Silent ACTHoma: A subclinical presentation of Cushing's disease in a 79 year old male

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Abstract

Pituitary adenomas are mostly benign tumors which may be clinically functioning or non-functioning. ACTH secreting tumors causing Cushing's disease are detected in 0.7 to 2.4 per million individuals per year. Most of the cases reported on such ACTHomas are microadenomas (<10mm) and very few macroadenomas (>10mm). We report an unusual case of 79 year-old elderly patient presenting with subclinical Cushing's disease due to pituitary macroadenoma (ACTHoma) found incidentally. It raises many possibilities of biochemical nature of hormone in such patients or early degradation of hormone. It certainly brings to our attention that more clinical research is needed to find causes of subclinical Cushing's disease.

Key words: pituitary macroadenomas, Corticotroph adenomas, microadenomas, hypercortisolism

Introduction

Pituitary adenomas are mostly benign tumors. They can be either clinically functioning or non-functioning adenomas. Incidence of adrenocorticotropic hormone (ACTH) secreting tumors causing Cushing's disease range from 0.7 to 2.4/million population per year depending on the population studied.[1, 2] Most of the cases reported on ACTHomas are microadenomas (<10mm in size) and few were macroadenomas (>10mm). Patients presenting with Cushing's disease are mostly children or adults in the age of 20-50 years.

Corticotroph adenomas (~10% of pituitary tumors) stain immunopositive for ACTH. They are associated with elevated circulating ACTH and cortisol levels leading to Cushing's disease with features of hypercortisolism.[3,4] Up to 20% of corticotroph adenomas do not manifest biochemical or clinical evidence of hypercortisolism [5,6] and are known as silent corticotroph adenomas (SCAs).

We report an unusual case of a 79 year old elderly patient presenting with subclinical Cushing's disease caused by pituitary macroadenoma (ACTHoma) found incidentally.

Case Report

Mr. JD was a 79 year old African American gentleman who presented with syncopal episodes and chest heaviness. Past medical history included diabetes mellitus type 2, chronic kidney disease (stage III), dyslipidemia, hypertension and coronary artery disease. On examination, he was lethargic with slurring of speech. He had no vision defects or other focal neurological deficits. Rest of physical examination was unremarkable. With stroke as the leading differential diagnosis, we performed CT scan of head without contrast. It was negative for any bleed or midline shift. He also had non-ST segment elevation myocardial infarction (NSTEMI) with elevated troponins. Continuing the work up for syncope, he underwent contrast enhanced CT scan of brain and subsequently MRI and MRA of brain which showed a 1.7 x 1.36 cm pituitary mass (Figure 1 & 2). It was causing suprasellar extension and abutment of optic chiasma. Cavernous sinus was not involved.

Further workup showed elevated serum cortisol and serum ACTH levels. Non supressibility to low dose dexmethasone suppression test and elevated 24 hour urine cortisol confirmed Cushing's disease. He also had low TSH and free T4 indicating some compressive effect. Other pituitary hormones including somatomedin (c-IGF1), growth factor and prolactin were within normal limits.

Typical cushinoid features such as moon face, centripetal obesity, buffalo hump, and violaceous striae were strikingly absent. But he could recall that recently he had difficulty in controlling his blood sugar levels.

Transphenoidal resection of his ACTHoma was postponed due to recent NSTEMI.

Discussion

ACTHomas with Cushing's disease represent 10–15% of pituitary tumors.[7] Most tumors are microadenomas with basophilic and strongly PAS-positive cells.[8] ACTH producing adenomas without clinical and/or biological signs of hypercorticolism may be discovered by the pathologist and are called as Silent ACTHoma. Our patient has various features to confirm Cushing's disease by endocrine panel and MRI brain showed macroadenoma but he did not have any clinical signs of Cushing's disease. His brain biopsy was deferred because of recent myocardial infarction.

ACTH secreting pituitary tumors without Cushinoid features, termed as subclinical Cushing's disease, has been rarely reported.[9] Galectin-3 (Gal-3) is highly expressed in

functioning corticotroph adenomas of the pituitary gland, while silent adenomas exhibit very focal to null expression of Gal-3. This observation can be used in pathological diagnosis to separate functioning and silent corticotroph adenomas of pituitary. Reason for these ACTH-secreting pituitary tumors to be clinically silent remains unknown. It raises many possibilities of biochemical nature of hormone in such patients or early degradation of hormone. It has been suggested that presumed Silent ACTHoma precursor cells represent a distinct subtype of Pro-opiomelanocortin (POMC) producing cells residing mostly in the vestigial pars intermedia of the human pituitary.[10] Corticotroph cells in this anatomic location may lack the ability to respond to cortisol excess causing Cushing's disease.

