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Case Report

Pituitary enlargement and hypopituitarism in patient with lung cancer treated with immune checkpoint inhibitors: Metastasis or hypophysitis? Role of imaging ☆

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ABSTRACT

Pituitary gland metastasis is an unusual event, and pituitary metastasis from lung adenocarcinoma is extremely rare and associated with poor prognosis. To date, approximately 16 cases have been reported. Symptoms of these lesions can mimic hypophysitis, that is a possible immune-related adverse event of ICIs (Immune Checkpoint Inhibitors). Pituitary metastases and hypophisitis are life-threatening diseases and making differential diagnosis is important, because therapy of these conditions is quite different. Differentiating a condition from the other one is difficult, because many imaging features are not specific. In this presented case, cross-sectional imaging, in particular Magnetic Resonance Imaging (MRI), has revealed itself helpful to suggest the diagnosis of pituitary metastasis rather than hypophysitis.

Introduction

Pituitary metastases are uncommon and their incidence is about 1 % [1–7]. Breast and lung tumors are the most common cancers that cause pituitary metastases, but also thyroid, prostate, kidney, liver and many other primary neoplasms may metastasize to the pituitary gland [1–8]. Although metastatic involvement of the pituitary gland is asymptomatic in most of the cases, clinical manifestations include

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diabetes insipidus, hypopituitarism, headache, fatigue, nausea, visual field disturbance and ophtalmoplegia [1–9]. Symptoms such as headache, hypopituitarism, diabetes insipidus and visual field defects can mimic hypophysitis, that is a possible immune-related adverse event of ICIs (Immune Checkpoint Inhibitors) [5,9–16]. These drugs have revealed themselves useful to treat many kinds of tumors, encompassing melanoma, lung cancer and non-Hodgkin lymphoma, bladder, urothelial, head and neck squamous cell cancers [11–13]. The most common molecular targets of ICIs are cytotoxic T-lymphocite protein 4 (CTLA4), programmed death ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1); these medicaments enhance T-cells activity against malignancies, so they can lead to immune response disregulation and a wide range of immune-related adverse effects [5,9–14]. Pituitary metastases and hypophisitis are life-threatening diseases and making differential diagnosis is important, because therapy of these conditions is quite different: in fact treatment of pituitary metastases include chemotherapy, radiation therapy, surgery, hormonal replacement or an association of the above modalities, while hormone replacement, immunosoppressive glucocorticoid administration or ICIs withdrawal are effective therapies for hypophysisitis [1–6,9,11,13,14]. In our clinical case cross-sectional Imaging, in particular Magnetic Resonance Imaging (MRI), has revealed itself helpful to suggest the diagnosis of pituitary metastasis rather than hypophysitis.

Case presentation

The patient of our clinical case was a 73 years old man who was diagnosed with primary lung cancer with small cell lung cancer. In the family history there was no positivity for this type of neoplasm. Result of the histological examination: TFN+, synaptophysin+, K67>95 %; stage IIIA (T2b, N2, M0). Therefore, the patient is treated with etoposide and a platinum drug (cisplatin), in particular: 4 cycles of chemotherapy treatment according to the Carboplatin AUC 4 (DT 440 mg) g1 + Etoposide 100 mg/m^2 days 1, 2, 3 (DT 170 mg) q21 regimen to which Atezolizumab (immune checkpoint inhibitor) flat dose 1200 mg was added from the second cycle. Three months later, a control CT scan showed a significant reduction in the primary lung lesion, compatible with a partial response. According to the protocol adopted by the Oncology Department of our Hospital, patients treated with ICIs underwent an evaluation of their clinical history before each treatment cycle, together with a hormonal evaluation of thyroid and adrenal functions. At the start of ICI therapy, the patient presented values within normal limits.

