primary care medicine and specialized practice. The characteristics of our population are close to the French study ENTRED obtained from the national health insurance and composed of 275 patients with T1D and 3894 patients with T2D in 2007 and 2010 [6]. The average ages of the patients with T1D or T2D are comparable, but the mean duration of diabetes was 2 years higher in our study. The metabolic control was worse in our population as the mean glycated hemoglobin was 8.2% compared to 7.0% in the ENTRED study. The Hb1Ac was superior or equal to 8% in 40% of our patients with T1D and 39% of the patients with T2D. Better results for T2D were reported in the ENTRED study as only 15% of the patients did not reach the goal. On the other hand, similar results were observed in T1D (38%). The prevalence of coronary heart disease was in the same range for T2D patients (16.7% in ENTRED and 19.3% in SURCOUF). Those differences can in part be explained by the predominance hospital recruited patients in our study (71% vs. 50% in ENTRED). A Swedish cohort of 435,369 patients also reported comparable data [3]: similar age (65.8 years), a better control of diabetes (mean HbA1c 7.1%) but with a shorter mean disease duration of 5.6 years. The treatment targets defined by the European guidelines were better achieved in SURCOUF for systolic blood pressure (133 mmHg vs. 140 mmHg) and LDL-cholesterol (104 mg/dL vs. 114 mg/dL). The cardiovascular prevention treatments were more extensively used in France, e.g. antihypertensive treatment (69.0% vs. 64.9%) and the lipid-lowering treatments (63.6% vs. 40.1%). All together these results underline the reliability of the data collected online on a voluntary basis and offering the possibility of longitudinal follow up or comparisons with other international registries. The main problem encountered was the initial poor involvement of physicians, partially improved by a clinical research visitor who directly assisted the practitioners in their offices. We observe consistency with previously published French or foreign data. The electronic health records reported from national care survey systems are probably the best option to get these data [7,8]. The online access allows extending the SURCOUF database in any part of the country or worldwide. It could be updated to provide regular data on the clinical and treatment trends, with a reasonable cost. It also offers the opportunity to have access to a large population potentially concerned by clinical trials.

We thank the GenGeps organization, Merck Sharp and Dohm for the financial support of this study.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

References

[1] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14.
[2] Risk NCD, Collaboration F. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet 2016;387:1513–30.
[3] Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–32.
[4] Fournier C, Chabert A, Mosnier-Pudar H, et al. Étude ENTRED 2007–2010, INPES - Sante Publique Fr (2011), report accessible online on http://inpes.santepubliquefrance.fr/etudes/pdf/rapport-entred.pdf, last accessed 10, September 2017.
[5] Detournay B, Cros S, Charbonnel B, et al. Managing type 2 diabetes in France: the ECODIA survey. Diabetes Metab 2000;26:363–9.
[6] Tiv M, Viel JF, Mauny F, et al. Medication adherence in type 2 diabetes: the ENTRED Study 2007, a French population-based study. PLoS One 2012;7:e32412.
[7] Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). Int J Epidemiol 2015;44:827–36.
[8] Birtwhistle RV. Canadian primary care sentinel surveillance network: a developing resource for family medicine and public health. Can Fam Physician 2011;57:1219–20.

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https://doi.org/10.1016/j.ando.2018.11.005

Case report: Ectopic ACTH secretion due to a metastatic atypical lung carcinoid tumor. From diagnosis to treatment

Cas clinique : sécrétion ectopique d'ACTH due à une tumeur carcinoïde atypique du poumon, au stade métastatique. Du diagnostic au traitement

