CLINICAL IMAGE

Asynchronous, double, growth hormone––secreting pituitary neuroendocrine tumor of a variable proliferative potential

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Pituitary neuroendocrine tumors (PitNETs) pose a significant challenge, and require multidisciplinary expert care as well as a patient-tailored diagnostic and therapeutic approach. Aggressive PitNETs are invasive, recur frequently, and are often refractory to standard therapies.[1] Double adenomas, defined as a coexistence of 2 separate pituitary tumors, are particularly demanding.[2-5] We present a case in which those 2 rare entities coexisted.

In 2012, a 37-year-old man presented with left-sided painful gynecomastia. He denied symptoms of excessive growth hormone (GH) secretion and showed minor acromegalic features. Due to low testosterone and luteinizing hormone concentrations with mild hyperprolactinemia, pituitary magnetic resonance imaging (MRI) was performed, which revealed a sellar tumor sized 11 mm × 13 mm (FIGURE 1A). An increased insulin-like growth factor 1 (IGF-1) concentration was noted (1482 ng/ml; reference range, 109–284 ng/ml), with a lack of GH suppression in the oral glucose tolerance test (OGTT). Combined treatment with lanreotide 120 mg every 4 weeks and bromocriptine 2.5 mg twice a day was introduced. After the second lanreotide injection, the patient reported a bilateral decrease in visual acuity. Ophthalmologic examination revealed bilateral retinal detachment; therefore, lanreotide was discontinued. Transsphenoidal resection of the pituitary tumor performed in 2012 led to biochemical (IGF-1, 260 ng/ml; GH, 0.08 ng/ml [GH <1 ng/ml indicates remission]) and

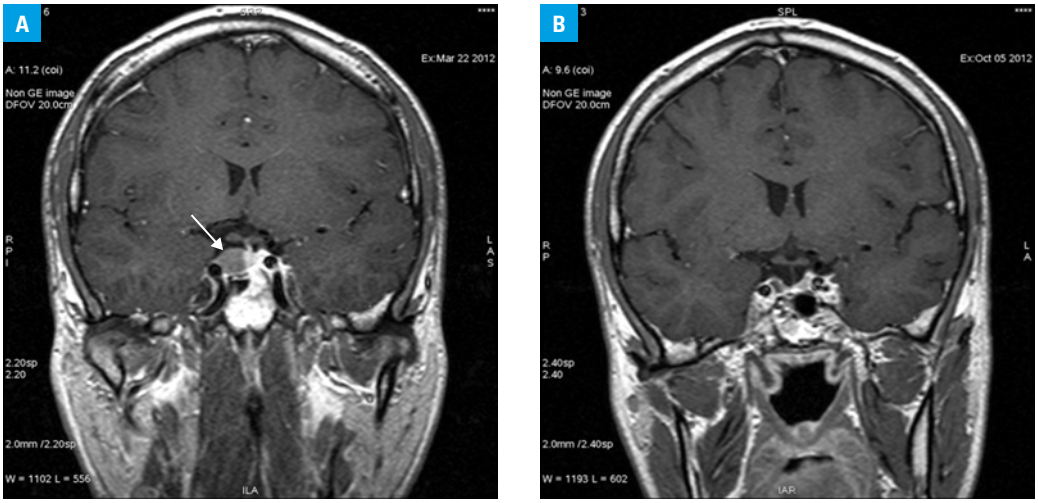

FIGURE 1 **A** – pituitary magnetic resonance imaging (MRI), a T1-weighted, contrast-enhanced coronal image of a 11 mm × 13 mm Knosp grade 1 tumor (arrow) before the first surgery (March 2012); **B** – pituitary MRI, a T1-weighted, contrast-enhanced image of the sella 3 months after the first surgery indicating a seemingly complete tumor removal (October 2012)

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Received: January 7, 2024.
Revision accepted: March 26, 2024.
Published online: March 28, 2024.
Pol Arch Intern Med. 2024; xx: 16716
doi:10.20452/pamw.16716

