ISSN Print 2594-3367 ISSN Online 2631-2107
Journal of Diabetes and Endocrinology
Association of Nepal

CASE REPORT V

OPEN ACCESS

Generalized Hyperpigmentation in Graves' Disease: A Case Report

Shah S, Shakya S, Shakya A, Bhari R
L.I. LEVINA Department of Medicine and Endocrinology,
AARUS Lifestyle Hospital, Kupondol

Abstract

Background: Hyperpigmentation is rarely described as a clinical feature of hyperthyroidism, however, it is one of the rare cutaneous manifestations of Graves' Disease. There are few reported cases of Grave's disease with diffuse hyperpigmentation. We hereby describe a rare case with diffuse hyperpigmentation induced by Graves' disease. Case: A 29-year-old woman came with the complaints of generalized hyperpigmentation of body since the past 3 months. On examination, hyperpigmentation was observed throughout the whole body, especially on the face, neck and the extremities. **Conclusion:** The pathophysiological mechanism is not well elucidated. It has been hypothesized that thyrotoxicosis is associated with an increased ACTH release causing overproduction of melanin and that melanocytes express TSH receptors resulting in their proliferation when stimulated with TRAb. More studies are needed to understand the relationship between skin color modification and thyroid function status.

Key words: Graves' Disease, Hyperpigmentation, TRAb: TSH Receptor Antibody, ACTH: Adrenocorticotrophic hormone

Introduction

When we talk about hyperpigmentation in endocrine practice, few of the endocrine disorders that come to mind is Addison's disease, ACTH dependent Cushing's like Cushing's Disease, Ectopic ACTH Syndrome, Ectopic CRH Syndrome, Nelsons Disease, Congenital Adrenal Hyperplasia and infiltrative disorders like hemochromatosis. Hyperpigmentation due to Graves' Disease is less talked about, there are sparse reports in the literature of hyperpigmentation associated with hyperthyroidism. Hyperthyroidism mainly leads to dermal symptoms like localized myxoedema, eczematous dermatitis, pruritis, alopecia, palmar erythema, onycolysis and telangiectasia.[1] Some have hypothesized thyrotoxicosis is associated with an increased ACTH release causing overproduction of melanin, while others say that, thyrotoxicosis could also lead to hyperpigmentation through an increased capillary fragility, contributing to hemosiderin deposition and basal melanosis.[2] The cause of the pigmentary changes is still speculative; however, it is known that the pigment is melanin. Tyrosine is an amino acid common to both melanin and thyroxine; and it is well established that patients with thyrotoxicosis have tyrosine intolerance with elevated serum tyrosine levels.[3] Many theories have been advanced to explain the phenomenon of hyperpigmentation may be due to elevated tyrosine level. Informed consent was obtained in writing from the patient with use of photographs and publication of this case.

Case Report

A 29-yrs-old, single women came with the complaints of generalized hyperpigmentation since the past 3 months. She had diffuse

Correspondence Author
Dr Sukanti Shah, L.I. LEVINA Department of Medicine and Endocrinology, AARUS Lifestyle Hospital, Kupondol, Kathmandu, Nepal. Email ID: sukantishah@gmail.com

hyperpigmentation observed on the whole body including non-sun-exposed areas of the skin, especially on her face, neck, upper and lower extremities, there was no darkening of her skin creases. There was no obvious hyperpigmentation noticed in the oral cavity, axilla, nipples, groin and genital area. No history of any salt wasting symptoms. Over the past 5-6 months, despite a normal appetite, she had weight loss of about 22 kg. She also complained of palpitation, anxiousness, and tremors. Since the past 1 month, she has also experienced excessive thirst, fatigue, myalgia, polyuria and blurring of vision.

She has no exophthalmous, conjunctival edema, and myxoedema. Her thyroid gland was soft and diffusely enlarged (WHO goiter grading II), with no thyroid bruit. Her BP was 110/80 mmhg, pulse rate of 108 bpm, regular and a BMI of 22 kg/m2 (Ht 149 cm, wt 49.6 kg). Other local and systemic examination revealed no abnormality.