Two months after starting ICI therapy, visual field impairment was diagnosed and an alteration of blood chemistry values was observed, in particular: FT3= 1,2 pg/mL (n.v.: 2.0 - 4.4), FT4= 0.5 ng/dL (n.v.: 0.9 - 1.72), TSH= 0,21 uUI/mL (n.v.: 0.27 - 4.20), Cortisol = 19.4 ng/mL (n.v.: 50 - 250), ACTH= 8.4 pg/ml (n.v.: 0.0 - 46.0), Prolactin = 47.86 ng/mL (n.v.: 4.0 - 15.20). The above values were indicative of diabetes insipidus. Therefore, vasopressin analog administration was needed. In consideration of the fact that diabetes insipidus, although rarely, represents a side effect of the use of ICIs, the therapy with ICI was suspended.

However, not appreciating the reduction/resolution of diabetes insipidus and not being able to exclude the presence of a pituitary metastasis, although rare, we first proceeded to perform a CT scan of the brain without and post contrast medium, in order to evaluate the pituitary gland as well as the bony profile of the diaphragm sellae. CT scan (Fig. 1A, B) showed an enlarged pituitary gland and a significantly thickened pituitary stalk with moderate contrast-enhancement; erosion of the clivus was not visible. Brain MRI scan with and without contrast medium was needed to highlight any aspects that could discriminate hypophysitis from metastasis. We performed, about twenty days later, a brain MRI scan with contrast agent (gadolinium) on 1.5 T MRI scanner. In addition to the morphological sequences, we obtained Diffusion-weighted sequences and MR spectroscopy using 2D PRESS sequences. Apparent diffusion coefficient (ADC) values were measured by placing a region of interest (ROI) in the site of the lesion on ADC maps. MRI scan confirmed enlargement of the pituitary gland and thickening of the pituitary stalk. The FLAIR sequence (Fig. 2A) highlights the presence of an expansive lesion affecting the pituitary gland with predominantly suprasellar development, poor differentiation between the adenohypophysis and the neurohypophysis, arriving in close contiguity with the optic chiasm. The FFE T2 sequence (Fig. 2B) highlights some spots, within the pituitary lesion (yellow arrow), hypointense: hypointensity on FFE T2-weighted sequences suggested the presence of microbleeds in the lesion. The pituitary lesion was visible in the suprasellar region, it was characterized by inhomogeneous contrast-enhancement (Fig. 2C), restricted signal on diffusion-weighted sequences and hypointensity on ADC maps. ADC values (Fig. 3A, B) were low, between 0.4 and 0.6 $\times$ 10^{-3} mm^2/sec, on ADC maps. MR spectroscopy (Fig. 4) showed high lipid (Lip) and lactate (Lac) peaks, high choline (Cho) peak, high choline/N-acetylaspartate (Cho/NAA) ratio, that was equal to 4.37 (Cho/NAA= 4.37). MRI features suggested the diagnosis of pituitary metastasis rather than diagnosis of hypophysitis, so a trans-sphenoidal biopsy of the mass was needed and the diagnosis of small cell lung cancer metastasis was confirmed. The patient underwent radiotherapy (2750 cGy in 5 fractions). 12 weeks later we performed a follow-up brain MRI scan (Fig. 5A–C), that revealed lesion decrease in size; this was associated with a reduction in visual field disorders. Therefore, these results were indicative of therapeutic efficacy.

Two months later, due to the progression of the primary disease and the onset of respiratory complications, the patient died.

Discussion

Imaging Diagnostic tools, especially MRI, play a key role in pituitary metastases and hypophysitis diagnosis, but many imaging radiological findings are not specific, so differentiating a condition from the other one is difficult [1–13]. In our case, CT scan and conventional MRI sequences detected enlargement of the pituitary gland and thickening