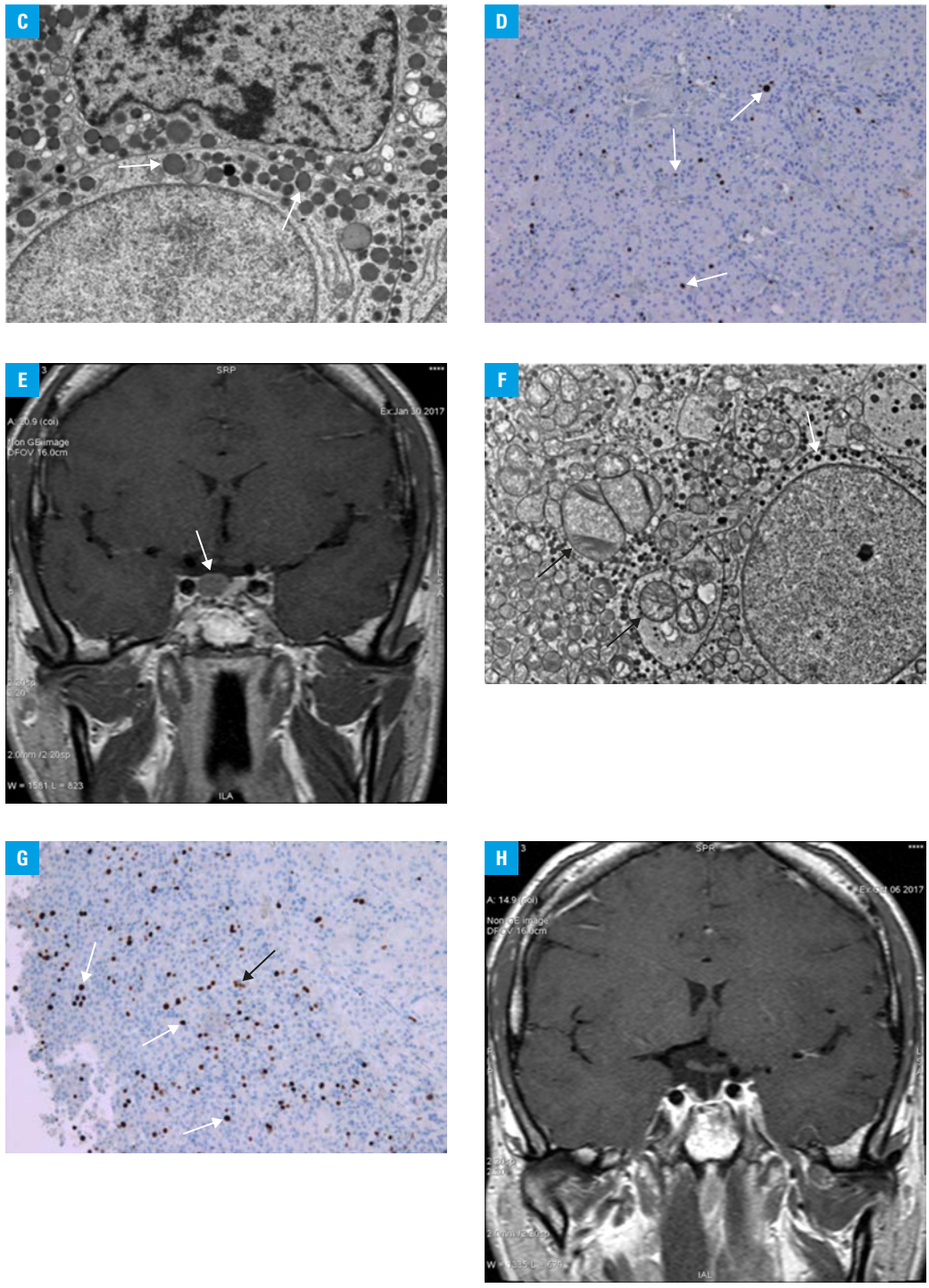

FIGURE 1 **C** – electron microscopy features of the tumor at the first surgery: densely granulated somatotroph adenoma; round secretory granules of medium electron density (arrows), with a diameter of about 350–500 nm (original magnification × 9700); **D** – Ki-67 staining (arrows) of the tumor at the first surgery: Ki-67 <1%, no mitotic figures; **E** – pituitary MRI, a T1-weighted, contrast-enhanced image showing tumor regrowth (7 mm × 4 mm × 9 mm Knosp grade 0 adenoma; arrow) 5 years after the first surgery (January 2017); **F** – electron microscopy features of the tumor at the second surgery: oncocytic somatotroph acidophil stem cell adenoma. The tumor exhibits oncocytic change and a unique mitochondrial abnormality (black arrows). Round electron-dense secretory granules (white arrow) are less numerous, with a diameter of about 150–200 nm, located under the cell membrane (original magnification × 7400). **G** – Ki-67 staining (white arrows) of the tumor at the second surgery: Ki-67 >3%, single mitotic figures (black arrow); **H** – pituitary MRI, a T1-weighted, contrast-enhanced image of the sella 3 months after the second surgery, indicating an apparently complete tumor resection (October 2017)

radiologic (FIGURE 1B) remission of the disease. Histopathologic examination revealed a densely granulated somatotropic pituitary adenoma (FIGURE 1C) with mild nuclear atypia (Ki-67 index <3%), expressing somatostatin receptors (SSTR2A[+], SSTR5[+/–]) (FIGURE 1D). In 2016, however, acromegaly recurrence was confirmed biochemically (increased IGF-1 concentration, 664 ng/ml, and unsuppressed post-OGTT GH level) and, in 2017, on MRI (FIGURE 1E). The patient was reoperated via a transsphenoidal approach in June 2017. The second histopathology examination revealed oncocytic somatotropic acidophil stem cell pituitary adenoma (FIGURE 1F) with a Ki-67 index above 3% and mitotic figures (6 per 10 high-power fields) (FIGURE 1G). Subsequent pituitary insufficiency