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RESEARCH ARTICLE

UNEXPECTED IMMUNOHISTOCHEMICAL SURPRISE OF A CUSHING'S DISEASE MACROADENOMA CO-EXPRESSING ACTH AND PROLACTIN: A CASE REPORT

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Abstract

Pituitary adenomas (PA) are benign well-differentiated tumors, with monoclonal development from the anterior pituitary gland, which can result in serious complications, in particular endocrine, metabolic and visual. Mixed ACTH and prolactin- secreting pituitary adenomas (PA) represent a rare association. We report a rare case of a patient who has Cushing's disease with macroadenomaand the immunohistochemistry surprisinglyrevealed a co-expression of ACTH and PRL, with a silent prolactin lineage. She was a 41 years old female, admitted with aCushing syndrome ACTH-dependent of 73.63pg/ml, complicated with diabetes, dyslipidemia and hypertension. The hypothalamic-pituitary MRI revealed an 11.4x7 mm minimally invasivemacroadenoma,and thevisual fieldwas slightly reduced in both eyes. Her PRL level was normal. She had undergone transsphenoidal removal of the tumor. The immunohistochemical study showed90% expression of ACTHantibodies and 10% of PRL antibodies, the KI67 proliferation index was at 5%. The outcomes showedregression of clinical syndrome with persistent biological cortisolic activity, and the MRI performed 8 months later was normal. Immunohistochemistry remains the key element in diagnosing pituitary tumors and orientating their management. Mixed adenomas, in particularACTH co-secreting adenomas are difficult to manage because of their higher risk of recurrence and their secretory features.

Introduction:-

Pituitary adenomas (PA) are the second most common cause of intracranial tumors (15%) in adults after gliomas. They are benign well-differentiated tumors, with monoclonal development from the anterior pituitary gland, which can result in serious complications, in particular endocrine, metabolic and visual [1]. Mixed pituitary adenomas (PA) represent about 10 to 15% of all pituitary adenomas, about half of them co-express GH and PRL, and exceptionally wecould have a co-expression of ACTH and other hormonal lineages [2]. We report a rare case of a patient withmacroadenoma and ACTH-dependent Cushing's syndrome, who surprisingly co-express ACTH and PRL on immunohistochemistry with a silent PRL lineage.

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Observation:-

A 41 year old female patient was admitted to our department for asthenia, increased irritability and hair loss associated with amenorrhea of eighteen months of duration. The initial clinical statement revealed a Cushing's syndrome associatingcentripetal obesity with a round moonfacies, enlarged fatty supraclavicular regions, buffalo hump, facial and the trunk plethora, red-purple livid striae on lumbar abdominal regions, thin limbs with weakness and difficulty standing up from seated position and a frontal alopecia. The diagnosis was confirmed by a urinary free cortisol (UFC) test 4 times the upper limit and a negative overnight 1mg dexamethasone suppression test. In terms of complications of hypercortisolism, the patient had hypertension, dyslipidaemia and diabetes mellitus. In addition, the patient had melanoderma with a high ACTH level at 73.63pg/ml, a normal PRLlevel at 8.72ng/ml, a gonadotropic deficiency,otherwise the thyrotropic axis was normal, and the somatotropic axis was not investigated. In view of these clinical and biological elements, the hypothesis of Cushing's disease had been raised, and a hypothalamic-pituitary MRIwas performed showing a pituitary macroadenoma of 11.4x7 mm exerting: at the bottom a scalloping on the sellar floor without endosphenoidal extension, laterally it comes into contact with the cavernous sinuses which appear to be intact. The visual field had noted a slight narrowing in both eyes. Facing this pituitary macroadenoma, the therapeutic optionchosewas the surgery. The resectionof the tumorwas performed in the neurosurgical department by transsphenoidal approach. The immediate postoperative assessment showed no complications; the patient did not develop adrenal insufficiency and her cortisolwas of 14µg/dl as well as an increasedUFC of 164µg/24h,signifying the absence of initial remission.

Pathology showed a proliferation of monomorphic tumor cells of endocrine architecture, arranged in trabeculae of varioussizes. Silver impregnation of reticulin showed a partial disappearance of the reticulin meshwork suggesting an adenoma. The pathology was complemented by an immunohistochemical study which revealed the expression of 90% of ACTH antibodies and 10% of PRLantibodies, with a KI67 at 5%.The pituitary MRI performed 8 months after the procedure showed the absence of tumor residues which support the clinicalregression of the Cushing syndrome despite the UFC that remained very high, and the overnight dexamethasone suppression test that still negative; thePRLlevel remained normal at 7ng/ml. Our management consisted of trimestral clinical monitoring and a 6 months imaging monitoring to discuss a surgical revision.