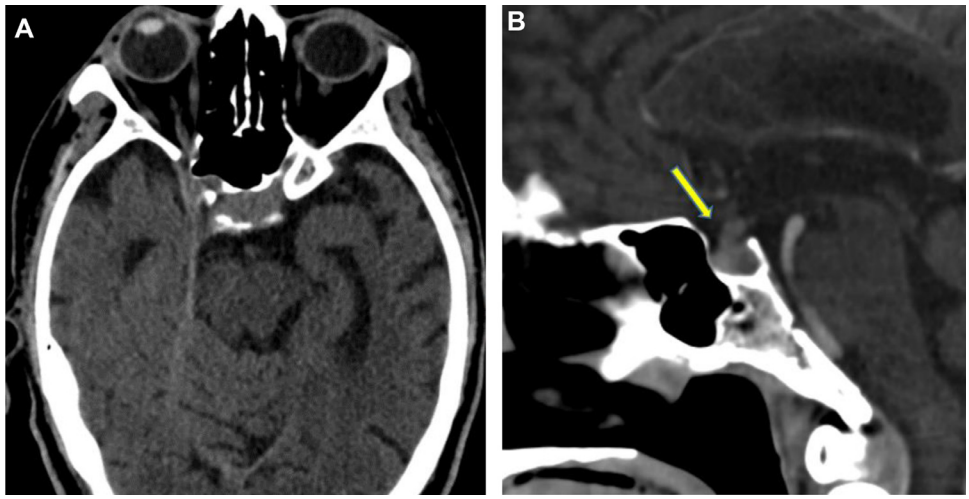

Fig. 1 – (A, B). Enhanced cranial CT scan axial (A) and sagittal plane (B) revealed an enlarged pituitary gland and a significantly thickened pituitary stalk (yellow arrow) with moderate enhancement. No evident erosion of the clivus.

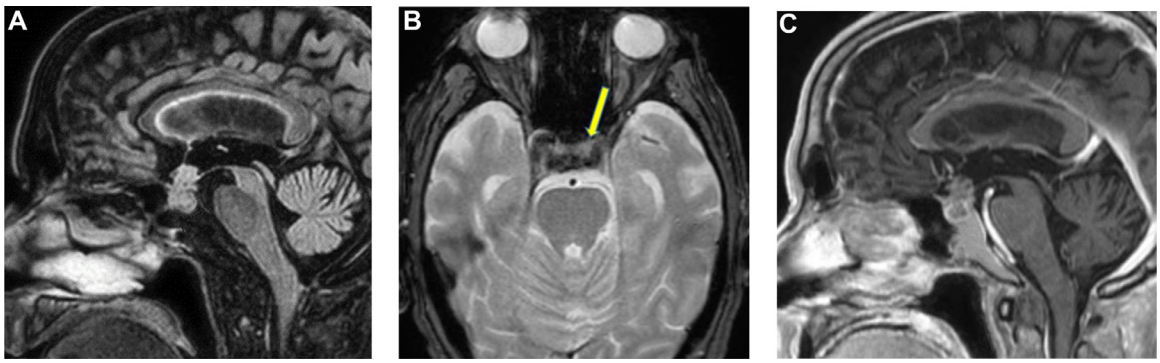

Fig. 2 – (A-C). The FLAIR sequence (A) highlights the presence of an expansive lesion affecting the pituitary gland with predominantly suprasellar development, poor differentiation between the adenohypophysis and the neurohypophysis, arriving in close contiguity with the optic chiasm. The FFE T2 sequence (T2*) highlights some spots, within the pituitary lesion (yellow arrow), hypointense, compatible with contextual hemorrhagic microfoci (B). T1 post contrast sequence (C), sagittal plane, shows a non-homogeneous enhancement of the pituitary expansive lesion.