Her laboratory data revealed overt hyperthyroidism with a positive anti-TSH receptor antibody (TRAb) and anti-TPO Antibody. Addison's disease, ACTH dependent Cushing's and haemochromatosis were ruled out. Sugar profile showed hyperglycaemia along with Vitamin D Insufficiency. Other lab parameters were in normal limits. (Table 1)

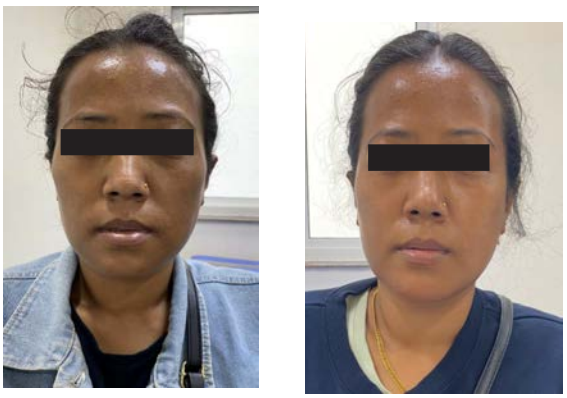
Table 1:

Clinical Parameter	Value	Lab Reference
TSH	<0.005 mIU/mL	0.35–4.94
FT_4	6.99 ng/dl	0.78-2.19
FT_3	22.80 ng/dl	2.7-5.2
TRAb	3.09	<1.22
Anti-TPO Antibody	185.5	0-34
Basal cortisol (8AM)	13.68 ug/dl	8-16
ACTH	28 pg/mL	0-46
Ferritin	65.3 µg/L	10-300
Fasting blood glucose	126 mg/dl	74-100
Post Prandial	279 mg/dl	90-140
HbA1C	7.2%	<5.6%
Vitamin D	13.14 ng/ml	30-100
Calcium	9.9 mg/dl	8-11
Hemoglobin	12.5 gm%	12.5-16
TLC	7380 cells/Cumm	4000-11000
	N^{69},L^{25},E^{1},M^{5},B^{0}%	
Platelets	258 10^3/uL	150-400
ESR	38	0-20
Creatinine	0.2 mg/dl	0.5-1
Urea	20.9 mg/dl	15-45
Sodium	139 mEq/l	135-145
Potassium	4.10 mEq/l	3-5
SGOT	29 U/L	14-36 U/L
SGPT	29 U/L	<35 U/L

ECG revealed a sinus rhythm with heart rate of 90 beats/min at rest. 99m Technetium Thyroid scintigraphy showed diffuse homogeneous increased uptake, total uptake of 25% in B/L thyroid gland (Rt 12.4%, Lt 12.5%), a pattern consistent with Grave's disease. Thyroid ultrasonography scans showed mild goiter and Color flow Doppler imaging demonstrated high blood flow, while adrenal ultrasonography was normal. Presence of osteoporosis and ospteopenia as evidenced by BMD: DEXA-scan, AP spine T-score -2.6, Dual Femur Left/ Right -1.8, -1.6, -2.2, -2.3.

Overall, the patient was given the diagnosis of thyrotoxicosis and hyperpigmentation due to Grave's disease, T2DM, Vitamin D Insufficiency with Osteopenia and Osteoporosis. Thus, she was started with low dose of oral Carbimazole (20 mg/day) keeping in mind the side effects of the drugs and beta blocker for thyroid dysfunction and titrated upwards. For management of T2DM, she was started on Tab Metformin 1000 mg/day with dietary and lifestyle modification. Osteoporosis was managed with Tab Ibandronate 150 mg monthly for 6 months, with Vitamin D 60000 IU once weekly for 3 months.

About 2 months later, the hyperpigmentation abated and although there was clinical improvement but TFT showed little improvement TSH <0.005, FT4 16.69 (12-22 pmol/L). There was good improvement in her glycemic status with HbA1c of 6.4%. There was no side effect of the anti-thyroid drug. After 6 months of treatment with Carbimazole up to 50 mg/day, although the skin pigmentation further subsided, she was still not biochemically euthyroid {TSH <0.005, FT4 9.55 pmol/l (12-22), FT4 3.36 pmol/l (3.10-6.80)} even with good compliance to the drug, and so she was planned for RAIT Therapy.



A. Picture of the patient prior treatment (Rt)
B. Post 6 months' treatment (Lt)

Discussion:

This case presented with particularly unique extensive skin pigmentation which may or may not be attributed to Grave's disease. There have been a few cases of hyperpigmentation with hyperthyroidism, but a definite causal relationship remains incompletely understood. Banba et al hypothesized that evident pigmentation may be related to hemosiderin deposition caused by increased capillary fragility in hyperthyroid patients.[2] On the other hand, some researchers proposed that increased release of pituitary ACTH compensating for accelerated cortisol degeneration was responsible for the hyperpigmentation through increasing melanotropic activity.[4] Moreover, other study speculated the expression of TSH-receptor on epidermal melanocytes may be related to the skin pigmentation in Graves' hyperthyroidism patients.[5]

