Cushing's syndrome  Revealing A Bronchial Carcinoid:  Report A New Case With Review Of Literature

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Abstract: Paraneoplastic Cushing’s syndrome is a rare cause of endogenous hypercortisolism . It is due to ectopic ACTH secretion by a non-pituitary endocrine tumor. It can precede, accompany or follow the discovery of the tumor. The differential diagnosis of Cushing’s disease is not evident. We report the case of a man of 20 years old, admitted on suspicion of cushing’s syndrome. Somatic exam found clear signs of hypercortisolism without melanodermia or high blood pressure. Carbohydrate and ionic level were normally. Hormonal exploration confirmed the diagnosis of endogenous hypercortisolism. Etiologically, the dosing of ACTH was elevated at 129 pg / ml and the high dose dexamethasone suppression test on plasma cortisol was positive eliminating non ACTH-dependent Cushing’s syndrome. Radiologically, RMN of the hypophysis region was normal. Thoracic and abdominal CT scan performed in a second time to remove a likely paraneoplastic ACTH was without abnormalities. Eight months later. Meanwhile the picture had worsened particularly with the appearance of skin pigmentation, a difficult to control severe hypertension, a weight gain of 15 kg with impaired general condition. Hormonal revaluation showed a major rise of ACTH levels at 400 pg / ml with hypokalemia. The diagnosis of paraneoplastic Cushing's syndrome is strongly evoked. Catheterization of petrosal sinus realized at that moment, showed no centro peripheral gradient. The chest X-ray that has been redone showed a right para hilar thoracic lesion unrecognized during the first evaluation. CT scan confirmed the presence of the image of 2 cm long axis.

Keywords: Paraneoplastic Cushing's syndrome, melanodermia, hypokalemia, Catheterization of petrosal sinus, bronchial carcinoid

I. Introduction:
Paraneoplastic Cushing's syndrome is a rare cause of endogenous hypercortisolism (9-18% depending on the series) (1) (2). It is due to ectopic ACTH (adrenocorticotropic) secretion by a non-pituitary endocrine tumor. It can precede, accompany or follow the discovery of the tumor. These tumors are often occult and differential diagnosis of Cushing's disease is not evident. Its management is highly complex. The case report illustrates the difficulties of its management.

II. Case Report
He is a man of 20 years old, admitted to the department of endocrinology on suspicion of cushing’s syndrome. Somatic exam found clear signs of hypercortisolism with truncal and facial distribution of obesity, wide and colorful stretch marks, diffuse, spontaneous bruising and an atrophy of the lower extremities (Fig 1). There was however no melanodermia or high blood pressure.

Figure 1: Patient with a typical Cushing syndrome
Laboratory tests were normal especially on carbohydrate and ionic level. Hormonal exploration confirmed the positive diagnosis of endogenous hypercortisolism showing a ruptured nyctéméral cycle of cortisol, a weak braking negative plasma and urinary cortisol (TABLE I) On the etiological map, the dosing of ACTH was elevated at 129 pg / ml (n <60) and the high dose dexamethasone suppression test on plasma cortisol was positive eliminating non ACTH-dependent Cushing’s syndrome (TABLE I).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Cortisol (nmol/l)</td>
<td>854</td>
<td>275-685</td>
</tr>
<tr>
<td>8H</td>
<td>340</td>
<td>55 – 190</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>129</td>
<td>N &lt; 60</td>
</tr>
<tr>
<td>Low dose dexamethasone suppression / Plasma cortisol</td>
<td>800→456</td>
<td>N&lt; 50</td>
</tr>
<tr>
<td>High dose dexamethasone suppression / Plasma cortisol</td>
<td>784→380</td>
<td>N : ↓de 50%</td>
</tr>
</tbody>
</table>

Radiologically, magnetic resonance imaging of the hypothalamic region was normal. Thoracic and abdominal CT scan performed in a second time to remove a likely paraneoplastic ACTH was without abnormalities.

