CLINICAL IMAGE

Pituitary carcinoma as a rare cause of liver metastases successfully treated with temozolomide

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Pituitary carcinoma (PC) is an extremely rare malignancy accounting for 0.1%–0.2% of all pituitary neuroendocrine tumours (PitNETs). PC diagnosis requires either intracranial or distant metastases that appear on average 9 years (range, 0–31) after the first presentation of PitNET.[1,2] The prevalence of PC could be underestimated, as the identification of distant metastases requires a high index of suspicion due to their sometimes asymptomatic course, only being identified at autopsy.[3,4]

We present a unique case of adrenocorticotropic hormone (ACTH)-producing PitNET with incidentally found liver metastases. A 55-year-old woman with visual field deficits, headaches and pituitary deficiency was referred to our department due to a large (33 × 28 × 37 mm) invasive pituitary tumor with suprasellar and cavernous sinus invasion (FIGURE 1A). The clinical features of Cushing's syndrome were subtle, with only facial rounding and androgenic hair loss. Hormonal evaluation revealed increased ACTH level, lack of diurnal rhythm of ACTH (8 am, 232 pg/ml, 11 pm, 236 pg/ml; normal range, 5–46 pg/ml) and cortisol (8 am, 15.7 µg/dl; 11 pm, 16.3 µg/dl; normal range, 5–22 µg/dl), and elevated urinary free cortisol (UFC) 3 times above the upper limit of normal. The results of high-dose dexamethasone suppression test (48 h, cortisol 4.8 µg/dl) and 100 µg intravenous corticotropin-releasing hormone-stimulating test (peak ACTH 352 pg/ml) indicated Cushing's disease. The patient underwent debulking transsphenoidal surgery (TSS) (FIGURE 1B). Histopathological examination confirmed a corticotroph PitNET with Crooke-cell changes (Supplementary material, *Figure S1A–E*) staining positive for p53 and negative for O6-methylguanine-DNA methyltransferase, with Ki-67 labelling index of 3%–5%. TSS resulted in vision improvement, reduction of ACTH (8 am, 79.2 pg/ml) and cortisol (8 am, 8.5 µg/dl) levels, and normalization of UFC. However, 6 months later deterioration of vision and right ptosis occurred due to residual mass progression (FIGURE 1C). The patient underwent a second TSS and received adjuvant stereotactic fractionated radiotherapy (total dose, 54 Gy). Pituitary magnetic resonance imaging over the next 3 years demonstrated stable disease (FIGURE 1D). The patient had no new symptoms, showed stable ACTH (8 am, 60 pg/ml) and normal UFC. However, 4.5 years after the first presentation, liver metastases were detected incidentally during abdominal ultrasound and were confirmed on abdominal computed tomography (CT) (FIGURE 1E). Then, 18-fluorodeoxyglucose positron emission tomography confirmed the presence of 3 liver metastases (FIGURE 1F). The liver biopsy revealed poorly differentiated carcinoma most likely with neuroendocrine activity but of unknown origin (Supplementary material, *Figure S1F*). Additional immunostaining for ACTH was positive (FIGURE 1G). A significant increase in ACTH (8 am, 150.2 pg/ml) and UFC levels were noted despite stable pituitary tumor size. Chemotherapy with temozolomide was started at a dose of 150 mg/m^2 for 5 days every 4 weeks. After 3 cycles shrinkage of the liver lesions was observed on CT (FIGURE 1H). The treatment was continued for 8 months in total with stabilization on CT after 8 cycles. Six months later symptoms suggesting adrenal insufficiency were noted,

