110/70. His subsequent BP, during the time he was bedridden and treatment measured: 110/60, 120/80, 110/80, 110/80 and 110/70. his chest X-rays were normal. During the 5 days he was in the hospital, he was given: Acetaminophen codein, inderal, beladona, ergotamin, alperazolam and ceftriaxone. However, he did not feel better, and was then admitted to the Imam-khomeini hospital located in Tehran. There, new signs were detected:

Hypotension, hyponatremia (Na=100), raised ALT and TSH, macrocytic anemia.

The especialist suspected primary adrenal insufficiency. Then, more tests were done:

- ACTH= 52 (NL: up to 80), morning cortisol (8:00 AM)= 0.5 (NL: > 5)
- Cosyntropin test: cortisol 1h: 0.8, cortisol 4 h: 1.1, cortisol 24h: 0.7

At this point, a diagnosis of Addison's disease was confirmed. He was given prednisolone, fludrocortisone and levothyroxin. During the time he was inn the hospital, a BMA/B was done which showed "mildly hypocellular marrow; negative for tumor". So noticing macrocytic anemia, folic acid and vitamin B12 were given to the patient.

He was discharged after 3 weeks of being in the hospital. In 2003, some longitudinal brown lines appeared on the patient's nails. In 2005, the dermal hyperpigmentation suddenly intensified. After investigating the patient's past medical history and family history, no history of thyroid or adrenal disease or anemia had been found. Because of his history and the lab data of 19 October, 2009, other lab tests were requested, which were reported in 22 October, 2009: Vit. B_{12}= 324 pg/ml (Nl: 197- 866), Folate= 7.5 ng/ml (Nl: 105-17), LDH= 900 Iu/dl (Nl: up to 480), TSH= 27.5 mIU/dl, T4= 8.2 µg/dl, Na= 136.5 mEq/l, K= 4.235 mEq/l, Cortisol 8:00 AM= 184.6 ng/ml (Nl: 50-230). Then BMA/B was performed, and the results were reported as "erythroid megaloblastic changes". The patient underwent follic acid and vitamin B12 therapy. A month later, in November, 2009, he was given new lab tests. His general status and feeling improved: LDH= 384 IU/dl, RBC= 3.54, Hb= 11, Hct= 35.5, Retic= 1.4%, MCV= 100.3, MCH= 31.1, MCHC= 31.

Discussion

When Thomas Addison described the disease in 1855 which now bears his name, bilateral adrenal destruction by tuberculosis was its most common cause. Nowadays tuberculosis accounts for only 7 to 20 percent of cases; autoimmune disease is responsible for 70 to 90 percent. The prevalence of Addison's disease in western countries has been estimated at 35 to 60 per million, but three studies indicate it may be as high as 120 per million. Hypoparathyroidism does not occur in this disorder, and alopecia and pernicious anemia are much less frequent than in the "type I" syndrome. The incidence of other endocrine and autoimmune disease in 365 patients with autoimmune adrenal insufficiency is shown in Table- 1. Based on this table, the incidence of pernicious anemia was 5 percent (Table- 1).(1)

But in some cases, pernicious anemia has been reported in idiopathic Addison's disease(2, 3, 4) and gastric mucosal biopsies revealed a high incidence of chronic gastritis in patients with idiopathic Addison's disease(5,6). In addition, gastritic parietal cell antibodies are more prevalent in idiopathic Addison's disease than in cases of tuberculous.(6) Therefore, there is strong, clinical,

histological, and immunological evidence, which points to an association among idiopathic Addison's disease, chronic thyroiditis and chronic gastritis (which predisposes to pernicious anemia). Williamson, et al, reported a case of idiopathic Addison's disease and pernicious anemia. In available laboratory data, Waaler-Rose, latex particle, and hemoglobin tests were recorded in 77 patients suffering from pernicious anemia.(7) It is more common in families of the patients with pernicious anemia and other immune diseases. Duda-Krol, reported two cases of a family incidence of anemia in Addison's patients.(8) Therfore, In our opinion, the precise taking of family history is very important in the treatment and prevention of Addison-induced anemia. Kazimierska, et al, reported two cases (44 and 26 years old) who suffered from severe macrocytic and megaloblastic anemia during the course of Addison-Biermer disease. Also, they found vitamin B_{12} deficiency causes, there were chronic autoimmune thyroiditis and surely Helicobacter pylori infection. They recommended to antithyroid antibodies detection and H. Pylori test in all patients with Addison's disease.(9) Kuliszkiewiez-Janus, observed on 24 patients, that, megaloblastic anemia occurred characteristic schedule depending on the appearance of autoimmune diseases such as hypothyroidism, polyglandular autoimmune syndrome (PGA) and Addison's disease.(10)

Table- 1: Incidence of other endocrine and autoimmune diseases in 365 patients with autoimmune adrenal insufficiency (Addison's disease).

Disease	Incidence/percent
Thyroid disease	
Hypothyroidism	8
Nontoxic goiter	7
Hyperthyroidism	7
Gonadal failure	
Ovarian	20
Testicular	2
Type 1 diabetes mellitus	11
Hypoparathyroidism	10
Pernicious anemia	5
None	53

Compiled from multiple reports.

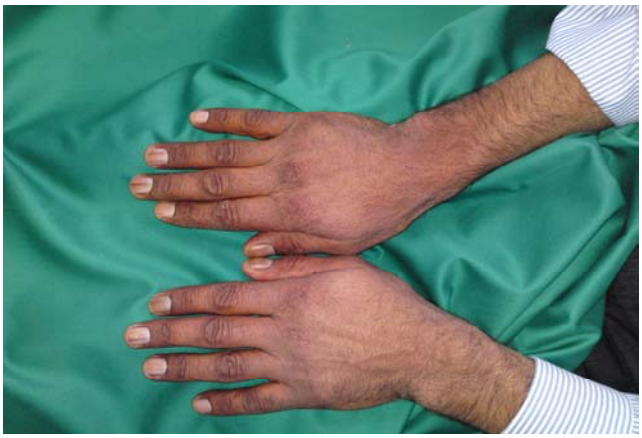

Figure- 1: Longitudinal brown lines on the nails. (Nov. 2009)

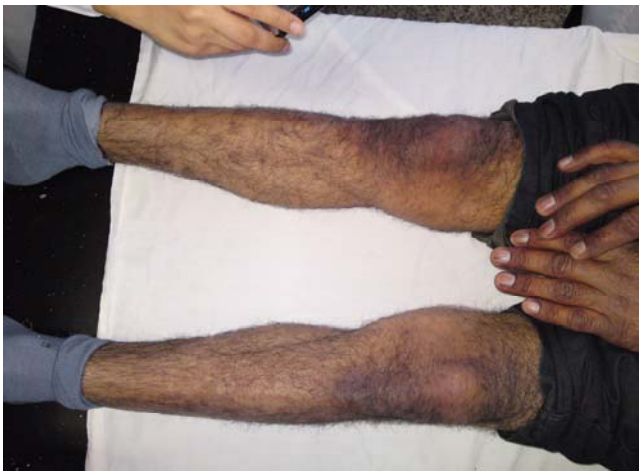

Figure- 2: Symmetric hyperpigmentation and Thickening on the elbow, hand, and knee. (Nov. 2009)

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