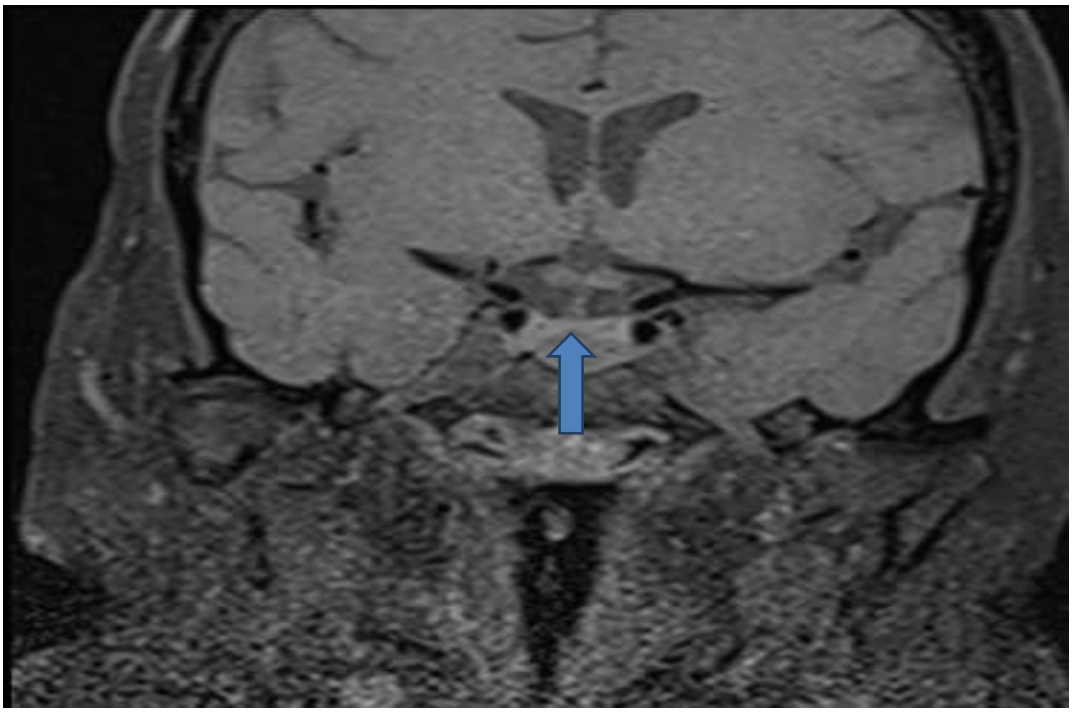

Figure 1:- Preoperative coronal hypothalamic-pituitary MRI showing a pituitary macroadenoma.

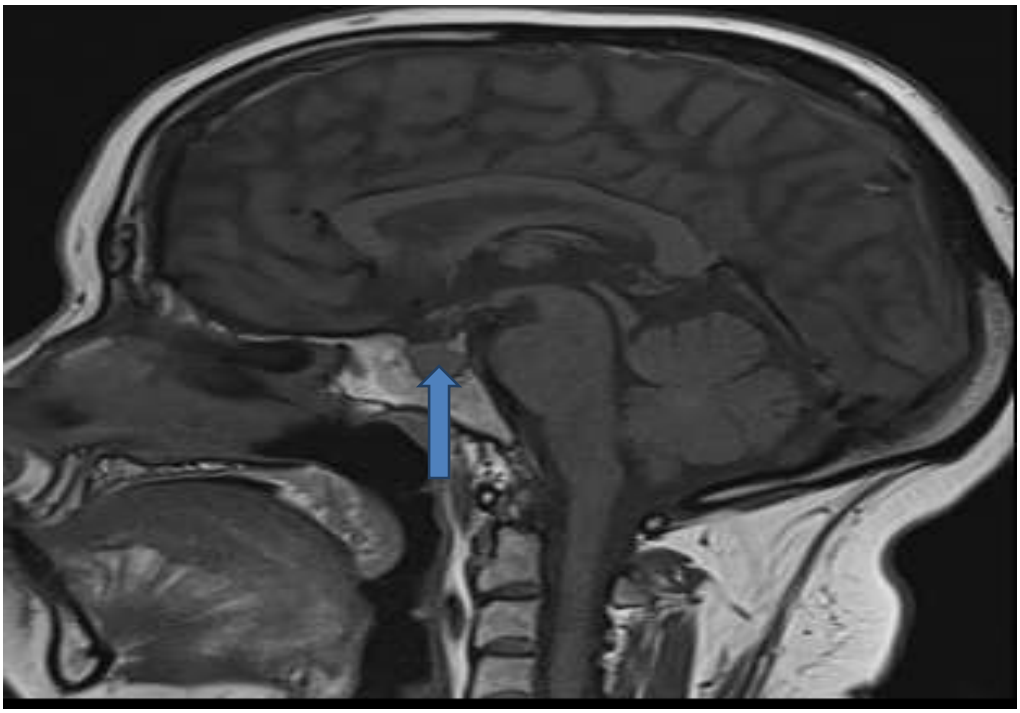

Figure 2:- Follow-up sagittal section MRI showingnotumorresidue.

