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**Case Report**

# Melanosis secondary to Addison disease: a case report

**Dhaval Dave*, Anannya Mukherji, Manohar Joshi, Spandan Patel, Ashwini Jain, Ketan Pakhale, Archana Bhate**

Department of Medicine, Padmashree Dr. D Y Patil Medical College, Nerul, Navi Mumbai, Maharashtra India

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***Correspondence:**
Dr. Dhaval Dave,
E-mail: dhavald9488@gmail.com



## ABSTRACT

Addison disease is a rare but potentially fatal disorder of the adrenal glands. Its manifestations are often confused with many common disorders, and a high index of suspicion is required for the diagnosis. In this case we observed that initially the manifestation were confused with melanosis secondary to consumption of Ayurvedic medication and pangastritis, but a high level of suspicion helped to reach the diagnosis of Addison disease.

**Keywords:** Addison disease, Rare case, Melanosis secondary to Ayurvedic medication, Pangastritis adrenal, Glucocorticoid, Mineralocorticoid

## INTRODUCTION

Addison disease, or primary adrenal insufficiency, is a chronic disorder of the adrenal cortex resulting in inadequate production of glucocorticoid and mineralocorticoid.[1] It is a relatively rare disease with a prevalence of about 140 per million and an annual incidence about 4 per million in Western populations.[2] Addison disease is a potentially lethal condition if left untreated, yet its diagnosis is often missed or delayed.

## CASE REPORT

44 year old male patient, security guard by occupation, presented with chief complaints of:

1) Hyperpigmentation of skin all over the body since 6 months, gradually increasing.

2) Nausea, vomiting, giddiness, syncopal attacks, fatigue, malaise, anorexia, abdominal discomfort on and off since 6 months.

3) History of weight loss 3 kg in 6 months.

No history of fever, cough, cold, breathlessness, head injury, seizure disorder, No history of diabetes, hypertension, cerebrovascular accident or ischaemic heart disease, any thyroid disorder in the past.

No history of Koch's or Koch's contact.

History of consumption of some Ayurvedic medication in powder form to relieve constipation for almost 3 years.

For the same patient consulted dermatologist, and his skin biopsy was done and results showed Melanosis secondary to Ayurvedic medication.

After 5 days patient again presented with the similar complaints, however this time vomiting and abdominal discomfort was severe, so patient was admitted under surgery department, his OGD scopy was done and was diagnosed to have pangastritis.

After 10 days patient continued to have symptoms like vomiting, abdominal discomfort, syncopal attacks, fatigue, generalized weakness to the level that was not able to walk. Then was admitted under Medicine

department, and on investigation he was found to have hyponatremia, hyperkalemia, hypoglycemia and hypotension.

Na: 112, K: 6.0, RBS: 66 mg/dl, BP: 90/60 mmHg

Keeping in mind the suspicion of adrenal insufficiency, his cortisol levels were sent at 8:00 AM and were found to be low 3.3 mcg/dl (Normal: 6.20-19.40 mcg/dl).

Then short synacthen test was performed, wherein 250 mcg of synacthen was injected iv and blood samples for cortisol was sent at 0, 30 and 60 minutes. All of them were found to be on the lower side.

Finally ACTH levels were sent at 12:00 PM, which turned out to be high 25.2 pg/ml (Normal: 12 PM <20 pg/ml).

Followed by which his TSH levels were sent which turned out to be normal 1.7 uIU/ml (0.4-4.2 uIU/ml).

Then his CT-abdomen (P+C) was done which showed bilateral enlarged adrenal glands with multiple non enhancing necrotic areas are seen within the adrenal glands.

Finally the diagnosis of Addison disease most likely due to adrenal tuberculosis was made.

Patient was initially given all the symptomatic treatment, and then was started on low dose glucocorticoid and mineralocorticoid therapy.

Tab prednisolone (5 mg) 1-0-1/2, Tab fludrocortisone (100 mcg) 1-0-0 was started.


**Figure 1: The comparison picture showing patient developing significant hyperpigmentation of skin.**

Patient responded well to this therapy, symptoms were relieved and was educated well regarding the disease, its complications and its treatment.