Older studies recommend to considering adjuvant radiation to these silent corticotroph. But recent studies suggest adopting an initially more conservative follow-up surveillance and delay of upfront radiation until there is clear evidence of tumor recurrence. The published reports on the prognosis of Silent ACTHomas are limited, mostly consisting of series of 13–28 patients. Based on data from 13 subjects with SCA followed-up for at least 3 years, researchers found that persistent or recurrent pituitary tumors on sellar imaging was exhibited in 54% cases.[9]

Medical treatment is currently not included in the management of SCAs. A case of shrinkage of a recurrent tumor expressing D2 receptors following treatment with cabergoline has been reported suggesting that use of dopamine agonists may be an alternative option.[11] Further studies are needed to investigate this hypothesis.

Conclusion

This case report highlights the difficulty in diagnosing silent ACTHomas. The diagnosis of depends on correct interpretation of specific pathological features in context of clinical and biochemical parameters during perioperative period. Good communication between pathologist and endocrine team is therefore important for making the diagnosis. The pathogenesis of Silent ACTHomas remains unclear. Surgery remains the main therapeutic approach. Management and follow-up protocols should be planned taking into account their potential aggressive behavior, particularly upon recurrence.

Conflict of Interest: None

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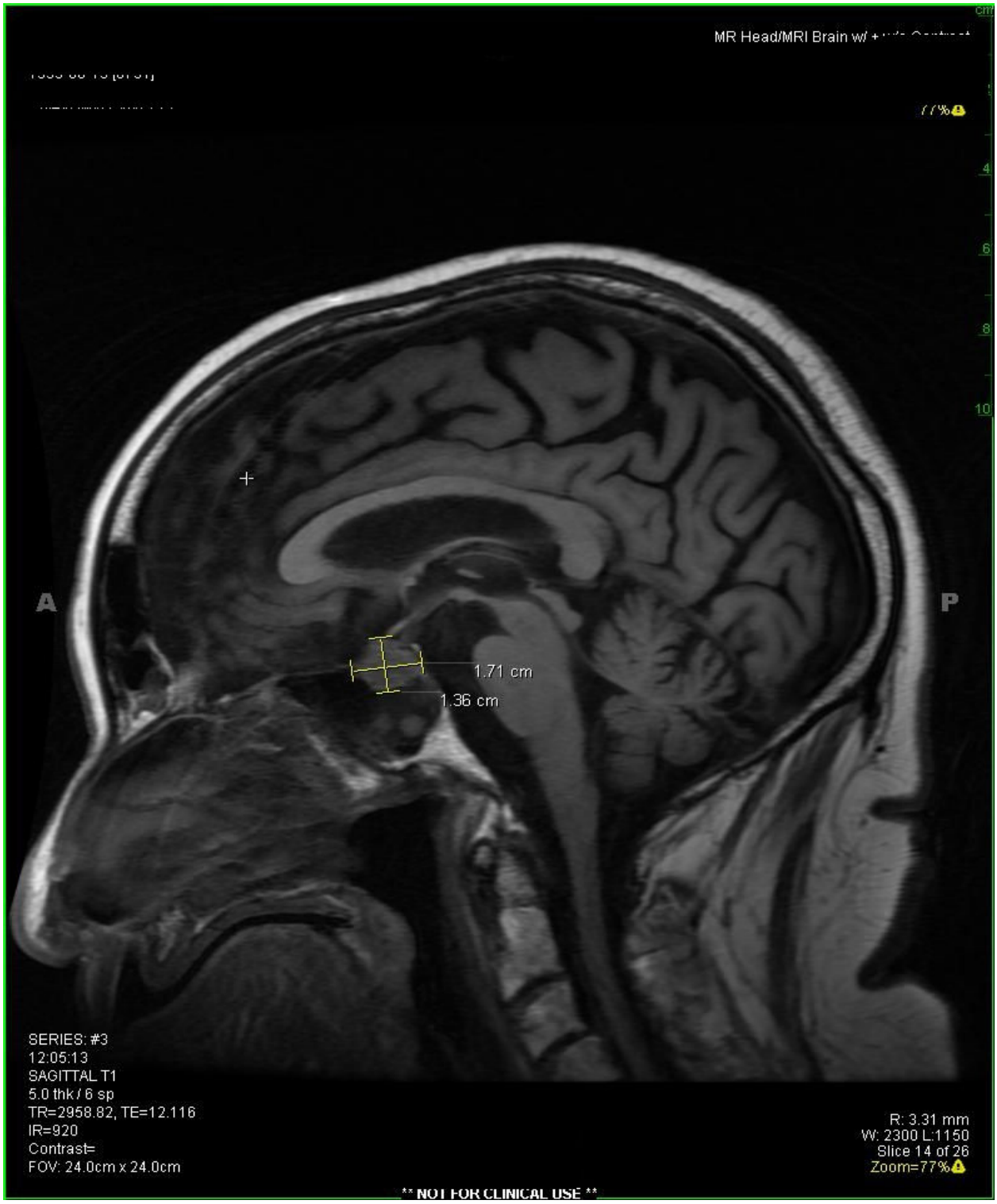