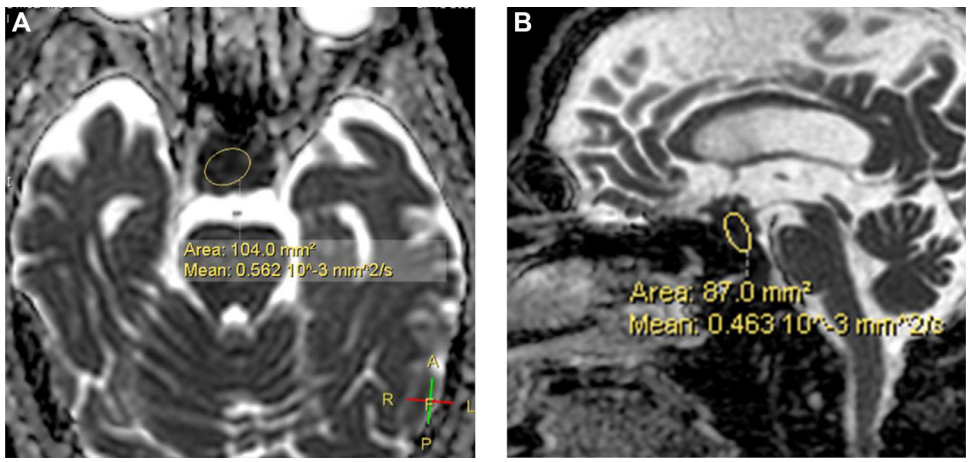

Fig. 3 – (A, B) DWI sequence, axial plane (A) shows signs of restriction of the pituitary lesion with low values in the ADC map (0.5 x 10^{-3} mm^2/sec). DWI sequence, sagittal plane (B) shows signs of restriction of the pituitary lesion with low values in the ADC map (0.5 x $10^{-3}$$mm^2$/sec).