was diagnosed and adequately treated with levothyroxine and hydrocortisone. Complete tumor removal was confirmed 3 months later by MRI (FIGURE 1H) and a suppressed post-OGTT GH level, although accompanied by a borderline IGF-1 concentration (277 ng/ml). Eight months after the reoperation, remission of secondary hypocortisolism was confirmed based on the cosyntropin stimulation test result, and therapy with hydrocortisone was discontinued. Eighteen months after the surgery, recurrence of acromegaly was confirmed again, with adenoma regrowth and increased GH (2.31 ng/ml) and IGF-1 (474 ng/ml) concentrations. Pharmacotherapy with octreotide long-acting release was started (30 mg intramuscularly every 4 weeks), which led to normalization of GH (0.96 ng/ml) and IGF-1 concentrations (152 ng/ml), as well as partial radiologic regression of the pituitary tumor (from 6 mm × 8 mm to approximately 2 mm) after 6 months of therapy.

To the best of our knowledge, this is the first report of an asynchronous, double pituitary neuroendocrine adenoma with oncocytic somatotropic acidophil stem cell features, which initially seemed to be a classic case of acromegaly.

Pathologists and clinicians should be aware of the possibility of double / multiple PitNET occurrence. Histopathologic predictors of a more aggressive disease course should be thoroughly investigated. Failure to take these factors into account may result in recurrence of symptoms, the need for repeated surgical procedures, and, consequently, a decrease in patient quality of life.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The authors thank the patient for agreeing to publish his case.

FUNDING None.

CONFLICT OF INTEREST None declared.

HOW TO CITE Trofimiuk-Müldner M, Domagała B, Maksymowicz M, et al. Asynchronous, double, growth hormone–secreting pituitary neuroendocrine tumor of a variable proliferative potential. Pol Arch Intern Med. 2024; XX: 16716. doi:10.20452/pamw.16716

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