Patient was discharged with the steroid therapy card and kit containing injection hydrocortisone 100 mg prefilled syringe with diluent which has to be given intramuscularly in emergency condition of adrenal crisis.

Patient has been asked to follow up after 2 months.

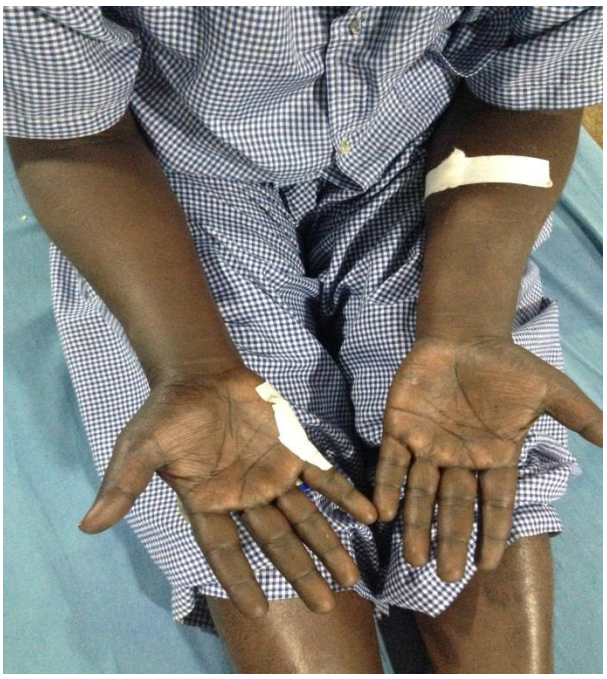

**Figure 2: Hyperpigmentation of forearms and palms.**

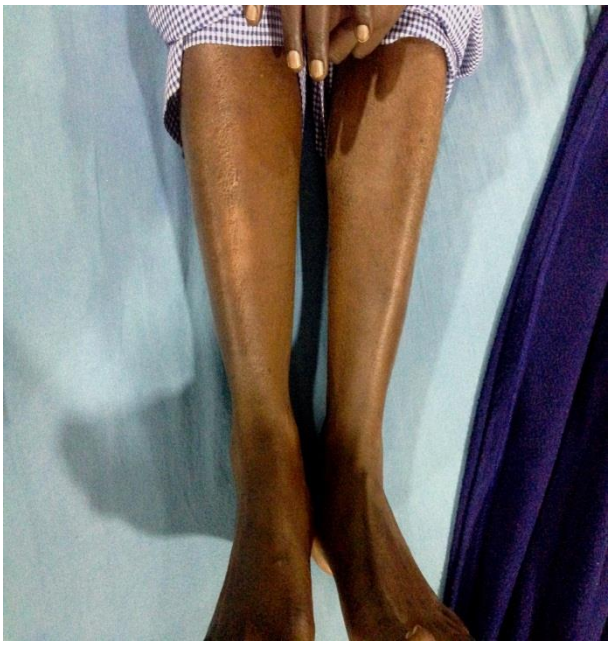

**Figure 3: Hyperpigmentation of Lower limbs.**

## DISCUSSION

Causes and presentation of primary adrenal insufficiency show in Table 1.