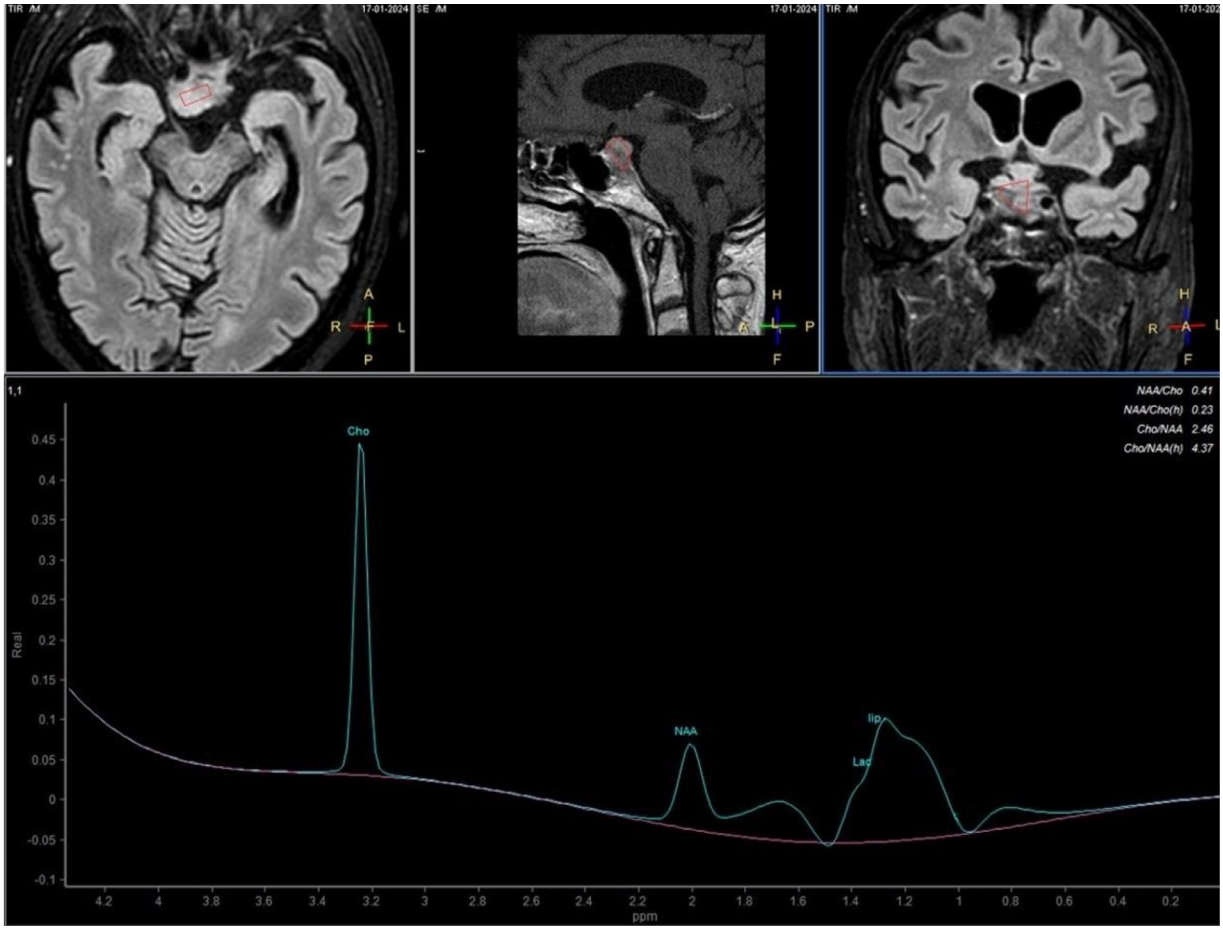

Fig. 4 – MR Spectroscopic imaging (MRSI) shows choline peak with choline/NAA ratio= 4.37 and increase in lactate and lipid values compatible with contextual necrotic components.

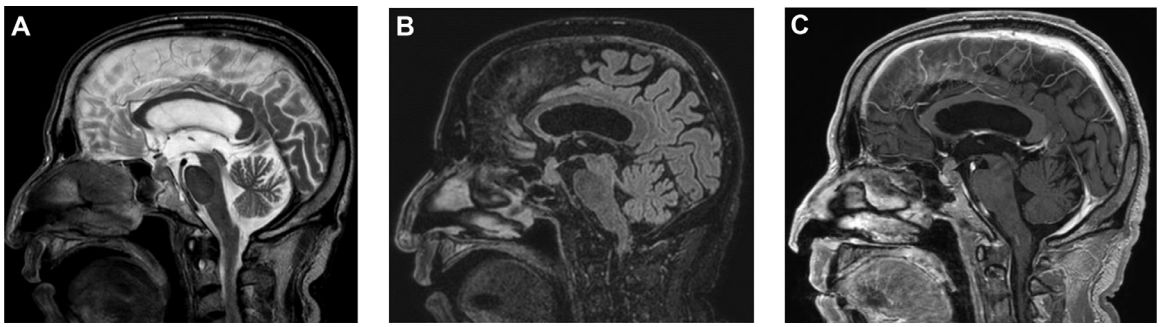

Fig. 5 – (A-C). 12 weeks after CRT treatment, sagittal plane TSE T2 (A), FLAIR (B) and T1 post contrast (C) sequences show a discrete dimensional reduction of the known pituitary lesion, especially in its suprasellar component.

of the pituitary stalk; beside the lesion showed low signal intensity on T1-weighted sequences and high signal intensity on T2-weighted sequences: these features can be observed in hypophysitis and in pituitary metastases [5–15,17]. Bone destruction and/or erosion and heterogeneous contrast-enhancement suggest the diagnosis of pituitary metastasis [1–5,7,9]. In our case bone destruction of the clivus was not visible, but the lesion detected on CT and MRI images showed inhomogeneous contrast-enhancement, unlike in hypophysitis, which is characterized by a homogeneous contrast-enhancement [5,9,10,14,15,17]. Advanced MRI techniques, including Diffusion-Weighted Imaging (DWI) and MR spectroscopy, can be used to differentiate brain metastases from other lesions, but they also may provide useful infor-

mation on sellar and parasellar diseases diagnosis [4,17–19]. DWI allows qualitative and quantitative assessment of diffusion activity [20]. ADC is calculated from Diffusion-weighted sequences and its values is correlate with predictive histopatological characteristics of brain metastases, so this parameter provides useful information for making treatment decision [20]. In the case we present, the pituitary lesion showed restricted diffusion on DWI: this finding may be observed in pituitary metastases and in hypophysitis [7,16], but ADC values that were measured within the mass were between 0.4 and 0.6 $\times$ 10^{-3} mm^2/sec: these values were quite similar to ADC values of brain metastases from small cell lung carcinoma that are 0.68 $\pm$ -0.12 $\times$ 10^{-3} mm^2/sec [19].