We tried to differentiate other endocrine causes that may lead to the appearance of hyperpigmentation both clinically and biochemically. As far as autoimmune adrenal insufficiency remains the most common endocrine disorder for hyperpigmentation, the distribution of the pigmentation in our case was a bit different from that in Addison's

disease which presents as diffuse pigmentation with a preferential occurrence on the mucous membranes and over pressure points, such as oral cavity, palmar crease and genitalia.[6,7] Adding to the clinical features, there was no evidence of salt wasting symptoms and the blood tests for Basal Cortisol (8 AM), ACTH, RFT did not support our differential. On the other hand, cortisol excess was also less likely as the patient did not have any history or features suggesting of cushingoid appearance and given the normal ACTH level, and very low evidence for ACTH Dependent Cushing's, no further Dexamethasone Suppression test was done.

Hereditary hemochromatosis (HH) is an autosomal recessive disorder characterized by enhanced intestinal absorption of dietary iron. The overloaded iron always leads to the skin pigmentation.8 Hemochromatosis related pigmentation is more likely to happen in sun-exposed skin and scar areas. According to the laboratory examination, the diagnosis of HH can only be made once the ferritin level is elevated. Furthermore, increased level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) will also be meaningful, which was absent in our case.[9]

Accelerated thyrotoxicosis is generally associated with increased excretion of calcium and phosphorus in urine and stool, with demineralization of bone, as demonstrated by routine bone densitometry and occasionally may present with pathologic fractures. In such instances, the pathologic changes are variable and may include osteitis fibrosa, osteomalacia, or osteoporosis as evidenced in our case.10 As the thyrotoxicosis is treated, bone density may normalize in many younger patients, but not in all.[11]

In the case we present here, the hyperpigmentation displayed good response to carbimazole. As required euthyroidism was not achieved after 6 months of treatment we decided to go for RAIT. As far as hyperglycemia due to T2DM was concerned, there was good results with proper diet and lifestyle adherence along with Metformin. There was improvement in her Vitamin D level as well.

Limitation:

The histopathological examination from pigmented skin was not done, studies have shown that the pigmented skin revealed hyperpigmented basal cells in the epidermis as well as lots of melanophages in the superficial dermis and iron staining to rule out and identify the presence of hemosiderin deposition was also not done.

Conclusion

The pathophysiological mechanism is not well elucidated. It has been hypothesized that thyrotoxicosis is associated with an increased ACTH release causing overproduction of melanin and that melanocytes express TSH receptors resulting in their proliferation when stimulated with TRAb. More studies are needed to understand the relationship between skin color modification and thyroid function status.

Conflict of Interest: No Conflict of interest from the Author and Co-author Side.

Author's Contribution: Sukanti S involved in the evidence collection and conceptualization of the study. Shakya S, Shakya A and Bhari R drafted the initial version of the manuscript and guided through whole process of conceptualization and finalization of the manuscript. All the authors approve of the final version of the manuscript.

References:

1. Lause M, Kamboj A, Faith EF. Dermatologic manifestations of endocrine disorders. Translational pediatrics. 2017 Oct;6(4):300.

2. Banba, Tanaka, Fujioka, Tajima. Hyperpigmentation caused by hyperthyroidism: differences from the pigmentation of Addison's disease. Clinical and experimental dermatology. 1999 May;24(3):196-8.
3. Miller R, ASHKAR FS, Jacobi J. Hyperpigmentation in thyrotoxicosis. JAMA. 1970 Jul 13;213(2):299.
4. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiological reviews. 2004 Oct;84(4):1155-228.
5. Leonhardt JM, Heymann WR. Thyroid disease and the skin. Dermatol Clin 2002;20:473–81.
6. Meleti M, Vescovi P, Mooi WJ, van der Waal I. Pigmented lesions of the oral mucosa and perioral tissues: a flow-chart for the diagnosis and some recommendations for the management. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2008 May 1;105(5):606-16.
7. Sarkar SB, Sarkar S, Ghosh S, Bandyopadhyay S. Addison's disease. Contemporary clinical dentistry. 2012 Oct;3(4):484.
8. Santos PC, Krieger JE, Pereira AC. Molecular diagnostic and pathogenesis of hereditary hemochromatosis. International journal of molecular sciences. 2012 Feb 1;13(2):1497-511.
9. Borgaonkar MR. Hemochromatosis. More common than you think. Canadian family physician. 2003 Jan 1;49(1):36-43.
10. Wakasugi M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T. Bone mineral density in patients with hyperthyroidism measured by dual energy X-ray absorptiometry. Clinical endocrinology. 1993 Mar;38(3):283-6.