MULTIPLE pituitary adenomas are rare occurrences, as the reported prevalence among autopsy and surgical series is less than 1% [1-5]. Multiple adenomas may also be detected prior to surgery, thanks to the increasing sensitivity of modern neuroradiological techniques [3, 6].

A variety of tumour combinations have been reported, with the three most common pituitary tumours, i.e., non-functioning pituitary adenomas, GH-secreting and prolactin-secreting adenomas, making up the lion’s share [2-12]. ACTH-secreting tumours are more rare, both as single and multiple tumours [13], and, to our knowledge, two ACTH-producing adenomas within the same pituitary have never previously been reported.

We describe the first case of Cushing’s disease due to two clearly distinct ACTH-secreting pituitary adenomas.

Case report

A 56 year-old woman came to our attention with signs and symptoms of hypercortisolism, i.e. weight gain with central fat distribution, hypertension, hypokalemia. Endocrine investigation showed ACTH-dependent hypercortisolism, and dynamic testing (CRH stimulation, 8 mg dexamethasone suppression) was indicative for pituitary ACTH hypersecretion (Table 1). Sellar MRI visualized an asymmetric pituitary gland with a contrast-enhanced microadenoma on the left side and an inhomogeneous area on the right (Fig. 1).

Transphenoidal adenomectomy was advised and careful surgical exploration allowed the removal of two clearly distinct lesions: one in the left lobe, para-medial and close to the neurohypophysis (sample 1)
Pathology

Examination of pituitary specimens by light microscopy showed two distinct adenomas: a 2-mm microadenoma close to the neurohypophysis in sample 1 (adenoma 1, Fig. 2A) and a 9-mm microadenoma in the right side of the pituitary in sample 2 (adenoma 2, Fig. 3A). The two adenomas presented distinct morphological features. Adenoma 1, located in transitional area between adeno- and neurohypophysis, was characterized by blurred margins, small cells with peripheral nuclei and highly basophilic cytoplasm; it also contained sparse haemorrhagic areas (Fig. 2B). Conversely, adenoma 2 was well demarcated from surrounding adenohypophysis by a thin fibrous capsule and made of larger, weakly basophilic cells (Fig. 3B). Both adenomas were intensely positive for ACTH, with adenoma 1 exhibiting stronger staining than adenoma 2 (Figs. 2C and 3C), and negative for GH, PRL, TSH, FSH and LH. The remaining surgical specimens presented normal pituitary morphology. These distinct locations and morphological features argue against a single, horse-shoe adenoma.

Discussion

Double pituitary adenomas are defined as simultaneous, morphologically or immunocytologically dis-
Distinct tumours in the pituitary. They are classified as clearly separated double tumours, visible at preoperative imaging or during surgical exploration, and contiguous double tumours which are too close to be easily distinguished as separate tumours before surgery and are often removed as a single lesion with the pathologist providing the final diagnosis. Of note, double pituitary adenomas should be distinguished from composite, plurihormonal pituitary adenomas as the latter feature a single pituitary lesion with diverse immunohistochemical reactivity [14]. Indeed, multiple hormonal staining at immunohistochemistry is not infrequent.

Conversely, the reported prevalence of double pituitary adenomas is quite low, ranging from 0.004-0.01% in surgical series [2, 3, 5, 13] to 0.05-0.9% in autopsy series [1, 4]. The higher detection rate in postmortem series might reflect the difficulty in identifying these small tumours during surgery, their possible loss by suction and surgical manipulations, and the fragmentation of specimens sent to the pathologist. However, the clinical importance of detecting all pituitary lesions is readily apparent as failure to detect and remove a hormone-secreting adenoma may lead to poor surgical outcome if the noncausative lesion was removed [15, 16]. Indeed, absent pathological confirmation of tumour resection is considered, by some, a criterion for immediate repeat transsphenoidal surgery in patients with Cushing’s disease [15] although not all agree [17, 18].

ACTH-secreting pituitary adenomas account for a small share of pituitary tumors and are similarly rare as second tumours [2, 5, 13, 19]; indeed, the majority of double adenomas feature GH- or prolactin-secreting or non-functioning adenomas [2, 3, 5, 7, 8, 20]. ACTH-secreting pituitary adenomas have been described together with FSH-secreting lesions [21], GH-secreting [13] and, most commonly, with prolactin-secreting adenomas [2, 13, 19, 22-24] or silent prolactin-immunoreactive adenomas [19, 25].
To our knowledge, a case with two pathologically well-characterized, distinct ACTH-secreting adenomas within the same pituitary have never previously been documented in the English literature and our patient probably represents the first report of Cushing’s disease due to double ACTH-secreting pituitary adenomas. Of note, in an extensive review of over 660 pituitary specimens removed from patients with Cushing’s disease, none presented two ACTH-secreting lesions [13]. A suspicion as to the possibility of multiple pituitary lesions already arose with MRI which revealed lesions in both pituitary lobes. Indeed, advances in neuroradiological techniques have led to an increased awareness of multiple pituitary adenomas [3, 6] and encouraged the surgeon to perform a thorough pituitary exploration. However, it is worth recalling that ACTH-secreting adenomas are usually small and often escape neuroradiological detection [26] even with the most advanced equipment [27], or yield equivocal findings such as “inhomogeneous area” [28], thus extensive surgical exploration is commonly performed. In our patient, imaging guided the surgeon to accurately explore both pituitary lobes and led to the removal of two distinct pituitary adenomas, one close to the neurohypophysis and the other square in the right pituitary lobe. The different morphological features of the two adenomas e.g., differently sized cells, variable basophilism and cytoplasm appearance, concurred with surgical report, indeed proved crucial as both tumors stained for ACTH thus distinction based on immunohistochemistry alone could not be performed. Pathological and surgical findings also allowed to exclude “false” double adenomas which may occur if the tumor presents hourglass or horseshoe form and the surgeon fails to remove the entire lesion.

Careful surgical and pathological exploration are necessary not only to correctly identify double pituitary adenomas but also essential to avoid missing the causative adenomas and risking surgical failure. Indeed, failure to remove the ACTH-secreting lesion is the most frequent cause of persistent hypercortisolism [16] and the coexistence of multiple adenomas within the same pituitary gland has been suggested as a cause of surgical failure [29]. There have indeed been reports of patients with Cushing’s disease in whom initial surgery led to the removal of prolactin- or GH-secreting tumors and the causative ACTH-secreting tumour was removed only at repeat surgery [13, 22]. In these cases, the failure to stain for ACTH in the initially removed specimens and persistence of hypercortisolism, encouraged the surgeon to re-attempt pituitary adenomectomy. Conversely, surgical failure after removal of an ACTH-positive adenoma, an infrequent but not so rare occurrence [26], does not lend itself to simple solutions. In our case, had the surgeon failed to remove both ACTH-secreting adenomas then hypercortisolism would have likely persisted and the patient classified as surgical failure notwithstanding the removal of a causative lesion.

In conclusion, double pituitary ACTH-secreting adenomas may occur in patients with Cushing’s disease and could complicate surgical management. If pituitary imaging is suspicious for multiple lesions then surgical exploration has to be thorough in order to avoid surgical failures.

References