**Table 1: Causes and presentation of primary adrenal insufficiency.**

| Causes | Key associated features |
|---|---|
| Autoimmune polyglandular syndrome 1 | Hypoparathyroidism, mucocutaneous candidiasis, other autoimmune disorders. |
| Autoimmune polyglandular syndrome 2 | Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anaemia |
| Isolated autoimmune adrenalitis | |
| Congenital adrenal hyperplasia | 21- hydroxylase deficiency,<br>11B - Hydroxylase deficiency,<br>17A - Hydroxylase deficiency,<br>3B - Hydroxysteroid dehydrogenase deficiency,<br>P450 oxidoreductase deficiency. |
| Congenital lipoid adrenal hyperplasia | Gonadal failure |
| Adrenal hypoplasia congenital | Gonadal failure |
| Adrenoleukodystrophy | Demyelination of central nervous system, presence of very long chain fatty acids in males. |
| Familial Glucocorticoid deficiency | ACTH insensitivity syndromes due to mutation in the ACTH receptor. Tall stature, achalasia, neurologic impairment. Intact mineralocorticoid function. |
| Triple A syndrome / Allgrove Syndrome | Alacrimia, Achalasia, Adrenocortical insufficiency |
| Smith-Lemli-Opitz syndrome | Cholesterol synthesis disorder associated with mental retardation, craniofacial malformations, growth failure. |
| Kearns-Sayre Syndrome | Progressive external ophthalmoplegia, pigmentary retinal degeneration, cardiac conduction defects, gonadal failure, hypoparathyroidism, type 1 diabetes. |
| IMAGe Syndrome | Intrauterine growth retardation, metaphyseal dysplasia, genital anomalies. |
| Adrenal Infections | Tuberculosis, HIV, CMV, cryptococcosis, histoplasmosis, coccidiomycosis. |
| Adrenal Infiltration | Metastases, lymphomas, sarcoidosis, amyloidosis, hemochromatosis |
| Adrenal haemorrhage | Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome. |
| Drug Induced | Mitotane, aminoglutethimide, arbiraterone, trilostane, etomidate, ketoconazole, suramin. |
| Bilateral adrenalectomy | e.g.: In the management of Cushing's or after bilateral nephrectomy. |

***Signs and symptoms of adrenal insufficiency***

*Caused by glucocorticoid deficiency*

- Fatigue, lack of energy
- Weight loss, anorexia
- Myalgia, joint pain
- Fever
- Anaemia, lymphocytosis, eosinophilia
- Hypoglycemia
- Low blood pressure, postural hypotension
- Hyponatremia

*Caused by mineralocorticoid deficiency: (Primary AI only)*

- Abdominal pain, nausea, vomiting
- Dizziness, postural hypotension, low blood pressure
- Salt craving
- Hyponatremia, hyperkalemia

*Caused by adrenal androgen deficiency*

- Lack of energy
- Dry and itchy skin (in women)
- Loss of libido (in women)
- Loss of axillary and pubic hair (in women)

*Other signs and symptoms*

- Hyperpigmentation (Primary AI only) due to excess of proopiomelanocortin derived peptides

***Investigating the cause of Addison disease***

Once a diagnosis of Addison disease is confirmed, further investigations are needed to elucidate the underlying cause. There may be clues in the history and examination. For example, a presence of another autoimmune condition (e.g., vitiligo) will point to autoimmune Addison disease. Likewise, neurological manifestations in a young man should raise a suspicion of adrenoleukodystrophy. The presence of adrenal antibodies indicates autoimmune Addison disease. Ideally, both adrenal cortex antibodies and 21-hydroxylase antibodies should be measured.[4] 21-hydroxylase antibodies are more sensitive than adrenal cortex antibodies in the diagnosis of autoimmune Addison disease. In patients with autoimmune Addison disease, it is important to screen for other features of autoimmune poly-endocrinopathy syndromes. In men with negative adrenal antibodies, plasma very long-chain fatty acids should be checked to exclude adrenoleukodystrophy. If the cause still remains unclear, a computed tomographic scan of the adrenal glands should be carried out, which may show evidence of metastasis, infiltration, hemorrhage, infarction, or infection (for example, adrenal calcification in longstanding tuberculosis).[5]

***Management***

*Glucocorticoid replacement*

Hydrocortisone is most commonly used for glucocorticoid replacement, although other glucocorticoids, including cortisone, prednisolone, and dexamethasone are occasionally used. Long-acting glucocorticoids, dexamethasone, and prednisolone have the advantage of a once-daily dosing schedule but have the drawback of losing the diurnal pattern, resulting in excess glucocorticoid levels overnight.[5]