Proton MR spectroscopy is helpful to differentiate neoplastic brain masses from non-neoplastic brain lesions; it is also useful in differential diagnosis of lesions affecting pituitary-hypotalamus axis [4,17,18]. This technique provides information on metabolic composition within a tissue area by measure of metabolites, such as Cho, NAA, lactate, creatine (Cr), lipid and Cho/NAA ratio [18,19,21]. Lipid and lactate peaks, that are caused by cellular necrosis, high Cho peak, that is due to increase of cell membrane and myeline turnover and decresed NAA, that is a marker of neuronal integrity, can be observed in brain malignancies MR spectra [18,22]. The lesion we detected on MRI images showed increased Cho/NAA ratio (Cho/NAA ratio = 4.37), high lipid and lactate peaks: these MR spectroscopic features can be found in brain metastases [18,19,22]. Therefore, although there are no destructive phenomena of the cortex, inhomogeneuos contrast-enhancement, restricted diffusion, ADC values and MR spectroscopic findings of the lesion suggested the diagnosis of pituitary metastasis rather than diagnosis of hypophysitis. Added to this is the asymmetric appearance of the lesion (indicative of an expansive process). This diagnostic suspicion was confirmed by performing a trans-sphenoidal biopsy that revealed the presence of a small cell lung cancer metastasis. After radiotherapy treatment, the decrease in size of the lesion, appear to be indicative element of therapeutic efficacy.

Conclusion

In addition to presenting a rare case of pituitary metastasis (with an incidence of about 1 %), we highlight how advanced MRI techniques, in particular MR spectroscopy and DWI, have proved to be helpful to distinguish pituitary metastasis mass from hypophysitis in patients being treated with ICIs (Immune Checkpoint Inhibitors) in which hypophysitis is a collateral effect. Therefore, we suggest to include, in the MRI study protocol, the DWI sequence and Spectroscopy in the suspicion of pituitary metastases in a patient undergoing therapy with ICIs.

Patient consent

Written informed consent was obtained from the patient.

REFERENCES

[1] Wang Qing, Liu Xiao-Wei, Chen Ke-Yu. Pituitary metastasis from lung adenocarcinoma: a case report. World J Clin Cases 2024;12(15):2597–605. doi:10.12998/wjcc.v12.i15.2597.

[2] Costanza F, Giampietro A, Mattogno PP, Chiloiro S. Colon cancer presenting as pituitary mass and hypopituitarism: recognition and multidisciplinary approach of a rare case. JCEM Case Rep 2023;1:1–5. doi:10.1210/jcemcr/luad031.

[3] Kilbane Myers J, Abdelrahman A, Akpunonu B. Lung cancer metastasis to the pituitary gland. Cureus 2022;14(2):e22608. doi:10.7759/cureus.22608.

[4] He W, Chen F, Dalm B, Kirby PA, Greenlee JDW. Metastatic involvement of the pituitary gland: a systematic review with pooled individual patient data analysis. Pituitary 2015;18(1):159–68. doi:10.1007/s11102-014-0552-2.

[5] Tsutsui T, Hayashi K, Oda M, Kada S, Yamazoe N, Saiki M. Pituitary metastasis of salivary gland carcinoma mimicking hypophysitis: a case report and literature review. Int J Surg Case Rep 2023;109:108522. doi:10.1016/j.ijscr.2023.108522.

[6] EL Habnouny J, Jandou I, Latrech H, Bourgon C. Pituitary metastasis of a breast ductal adenocarcinoma. Ann Med Surg 2020;60:380–3. doi:10.1016/j.amsu.2020.10.054.

