What is in a name: Is it Nelson's syndrome?

Sir,

Nelson syndrome is clinical manifestation of an invasive corticotroph adenoma that occurs following total bilateral adrenalectomy (TBA) performed in the treatment of Cushing's disease. However, we have noticed similar clinical and hormonal features in a patient undergoing TBA for bilateral pheochromocytoma in a case of multiple endocrine neoplasia – 2B (MEN2B).

We previously reported a case of MEN2B.[1] She underwent bilateral adrenalectomy for bilateral pheochromocytoma (at

different time periods), total thyroidectomy for medullary thyroid carcinoma, and parathyroidectomy for parathyroid hyperplasia. She was initiated on replacement therapy with hydrocortisone (20 mg), fluodrocortisone (0.05 mg), and thyroxine (100 mcg). During follow-up at 6 months her husband had complained that she was turning darker. Comparing her previous photos showed her to be definitely hyperpigmented [Figure 1]. Apart from this she was asymptomatic. She denied noncompliance or features suggestive of malabsorption. She weighed 37 kg for a height of 150 cm with a body surface area of 1.24 m^2, her pulse was 78/min, blood pressure 110/70 mmHg with no postural fall, she was diffusely hyperpigmented, and her operation scar mark was hyperpigmented. Rest of systemic examination was essentially normal. Laboratory investigations revealed – sodium – 140 mEq/l (135- - 150); potassium – 4.1 mEq/l (3.5-5.5); 8:00 AM cortisol 0.9 μg/ dl; plasma adrenocoticotrophic hormone (ACTH) 955 pg/ml (15- 62). MRI brain showed normal pituitary and CT abdomen did not show any adrenal rest hyperplasia. In view of this her hydrocortisone dose was increased to 25 mg per day. Following this ACTH values showed a decreasing trend and at latest follow-up it was 333 pg/mL.

In a case of bilateral adrenalectomy, high requirement of steroid replacement could be due to noncompliance, decreased absorption or increased metabolism. Our patient declined noncompliance and there were no features of malabsorption. She had no symptoms suggestive of adrenal insufficiency to suggest suboptimal replacement. In spite of that she developed clinical and hormonal characteristics akin to Nelson syndrome. MEN2B phenotype results due to activating mutations of RET proto oncogene. The RET receptor when combined with glial neurotrophic receptor factor (GFRα1) form receptor for glial cell line derived neurotrophic factor (GDNF).[2] The RET/GFRα1/ GDNF receptor is involved in normal migration of several cell types during embryogenesis including the tissues of neural crest and ureteric buds. GDNF is also expressed in normal anterior pituitary, predominantly in somatotrophs and to a lesser extent in corticotrophs. Interestingly RET is expressed in 50% of corticotrophinomas.[3]

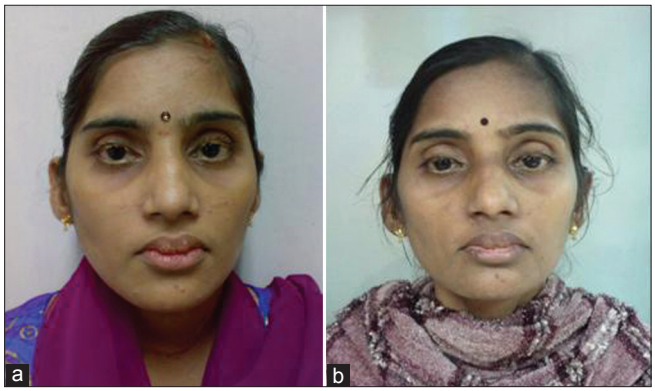

Figure 1: (a) The photo immediately after she was rendered total bilateral adrenalectomy (TBA) status; neuromas over conjunctiva, lips and face are seen. (b) Diffuse hyperpigmentation 12 months after TBA status. (With permission from patient)

Based on these findings we hypothesize that removal of negative feedback on the corticotrophs by adrenal may have activated the RET/GFRα1/GDNF receptor system in this patient who might be harboring mutant RET proto oncogene in corticotroph and lead to increase secretion despite adequate replacement. Clinically this becomes relevant as patient with MEN-2 undergoing TBA may require higher doses of steroid replacement to suppress ACTH from corticotroph. Also long term follow-up is required for the development of corticotroph adenoma which has been reported in a family of MEN2B.[4] It is interesting to note that after extensive search of medical literature we were unable to find similar features described in patients undergoing TBA for other indications.

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