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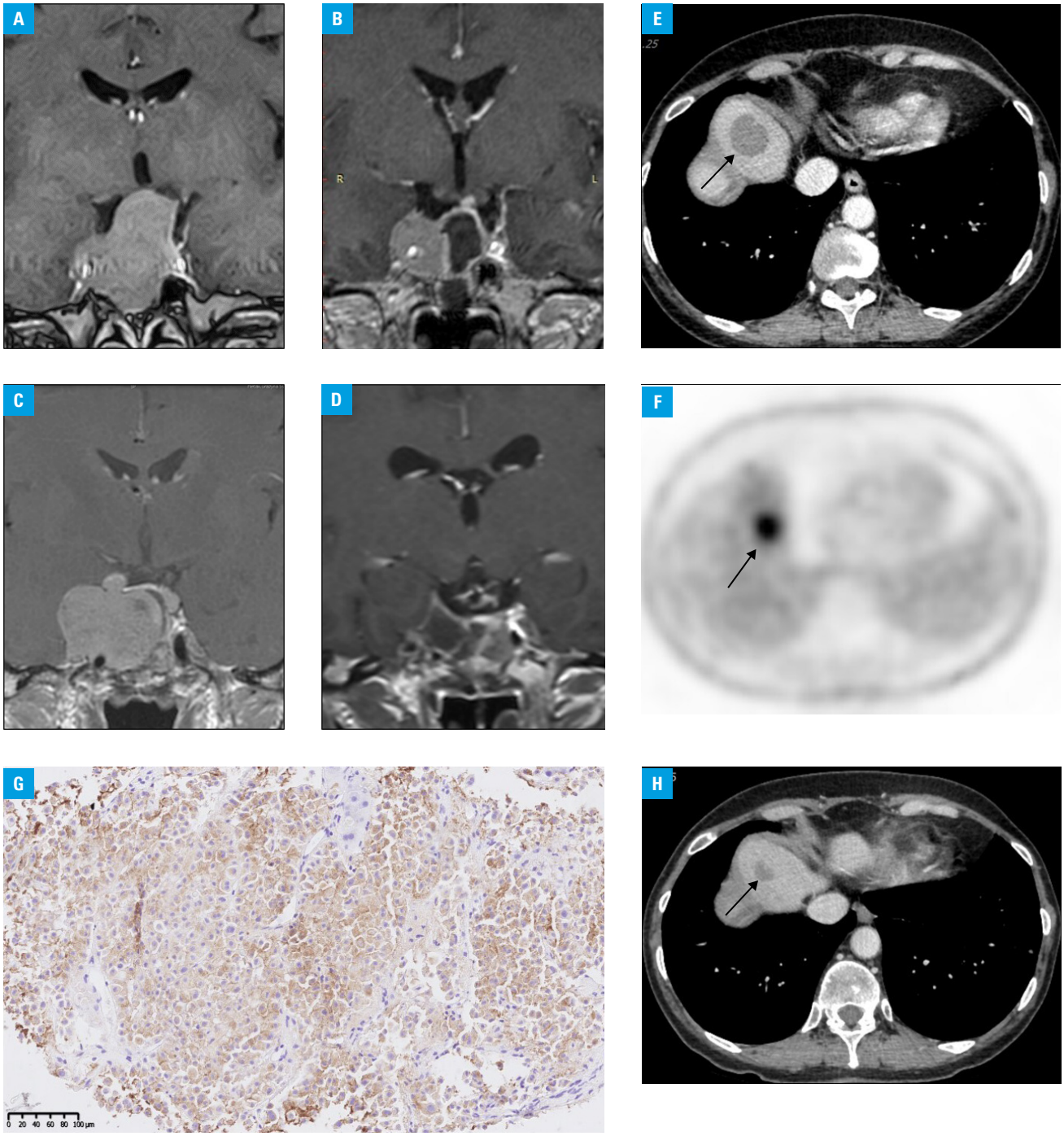

FIGURE 1 **A** – gadolinium-enhanced coronal pituitary magnetic resonance imaging (MRI) scan showing an invasive pituitary tumor 33 × 28 × 37 mm compressing the optic chiasm at diagnosis; **B** – gadolinium-enhanced coronal plane pituitary MRI scan showing residual tumor after the first debulking transsphenoidal surgery; **C** – gadolinium-enhanced coronal plane pituitary MRI scan showing progression of the residual tumor 6 months after the first debulking transsphenoidal surgery leading to deterioration of visual field and right ptosis; **D** – gadolinium-enhanced coronal plane pituitary MRI scan showing residual cystic tumor after 2 debulking transsphenoidal surgeries and stereotactic radiotherapy at the time when liver metastases were visualized; **E** – computed tomography of the abdomen showing one of the liver metastases (arrow); **F** – 18-fluorodeoxyglucose positron emission tomography confirming the presence of liver metastases (arrow); **G** – immunohistochemical staining for adrenocorticotropic hormone in the liver tumor; **H** – computed tomography of the abdomen revealing a significant shrinkage of liver metastasis (arrow) after 3 months of temozolomide therapy

manifested in low 8 am ACTH (7.6 pg/ml) and cortisol (3.8 μg/dl) levels. Hydrocortisone replacement was implemented. Two remaining metastatic foci in the fifth and eighth liver segments were surgically removed. The 2-year observation confirmed a remission proved by negative imaging studies and low ACTH (6.4 pg/ml) and cortisol (1.0 μg/dl) levels.

Although rare, PC is becoming an increasingly recognized entity. PC has to be suspected when metastases are found in a patient with a history of a recurrent, aggressive PitNET, especially when an increase in ACTH is noted despite stable size of the pituitary tumor.[1] Temozolomide is an effective first-line chemotherapy for PCs.[5]

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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