Figure 1: MRI Head Post-Contrast T1 Sagittal view showing Pituitary Macroadenoma

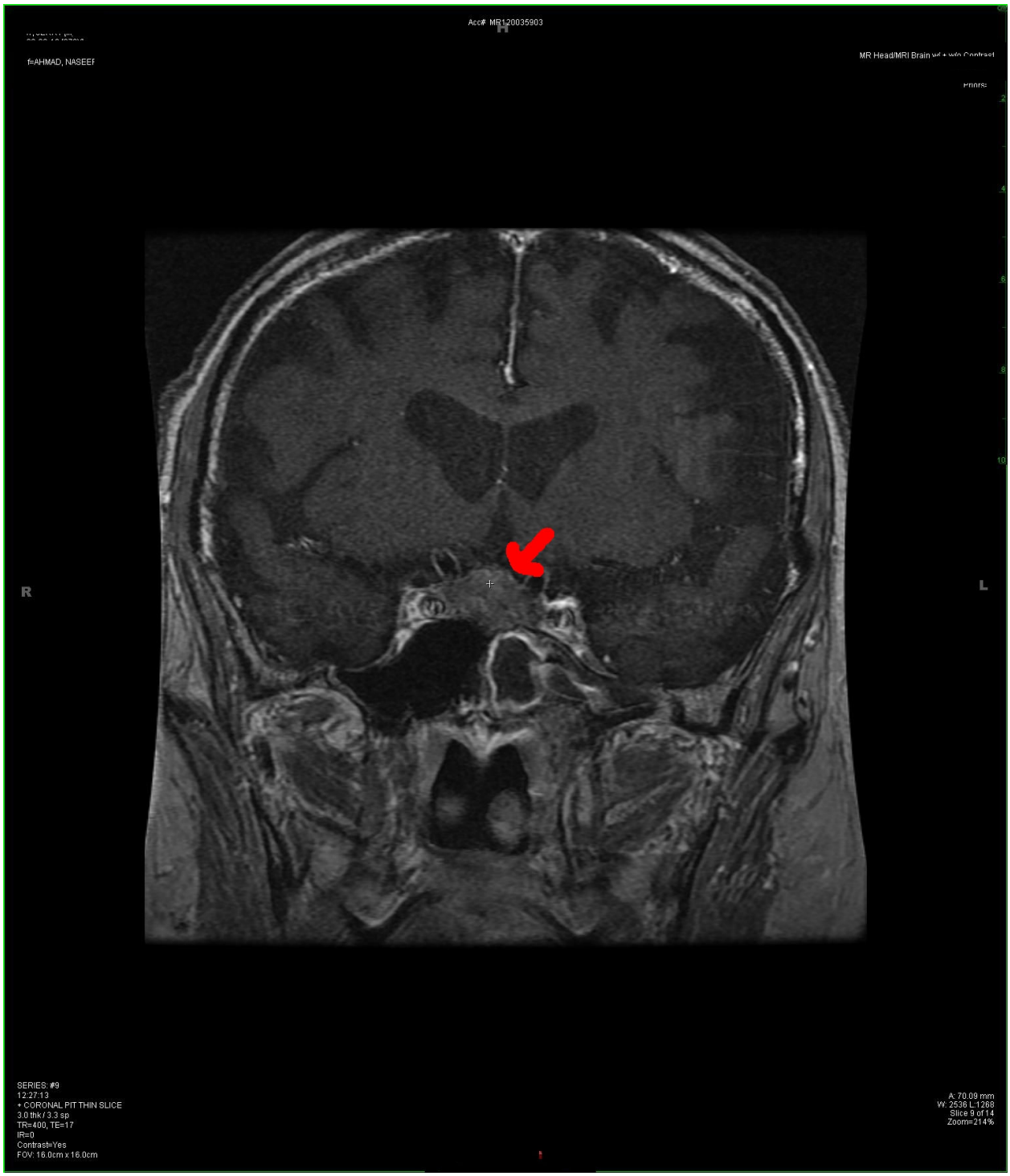

Figure 2: MRI Head Post-Contrast T1 Coronal view showing Pituitary Macroadenoma (red arrow)