A 71-year-old woman was admitted in our department for asthenia and biological and clinical suspicion of Cushing Syndrome (CS). She had a remarkable history as she suffered from post-vaccinal poliomyelitis at the age of three with residual paresis of her left arm and leg. She never smoked or drank alcohol. Since one month, she complained of progressive asthenia and edema (especially of the face), centripetal obesity, severe proximal muscle weakness and spontaneous ecchymosis. Depressive symptoms were reported by her relatives. She denied taking exogenous steroids. On clinical examination, she presented Cushingoid features (moon facies, skin atrophy, ecchymoses, centripetal obesity and peripheral edema). Cardiopulmonary examination revealed a systolic murmur (graded 2 on a scale of 6). Muscular testing revealed a loss of strength (graded 4 on the scale of 5). Routine blood examination disclosed an elevated fasting plasma glucose (141 mg %) and HBA1c (6.5%), hypokalaemia (2.1 mmol/L) associated with a metabolic alkalosis (HC03-: 51 mmol/L), and an elevation of the plasma LDH (598 mmol/L). Neutrophilic leucocytosis (neutrophils: $11.97 \times 10^3/mm^3$) without any inflammatory syndrome (CRP: 4.65 mg/L) and eosinopenia (eosinophils: $0 \times 10^3/mm^3$) were also observed. Adrenal investigation showed that her 24 hour free urinary cortisol was markedly increased (453 μg; norm <80 μg), as were plasma ACTH (117 pg/dL; norm < 49 pg/mL) and morning cortisol concentrations (40.7 mg/dL; norm < 18 mg/dL). The circadian rhythm of cortisol was also disturbed (40.7 mg/dL; norm < 18 mg/dL in the morning; 33.8 mg/dL (norm < 10.6 mg/dL) in the evening). A

low dose 1 mg dexamethasone suppression test earlier performed showed no suppression of serum cortisol (cortisol: 42.6 mg/dL; norm < 5 mg/dL). Given the severity of cortisol hypersecretion, an immediate exhaustive procedure to determine the etiology of the ACTH hypersecretion was engaged, including thoracoabdominal CT and pituitary MRI. No pituitary tumor was evidence, neither a lesion in favour of a neuroendocrine tumor. However, multiple intrahepatic nodular lesions were identified. They were mostly hypodense fleshy lesions. So, in second instance, a biopsy of one of the hepatic nodules was performed.

Histology revealed metastasis of a neuroendocrine tumor of grade II according to the WHO classification (KI67: 14%) with a positive TTF1immunoreactivity (pulmonary origin likely). An ectopic secretion of ACTH was therefore highly suspected and, an inferior petrosal sinus sampling was deemed unnecessary. As both thoracic and abdominal CTs did not reveal the primary localisation of the neuroendocrine tumor, an octreoscan was done and showed no uptake. In contrast, a FDG-PETCT showed a high uptake in several lesions in the liver but also in a lesion in the inferior left lobe which was at first not found on the CT of the chest. (Fig. 1)

Although no biopsy of the pulmonary lesion was made, based on the results of imaging, histology and immunochemistry of the liver metastasis, the diagnosis of a primary atypical carcinoid of the left inferior pulmonary lobe was raised. CGA (1330 μg/L; nl < 100) and NSE plasma levels (28 μg/L; nl < 18) as well as urinary 5HIAA levels (16.9 mg; nl < 8) were all increased, which also pleaded in favour of an atypical pulmonary carcinoid. The patient was successfully treated for her hypercortisolism by giving ketoconazole 600 mg daily in the first months . For the tumor, it was decided not to do a resection of the primary lesion as the patient presented a very distorted general state, being inter alia in a wheelchair due to her left hemiparesis. As there were no somatostatin receptors identified, our patient was treated by everolimus. However, it is important to acknowledge that ketokonazole is a mild inhibitor of CYP3A4. As everolimus is a substratum of this cytochrome, the posology of everolimus, was divided by two in this case. At the first consultation 12 days following the start of the treatment, she was well and had normal plasma levels of cortisol (7.6 μg/dL) and kaliemia (3.7 mmol/L). The lesions were stable and some were even in slight improvement. The levels of kaliemia and cortisol were stable during the next 3 months under the same treatment.