Discussion:-

Pituitary adenomas (PA) are classified according to the 4th edition of the World Health Organization (WHO) 2017 guidelines by their immunohistochemical labelling, according to thesomatotropic (GH), lactotropic (PRL), gonadotropic (FSH/LH), corticotropic (ACTH) or thyrotropic (TSH) contingent [3].

Pituitary adenomas (PA) can be revealed by a pituitary tumor syndrome, a hormonal hypersecretion syndrome or anterior pituitaryhormone deficiency. Mixed pituitary adenomas are usually macroadenomas in 80% of cases, with an invasive character in 50% of cases. The larger they are, the more likely they grow quickly, recur or resist to treatment [2].

Diagnostic criteria for refractory adenomas have also been proposed as follows: 1) tumor infiltration of adjacent structures based on imaging or intraoperative findings; 2) Ki67 proliferation index greater than 3% and growth rate greater than 2% per month; 3) failure of current therapies to control tumor growth and/or hormonal hypersecretion; and 4) tumor recurrence within 6 months of surgery [3].

Mixed ACTH and PRL adenomas are often manifested by the coexistence of Cushing's disease and prolactinoma. In fact, in humans the genes for PRL and ACTH production are too different to be simultaneously expressed in the same cell suggesting that these adenomas can only contain distinct tumor cell lineages, in the sense that two distinct tumors growing in a small space could join together in a single mass [4,5]. Another explanation could be neoplastic transformation of two different cell lineages or transdifferentiation of a single tumor cell line into a different hormone-producing cell lineage[6, 7, 8, 9, 10] . Another possibility is the neoplastic transformation of plurihormonal clones present in the normal pituitary gland that will proliferate and produce more than one hormone or simply a multidirectional differentiation of inactive pluripotent precursor cells that will acquire the ability to synthesise several hormones during tumor progression [8].

In a systematic review performed in the PubMed, Scopus and Web of Science Core Collection of the US National Library of Medicine databases by Renata M.Budan et al. approximately 1.6 to 3.3% of patients with Cushing's disease have double or multiple pituitary tumors. Silent cell PRL-secreting adenomas or functional prolactinomas most often coexist with tumors that predominantly secrete GH and to a lesser extent ACTH. In context of mixed adenomas, PRL-secreting tumors were the most common incidental lesion coexisting with ACTH-secreting adenomas [9].

In terms of treatment, conventionally the main therapeutic goals of any ACTH adenoma include: 1) normalisation of cortisol secretion; 2) regression of clinical signs; 3) prevention or recovery of concomitant clinical complications and comorbidities; and 4) long-term control of the disease without recurrence. The initial treatment of choice is pituitary surgery, usually consisting of selective removal of the pituitary tumor (adenomectomy) [13].

Our patient had undergone pituitary surgery with total resection of the tumor, as demonstrated by a follow-up MRI. She presented a significant clinical regression of the Cushing syndrome despite biological persistence of cortisolic activity, notably a UFC that remained high, and a negative overnight dexamethasone suppression test as well. This lack of remission also reflects the aggressiveness of these adenomas, as evidenced by the patient's KI67 of 5% even though the adenoma appeared to be minimally invasive.

In patients with no remission, there are still various therapeutic attitudes. In fact, in cases of very mild hypercortisolism and no clinical signs of active Cushing syndrome, a wait-and-see strategy can be practised if there are doubts about a recurrence. Treatment with e.g. low-dose Metyrapone, Ketoconazole or Pasireotide may be recommended in patients with a negative MRI. In patients with a positive MRI, a second pituitary surgery should be considered early. Radiation therapy and adrenalectomy are considered also treatment options [11]. Leah T. Braun et al. reported a follow-up study of 20 patients operated on for Cushing's disease, some of whom co-expressed ACTH and PRL on immunohistochemistry, and showed a possible therapeutic benefit with dopamine agonists. This study demonstrated the D2 receptor expression in 80% of pituitary corticotropictumors and the efficacy of Cabergoline treatment in 60%, with normalisation of cortisol secretion in 40% of patients with Cushing's disease, rationalizing the possible use of Cabergoline to control the hypersecretion of ACTH and cortisol associated with Cushing's disease[11].

Based on the literature, treatment with Ketoconazole or dopamine agonists had been discussed for our patient but finally abandoned due to availability, cost and moderate efficacy. Our attitude was to opt for clinical and imaging monitoring to assess the need for surgical revision over time.

Conclusion:-

Pathology and immunohistochemistry remain the key elements in the diagnosis of pituitary tumors and help the decision make on the appropriate management. Mixed adenomas, especially those involving ACTH secretion, are difficult to manage because of their high risk of recurrence and theirparticular secretory features.

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