The good condition of the patient, his age, clinical presentation and the results of the biological exploration took us to the diagnosis of Cushing’s disease. The decision to explore the pituitary by transsphenoidal way is taken. Unfortunately, because of administrative constraints, the patient is transferred to neurosurgery eight months later. Meanwhile the picture had worsened particularly with the appearance of skin pigmentation, a difficult to control severe hypertension with three antihypertensives, a weight gain of 15 kg with impaired general condition. Hormonal revaluation showed a major rise of ACTH levels at 400 pg / ml in serum electrolytes with hypokalemia 2.7 pmol / l. The diagnosis of paraneoplastic Cushing’s syndrome is strongly evoked. Catheterization of petrosal sinus realized at that moment, showed no centro peripheral gradient (Table2)

| ACTH: catheterization of petrosal left sinus | 29.8 pg/ml (tube N° 1) | 31 pg/ml (tube N° 2) | 36,8pg/ml (tube N° 3) |
|                                            | 29.1pg/ml (tube N° 4)  |                      |
| ACTH: catheterization of petrosal right sinus | 23,13 pg/ml (tube N° 1 ) | 30,17 pg/ml (tube N° 2) | 28,75pg/ml (tube N° 3) |
|                                            | 28,75pg/ml (tube N° 4)  |                      |
| Plasmatic peripheral ACTH                  | 32,38pg/ml (tube N° 1) | 27,04pg/ml (tube N° 2) |

The chest X-ray that has been redone showed a right para hilar thoracic lesion unrecognized during the first evaluation(Fig2).

Fig 2: chest radiography showed a right para hilar opacity. CT scan confirmed the presence of the image of 2 cm long axis (Fig3). Scintigraphy labeled octreotide did not show any fixing at this level.
The impact of assessment has not recovered from secondary locations. Lower lobectomy of the right lung is performed. Histological and immunohistochemical study concluded that the presence of an atypical bronchial carcinoid (Fig 4 and 2). The postoperative evolution was simple. The clinical signs of hypercortisolism and melanodermia have regressed after a few weeks as well as hypertension. The collapse of plasma cortisol and ACTH decrease witnessing the success of the surgery required the taking of a replacement therapy with hydrocortisone 30 mg / J. Careful monitoring is indicated.

The last revaluation in January 2016, 3 years after his intervention showed a patient in very good condition, with no clinical signs, biological or radiological recurrence.

### III. Discussion

The first description paraneoplastic Cushing’s syndrome was reported by Brown in 1928 [3]. He is the first who made the link between the symptoms of hypercortisolism such as obesity, hirsutism, polydipsia and hyperpigmentation (in a context of normal radiography sella) and a bronchial tumor discovered in autopsy of a 45 year old patient. The definition of the syndrome was established by Meador and Liddle in 1962 who were the first to demonstrate biologically active ACTH in a lung carcinoid tumour (4). This syndrome as a "heterogeneous group of tumors" from the point of view of topographic location (Half of the cases are of thoracic and intestinal locations), prognosis (excellent, slowly evolving to severe ) and molecular (2, 5).

The bronchial carcinoid is responsible of 1 to 2% of paraneoplastic Cushing’s syndrome (5). Represents 1 to 5% of all lung cancers in adults and is the most common lung cancer of the child (5). This is slow growing tumors. They are part of neuro endocrine tumors of the lung with neuroendocrine large cell carcinoma and small cell carcinoma group. Within all carcinoid tumors, bronchial locations represent 25% of topographies (6).

Therefore, the young age of the patients does not eliminate the diagnosis as is the case in our patient the young age of the patients don’t exclude the diagnosis (case of our patient). One third of patients are aged under 35 old years and cases of teenagers and children have also been reported (2, 5).

The bronchial carcinoid may be isolated or be part of a multiple endocrine neoplasia (MEN) type 1 (5%). The bronchial carcinoid is usually asymptomatic (20-50%) and carcinoid syndrome is rare (7). It has been suggested that all cells are originally totipotent biochemically and in carcinoid cells, the latent potentialities of the cell for secretion become manifest (10).

The normal ACTH is from a precursor known as pro-opiomelanocortin (POMC), which occur on many divisions giving rise to ACTH, to beta-endorphin, enkephalins and to beta or gamma lipotrophines. These divisions will take place, normally, at the level of the anterior pituitary cells. POMC is synthesized in small amounts by all neuroendocrine tumors, but some of them, after amendment cytogenetics, are capable of secreting the large quantity, resulting in high levels of ACTH and thus hypercortisolism. However, most patients with elevated ACTH have no signs of Cushing. it is likely that some tumor cells have an enzyme equipment responsible of a different degradation of POMC and therefore of secretion of a molecule having an immunoreactivity identical to that of ACTH but without biological activity.