The localization of the primary NET responsible for an extopic Cushing Syndrome (ECS) may be very challenging. ECS is usually due to a primary tumor situated in the lung (SCLC or carcinoid tumor), the thyroid (medullary carcinoma) or more uncommon due to a pheochromocytoma or an abdominal NET. So, patients with ectopic corticotropin secretion should at first be evaluated with computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and the neck, MRI being more performant for detection of thymic lesions. Several studies have reported that the tumor was found in a majority of these patients [1,2]. If nothing is found in the chest, MRI or CT of the abdomen has to be performed [1,2]. However, often a combined thoracoabdominal CT can be performed immediately to avoid losing time, as in our case. However, the ACTH source is not identified by conventional imaging modalities (such as CT, and MRI) in 30 to 50% of the patients with ACTH dependent CS [1,3,4]. As literature reports that NET express somatostatin receptors in up to 80% of the cases, octreoscan is a cornerstone for tumor localisation but also to identify if patients will respond to a treatment with somatostatin analogues. OctreoPET has a higher sensitivity than the octreoscan and a better spatial resolution, identifying lesions of smaller size. However, some tumors, do not express SSTR. The less the tumor is differenciated, the less it will express somatostatine receptors (WHO grade 2 or 3). Performing octreoscan or octreoPET will both lead to negative results [5]. FDG-PETCT is then the second-line diagnostic tool when other modalities have failed to identify the primary lesion. FDG- PETCT identifies some lesions with high metabolic activity. It is important to highlight that in spite of all the aforementioned exams, in approximately 10 to 19% of ECS, the primary origin remains undiscovered [3,4,6].

Recently, markers have also been discovered assigning the primary origin by immunohistochemical analysis performed on biopsies of metastases. Thyroid Transcription Factor-1 (TTF1) is a transcription factor used as a specific marker of lung origin. In the most recent immunohistochemical study of Yang and al., 3 markers were studied on biopsies: TTF1, CDX2, and ISL1. They predicted the primary site in 6 out of 10 NETs of unknown primitive origin (UPO), reducing the rate of UPO from 10 to 5%. In addition to immunohistochemical analysis, gene expression-based tests were also recently proposed as diagnostic additional tools in cases with uncertain diagnoses but these tests are not yet available in common practice [7,8]. In our case TTF1 marker was obviously positive

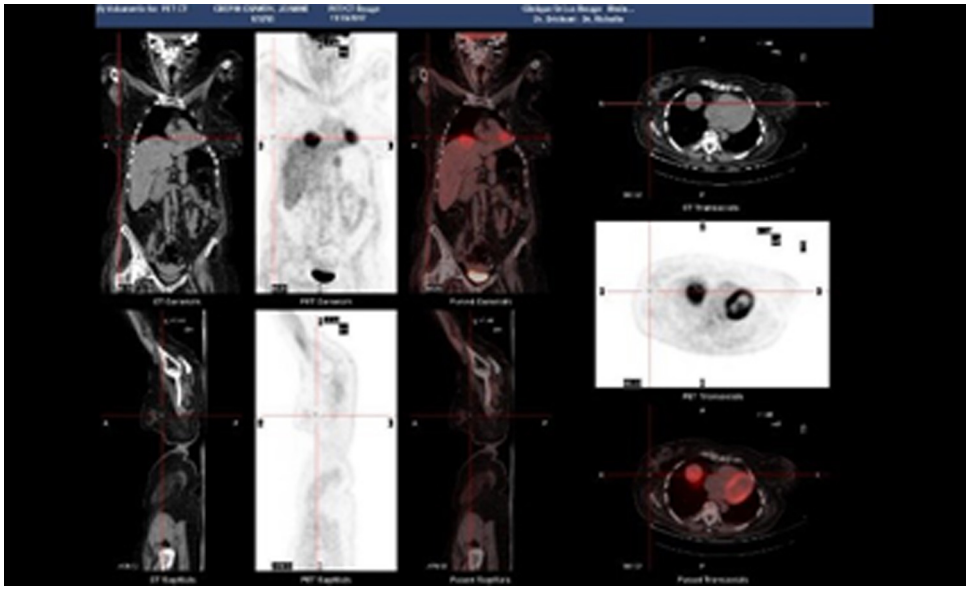

Fig. 1.

which further suggested that the lesion identified in the pulmonary inferior lobe was the primitive lesion.

The first-line treatment for patients with a metastatic lung NET consists in complete resection of the tumor-primary lesion and metastases- when possible. Surgical resection of liver metastases can be considered with curative intent, when more than 90% of the tumor can be removed [9,10]. Whenever total resection is not possible, locoregional options including surgery (for primary and metastases), transarterial embolization (TAE), and radiofrequency (RF) should always be considered for slow progressive ATCs [9,10]. The study of Davi and al proved recently that patients who underwent surgery (including just the resection of the primary lesion without metastases) had a better survival rate than those who didn't [11].