**Table 2: Glucocorticoid replacement.**

| Condition | Increment in hydrocortisone dose |
|---|---|
| Minor febrile illness (e.g., common cold, viral chest infection) | Double the dose. Taper down to the maintenance dose over 2-3 days after the illness |
| Persistent vomiting or diarrhea, or both (e.g., gastroenteritis) | Admission to hospital for intravenous hydrocortisone |
| Serious medical illness (e.g., severe sepsis, myocardial infarction, pancreatitis) or major trauma | Intravenous injections 50 mg every 8 h or continuous intravenous infusion 150 mg/24 h* |
| Minor surgery or invasive diagnostic procedure (e.g., dental extraction, herniorrhaphy, gastroscopy, colonoscopy) | Double the dose on the day |
| Major surgery (e.g., intra-abdominal surgery, cardiothoracic surgery) | Intravenous injections 50 mg every 8 h or continuous intravenous infusion 150 mg/24 h.* Following uncomplicated procedure, taper to maintenance dose, |
| Pregnancy | Dose increment usually not necessary, but may need to give parenterally if unable to take oral medication because of nausea.<br>During labor, double the dose. If unable to take orally, give a dose of 50 mg parenterally during the second stage |
| Physical exercise | Dose increment not necessary for gentle exercise. Increase the dose by 5 mg before strenuous exercise |
| Psychologically stressful situation (e.g. examination, interview) | Dose increment not necessary |

*No need to replace mineralocorticoid at these doses of hydrocortisone as high dose hydrocortisone has mineralocorticoid activity.[5]

In Addison disease, standard replacement dose of hydrocortisone is 15-25 mg a day, given in 2 or 3 divided doses.[1] A typical starting regime would consist of hydrocortisone 10 mg on waking, 5 mg at around noon, and 5 mg early evening. There are no satisfactory biochemical tests to assess the adequacy of glucocorticoid replacement. In practice, the dose of hydrocortisone is maintained on the basis of clinical assessment, taking an account of patient's well- being, and presence of any signs of over-replacement (e.g., hypertension, weight gain, thin skin, easy bruising, and glucose intolerance) or under-replacement (e.g., weight loss and pigmentation).

During intercurrent illnesses, perioperative periods, and other forms of stress, patients should increase the dose of hydrocortisone to mimic the normal physiological response. Some drugs (e.g., rifampicin, phenobarbitone, and phenytoin) increase hepatic metabolism of glucocorticoids, and patients starting on such drugs may need to increase the dose of hydrocortisone.[5]

***Mineralocorticoid replacement***

Fludrocortisone is the only available agent for mineralocorticoid replacement. The usual starting dose is 100 mcg a day. The dose is adjusted (usually 50-200 mcg a day) according to clinical response. Hypertension and presence of ankle edema suggest over-replacement, while salt craving, postural hypotension, and hyperkalemia are signs of under-replacement. An assessment of plasma renin activity also is helpful in optimizing the dose of fludrocortisone, as suppressed and elevated plasma renin activity indicate over-replacement and under-replacement, respectively.[5]

***Patient education***

Patient education is critical for the successful management of Addison disease. Information on management of steroid replacement during sickness can prevent acute adrenal crisis. Patients should carry a steroid card and a medic alert bracelet with details of the diagnosis. They and their family members should be taught to give intramuscular hydrocortisone injections during emergencies.[5]

***Follow-up***

Patients with Addison disease should be reviewed annually to assess well-being, monitor whether the glucocorticoid and mineralocorticoid replacement is adequate, and reinforce patient education. In patients with autoimmune Addison disease, you also should screen annually for associated autoimmune disorders with full blood count (pernicious anemia), fasting glucose (diabetes mellitus), and serum thyrotropin (thyroid dysfunction), and check the regularity of menstrual cycle in women (premature ovarian failure).[5]

## CONCLUSION

Addison Disease is a rare but a potentially fatal disorder. Detail knowledge about it is of utmost importance and high level of suspicion should always be kept to arrive at the diagnosis early, as manifestations are often confused with common disorders, like in this case initially was confused with melanosis due to consumption of Ayurvedic medication and pangastritis. Optimum steroid replacement and patient education are vital for good quality of life and to prevent acute adrenal crisis in this condition.

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