Furthermore, some tumors can exert corticotropin like activity, which causes secretion of ACTH by the pituitary. It takes several weeks of steroid impregnation before developing a classic Cushing’s syndrome. This may also explain the very limited number of hypersecretion with paraneoplastic clinical expression. [9]
When it exists, is then usually dominated by a weight loss, asthenia, hypertension, proximal muscle atrophy and edema. Similarly, biological disturbances are inconstant. This is especially hyperglycemia and hypokalemia with metabolic alkalosis (outside any context of diuretic treatment) that are most frequently encountered and which must then suggest the diagnosis (10)(11). When it exists, is then usually dominated by a weight loss, asthenia, hypertension, proximal muscle atrophy, edema. Similarly, biological disturbances are inconstant.

Hyperglycemia and especially hypokalemia with metabolic alkalosis (outside any context of diuretic therapy) are the most frequently encountered. When they are found, they must suggest the diagnosis (10) (11). Hypercortisolism is confirmed by measurement of serum cortisol and urinary cortisol, and Cushing's syndrome ACTH-dependent by the dosage of ACTH. Conventionally, ACTH levels are higher in paraneoplastic Cushing's syndrome than in Cushing disease (12) (13) (14).

The differential diagnosis between Cushing's disease and ectopic ACTH secretion uses hormonal (static and dynamic), radiological and interventional explorations that it may be necessary to combine and possibly repeat during evolution.

It exists a technique of selective catheterization (Internal jugular, petrosal sinus), arteriovenous gradients in the pulmonary circulation and imaging techniques (pituitary MRI, scintigraphy somatostatin analogues) (15) (16) (17). To date there is no diagnostic algorithm-consensus (18) (19).

At the stage of hormonal exploration, the first pitfall is the overlap of ACTH values for Cushing's disease (corticotroph adenoma) and ectopic ACTH values of tumors (occult or not). Slightly ectopic tumors have rates above 200 pg/ml (18). The ACTH levels were initially well below in our patient.

The second pitfall is the variability of hormonal secretion. The principle of dynamic tests (high dose dexamethasone suppression (8 mg daily), CRH test, test of métopyrone, test of desmopressin) is looking for a corticotropin response discriminating Cushing's disease who are often subject to regulation (called positive tests).

An corticotropin response discriminating Cushing's disease who remain often subject to a control (so-called positive tests). Ectopic Cushing syndromes are typically autonomous and are beyond the control (called negative tests).

Taken individually, these tests have a sensitivity and specificity averages from 80 to 90%. This is often the concordance of different explorations that allows the diagnosis.

Furthermore, 30 to 40% of the carcinoid tumors can respond to high dose dexamethasone suppression as is the case with our patient. Achieving a strong braking intravenous decadron could avoid it (12). The test at métopyrone should no longer be used because more than 50% of Cushing paraneoplastic syndromes respond to this test (12). Finally the association of CRF test to high dose dexamethasone suppression is some interest that almost all of Cushing paraneoplastic syndromes do not respond to CRF (14).

At radiographic stage and when pituitary MRI is negative associated with dynamic tests discordant, looking for a centro peripheral ACTH gradient between the lower petrosal sinus and peripheral blood during catheterization of petrosal sinus can be used to retain the diagnosis (20).

This invasive procedure should be performed by entrained teams for the results to be reliable on the one hand and the other hand to reduce the risk of complications.

When the ACTH assay is done under CRH, the sensitivity and specificity is nearly 100%. Diagnosis can be biased in case of antecortisolique treatment or in the very rare cases of exclusive ectopic secretion of CRF. The lack of centro peripheral ACTH gradient is characteristic of ectopic ACTH secretion (our patient) (20). Once the diagnosis of para neoplastic Cushing's syndrome is established, difficulties of localization of ectopic tumor may arise.

Indeed, the latency between the positive diagnosis of ectopic ACTH production and localization of the tumor varies from 1 month to 20 years depending on the case (8 months, our patient). Bronchial carcinoid are the most difficult to find. In over 15% of cases, the seat of the endocrine tumor with ectopic ACTH secretion is unknown at the initial evaluation (21, 22).