For patients with an unresectable, slowly progressive, metastatic lung NET with somatostatin positive receptors, guidelines also recommend treatment with a somatostatin analog (SSA), such as Octreotide or Lanreotide [9,10]. SSAs have been shown to inhibit tumor growth (by acting on antiangiogenesis and antiproliferative pathways) in patients with advanced NETs but also to control carcinoid syndrome by binding to the somatostatin receptors.

In patients with ATCs that are somatostatin receptor-negative, recent European guidelines recommend everolimus, a potent m-TOR inhibitor, as first-line treatment and cytotoxic chemotherapy as second-line treatment [9,10]. Everolimus may be an appropriate first-line option for patients with tumors that are somatostatin receptor-negative based on the results from the RADIANT-4 trial, a phase III study [12]. In this study, 302 patients with advanced, progressive nonfunctional NETs of the lungs were randomized to either 10 mg everolimus daily or placebo. PFS was prolonged by 7.1 months and the risk of progression of the disease was reduced by 52% in everolimus-treated patients.

In addition to the treatment of the tumor, the treatment of the Cushing syndrome has also to be considered as hypercotisolism may significantly alter life expectancy. The consequences of hypercortisolism can lead to the death of the patient, sometimes more rapidly than tumor progression [11]. The treatment of choice for ectopic Cushing syndrome is also the complete resection of the tumor. If the tumor cannot be completely removed, hypercortisolism should be controlled – at least during the first months – with adrenal enzyme inhibitors, such as ketoconazole, metyrapone, and etomidate (which is only used intravenously in severe cases of CS) [1,3,4,11].

But if the life expectancy is expected to be long (several years) and if the medical therapy failed, then those patients should be considered to be treated rapidly by bilateral adrenalectomy [1,3,4,11,13,14]. These patients will be adrenal insufficient lifelong [15].

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Isidori A, et al. The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. J Clin Endocrinol Metab 2006;91:371–7.
[2] Lynn Loriaux D. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med 2017;376:1451–9.
[3] Ilias I, et al. Extensive clinical experience: Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the national Institutes of health. J Clin Endocrinol Metab 2005;90:4955–62.
[4] More J, et al. Ectopic ACTH syndrome in children and adolescents. J Clin Endocrinol Metab 2011;96:1213–322.
[5] Barrio M. The impact of somatostatin receptor–directed PET/CT on the management of patients with neuroendocrine tumor: a systematic review and meta-analysis. J Nucl Med 2017;58:756–61.
[6] Lacroix A, Feelders R, Stratakis C, Nieman L. Cushing's syndrome. Lancet 2015;386:913–27.
[7] Alexandraki K, et al. Management of neuroendocrine tumors of unknown primary. Rev Endocr Metab Disord 2017;18:123–423.
[8] Yang Z, Klimstra DS, Hruban RH, Tang LH. Immunohistochemical characterization of the origins of metastatic weel-differenciated neuroendocrine tumors to the liver. Am J Surg Pathol 2017;41:915–22.
[9] Caplin ME, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol 2015;26:1604–20.
[10] Pavel M, et al. ENETS Consensus Guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 2016;103:172–85.
[11] Davi MV, et al. Prognostic factors in ectopic Cushing's syndrome due to neuroendocrine tumors: a multicenter study. Eur J Endocrinol 2017;176:453–61.
[12] Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016;387:968.
[13] Chow JT. Bilateral laparoscopic adrenalectomy for corticotrophin–dependent Cushing's syndrome: a review of the Mayo Clinic experience. Clin Endocrinol 2008;68:513–9.
[14] Guerin C, et al. Bilateral adrenalectomy in the 21st century: when to use it for hypercortisolism. Endocr Relat Cancer 2016;23:131–42.
[15] Reznik Y, et al. The guidelines of the French Society of endocrinology on adrenal insufficiency management. Ann Endocrinol (Paris) 2018;79:1–22.

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https://doi.org/10.1016/j.ando.2018.11.004