



Figure 1: CT scan abdomen showing hyperplasia of right adrenal remnant

A difficult to treat case of Cushing's syndrome

Sir,

An 18-year old girl presented in 1998 with clinical, biochemical, hormonal and radiological evaluation consistent with Cushing's disease. She underwent trans-sphenoidal resection for pituitary microadenoma. Serum cortisol level on third post-operative day remained elevated. She was re-evaluated in June 2001 and underwent bilateral adrenalectomy in May 2002. She had marked improvement in her symptoms and was on steroid replacement. In March 2003 her symptoms re-appeared and glycemic control deteriorated. She has already stopped steroid replacement. Her basal cortisol done twice was elevated (32 and 38 $\mu\text{g}/\text{dl}$) with raised ACTH levels (98.7 pg/ml). MRI of pituitary showed a focal hypodense lesion and CT adrenal showed hyperplasia of right adrenal remnant [Figure 1]. She underwent host of imaging studies to find missed ectopic ACTH secreting tumor, but were negative. She was advised second trans-sphenoidal surgery for which she refused. She was started on tab ketoconazole, which she took intermittently. Her cortisol levels done

every year, remained elevated. Gamma knife instrument was installed in this hospital in 2007. In 2010, we persuaded her to undergo gamma-knife surgery, which she refused. However, on repeated persuasion she agreed, and underwent it in September 2011. After surgery her symptoms gradually improved. In July 2012, she reported with persistent anorexia, vomiting, extreme asthenia with weight loss of about 20 kg. Examination revealed hypotension and investigations showed hyponatremia $\text{Na}-129 \text{ meq}/\text{l}$, hyperkalemia $\text{K}-6.0 \text{ meq}/\text{l}$ and hypoglycemia. Her insulin requirement had come down by 50% with no need for anti-hypertensive, and her cortisol was 2.6 $\mu\text{g}/\text{dl}$. Finally she had developed adrenal insufficiency with possible permanent cure of Cushing's disease.

This case highlights agony of patient and treating physician. She had first failed pituitary surgery indicated by persistent hypercortisolemia. She had recurrence even after bilateral adrenal surgery. Recurrence after adrenalectomy may be due either to regrowth of adrenal cells in the surgical bed or growth of adrenal rest tissue. Unsuccessful adrenalectomy is usually the consequence of failure to excise hyperplastic adrenal tissue extending around the right adrenal vein.^[1] At this stage, a missed or occult ectopic-ACTH secreting tumor was suspected. Common causes of such slow growing tumor are thoracic carcinoid (36-49%), small cell carcinoma of lung (18-37%) and others (15-44%) like pancreatic carcinoid, pheochromocytoma and medullary thyroid carcinoma.^[2] Her imaging studies for ectopic-ACTH secreting tumor were negative. Facilities for inferior petrosal sinus sampling were not available at this hospital at that time. Options at his stage were second TSS, remnant adrenalectomy, radiotherapy or medical therapy. Success rate of second TSS varies between 30 to 70% and predictors of success are correct diagnosis, initial incomplete TSS and residual tumor on CT/MRI. However, in absence of biochemical evidence such focal defects in the pituitary gland on CT/

MRI should not be taken as absolute evidence of presence of a corticotroph adenoma. Radiation therapy takes prolong period for effect (1-10 years), require medical therapy for intervening period and radiation induced hypopituitarism which will affect fertility. Hence on refusal for surgery she was started on medical therapy. Gamma knife therapy has been used in the treatment of Cushing's disease as primary mode of therapy and after failed surgery.^[3] During prolong course of illness with two failed surgery, it becomes difficult to persuade patient to undergo any intervention. But we could persuade patient to undergo gamma-knife surgery once it became available. She responded with development of adrenal insufficiency after 9 months. Several studies have been published in the use of gamma knife in functioning and non-functioning pituitary microadenomas. Remission rate defined by normalized 24hrs urinary cortisol levels ranged from 35 to 83% of cases.^[3-6] The efficacy of remission depended on the target volume^[4] and the pre-radiosurgery hormonal levels.^[5] Lower target volume and low hormonal levels indicated higher the chances of remission. The time to remission varied from 13 to 24 months. Our patient went into adrenal insufficiency nine months post-Gamma knife. Hypopituitarism is the most frequent side effect frequently seen 12-24 months post-gamma knife decreasing after about 120 months.^[6] She needs regular follow up for hypopituitarism. So here we had a case that underwent TNTS, bilateral adrenalectomy, medical treatment and Gamma knife and finally achieved remission of disease 14 years after the diagnosis of Cushing's disease suggesting there is light at the end of the tunnel.

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