The diagnosis of localization by conventional imaging (X-ray and CT scan) of bronchial carcinoid is not very efficient. Carcinoid is usually hilar or perihilar (our patient). 60% are located in the middle lobe of the right lung. Calcifications are present in 30% of cases (6).

These are nodules or masses with well-defined contours and richly vascularized stroma, hence the significant risk of bleeding (13) (23).

It is in this context that the isotopic functional imaging is fully place. Scintigraphy labeled octreotide Scintigraphy has interest diagnosis and prognosis (24). The sensitivity is 80% for the diagnosis of primary carcinoid tumors. The absence of fixations in our patient may be explained by the fact that the tumor does not express somatostatin receptors and or that their density is low.
Indeed a third of bronchial carcinoid do not express somatostatin receptors and therefore are not binding to the scan (24) (25).

The utility of fluorodeoxy glucose positron emission tomography in the evaluation of malignant tumors has been demonstrated. 18 F-FDG is a tracer of glucose metabolism of cells. Its retention is prominent in cells characterized by a rapid turnover with increased glycolysis (eg malignant cells). Tumors carcinoid are commonly reported as false negative. The low mitotic index of these tumors is the most likely cause (26).

Positron emission tomography (PET) may be useful to assess the size of carcinoid greater than 1.5 cm. Atypical carcinoid set mostly. The sensitivity of this examination is 54 to 74% (26) but it falls to 14% when the tumor is smaller (28). Unlike other tumors responsible for ectopic ACTH secretion (medullary carcinoma of the thyroid, pheochromocytoma, gastrinomas), tumor markers of bronchial carcinoid (chromogranin A, urinary 5HIAA) have poor diagnostic value (29) histologically and prognostically, the absence of necrosis and the presence of less than 2 mitoses per ten fields distinguish the typical carcinoid from atypical carcinoid with poorer prognosis (29). The positive for chromogranin A and synaptophysin immunohistochemistry, confirming the diagnosis of carcinoid. Therapeutic of these carcinoid is easy if the tumor is localized. The treatment is surgical and depends on the presentation of the lesion: Partial resection (segmentectomy, wedge resection) in the case of peripheral locations - Radical surgery (lobectomy or bi lobectomy, resection anastomosis or pneumonectomy) in the central forms (our patient) with systematic lymphadenectomy.

Intraoperatively, decreased plasma ACTH concentrations of 50% from baseline in the 15th minute is in favor of the completeness of resection. ACTH undetectable levels 10 days after surgery confirm the diagnosis (6, 29). An additional therapy with chemotherapy, octreotide or MIBG marked is not justified for typical carcinoid operated conventionally including cases with lymph node involvement. In patients with metastases, therapy is not well defined because of the lack of controlled studies: chemotherapy with cisplatin and etoposide is rarely reported as effective. The combination 5-FU and streptozotocin is widely used in gastrointestinal carcinoid tumors with response rates not exceeding 20%. Its effectiveness in bronchial carcinoid tumors is not confirmed (30).

Indeed, typical bronchial carcinoid have an excellent prognosis. Typical carcinoid with or without lymph node involvement were overall survival is 95 to 100% at 10 years after surgery alone. The size of the tumor is not a prognostic factor (29).

In resistant cases, we can reduce hypercortisolism by anticortisol tumor. When it is treated, changes in clinical and humoral factor produced by the tumor are correlated (6, 29).

Knowledge of paraneoplastic complications is helpful for early diagnosis of the tumor and to assess patient prognosis. Treatment is based on the etiologic support: surgical removal of the tumor. When it is treated, changes in clinical and hemorhoidal factor produced by the tumor are correlated. In resistant cases, we can reduce hypercortisolism by anticortisol tumor. The somatostatin analogues that block the receptors are very active on these symptoms. They are widely used (31).

IV. Conclusion

Early detection of adrenocorticotropic-secreting by bronchial carcinoid is challenging. Carcinoid tumor may be antedate the development of cushing’s syndrome or may first become manifest long after the onset of the syndrome. Knowledge of paraneoplastic complications is helpful for early diagnosis of the tumor and to assess patient prognosis. Treatment is based on the etiologic support: surgical removal of the tumor. When it is treated, changes in clinical and humoral factor produced by the tumor are correlated. In resistant cases, we can reduce hypercortisolism by anticortisol tumoral. The somatostatin analogues that block the receptors are very active on these symptoms. They are widely used (31).

Bibliography