[7] Quintero BM, Doe KK, Bunker B, Chow W, Yavuz S. Pituitary metastasis of small cell lung cancer: two case reports. J Clin Translat Endocrinol: Case Rep 2021;19:100080. doi:10.1016/j.jecr.2021.100080.

[8] Minami K, Ueno Y, Minamidate Y, Shigeyama K, Akita K, Terada k, et al. Case of pituitary metastasis discovered when diabetes insipidus developed in a patient 20 years after breast cancer treatment. Radiol Case Rep 2023;18:3904–7. doi:10.1016/j.radcr.2023.08.025.

[9] Kurokawa R, Kurokawa M, Baba A, Nakaya M, Kato S, Bapuraj J, et al. Neuroimaging of hypophysitis: etiologies and imaging mimics. Japanese J Radiol 2023;41:911–27. doi:10.1007/s11604-023-01417-y.

[10] Osborn AG, Hedlund GL, Salzman KL. Osborn's Il cervello. Imaging, patologia e anatomia. Piccin; 2019. p. 719–22.

[11] Galligan A., Iravani A., Lasocki A., Wallace R., Weppler A.M., Sachithanandan N. et al. Imaging for assessment of cancer treatment response to immune checkpoint inhibitors can be complementary in identifying hypophysitis. Front Endocrinol 14:1295865. 10.3389/fendo.2023.1295865.

[12] Jacques J.P., Valadares L.P., Moura A.C. et al. Frequency and clinical characteristics of hypophysitis and hypopituitarism in patients undergoing immunotherapy – A systematic review. Front Endocrinol 14:1091185. 10.3389/fendo.2023.1091185.

[13] Chiloiro S, Giampietro A, Bianchi A, Menotti S, Angelini F, Tartaglione T, et al. Pituitary enlargement and hypopituitarism in patients treated with immune checkpoint inhibitors: two sides of the same coin? J Pers Med 2023;13:415. doi:10.3390/jpm13030415.

[14] Langlois F, Varlamov EV, Fleseriu M. Hypophysitis, the growing spectrum of a rare pituitary disease. J Clin Endocrinol Metab 2022;107(1):10–28. doi:10.1210/clinem/dgab672.

[15] Tang F, Liu H, Zhou S, Liu J, Xiao E, Tan C. MRI manifestation of xanthomatous hypophysitis: a case report and review of the literature. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2015;40(2):228–32. doi:10.11817/j.issn.1672-7347.2015.02.019.

[16] Inoue E, Kesumayadi I, Fujio S, Makino R, Hanada T, Masuda K, et al. Secondary hypophysitis associated with Rathke's cleft cyst resembling a pituitary abscess. Surg Neurol Int 2024;15:69. doi:10.25259/SNI_947_2023.

[17] Vikas C, Shahina B. Imaging of the pituitary: rrecent

advances. Indian J Endocrinol Metabol 2011;15(Suppl3):S216–23. doi:10.4103/2230-8210.84871.
[18] Fink KR, Fink JR. Imaging of brain metastases. Surg Neurol Int. 2013;4(Suppl 4):S209–19. doi:10.4103/2152-7806.111298.
[19] Kaddah RO, Khalil ME. Malignant focal brain lesions. Value of MRS tumour biomarkers in preoperative prediction of grades of malignancy. Egypt J Radiol Nucl Med 2014;45:1201–8. doi:10.1016/j.ejrnm.2014.08.001.
[20] Hanafi M, Rahayu RF, Ardyanto TD. Apparent diffusion coefficient value of brain metastasis from lung carcinoma as potential predictor of epidermal growth factor receptor mutation. Egypt J Radiol Nucl Med 2023;54:194. doi:10.1186/s43055-023-01143-5.
[21] Hollingworth W, Medina LS, Lenkinski RE, Shibata DK, Bernal B, Zurakowski D, et al. A systematic literature review of magnetic resonance spectroscopy for the characterization of brain tumors. AJNR Am J Neuroradiol 2006;27(7):1404–11.
[22] Bulakbasi N, Kocaoglu M, Ors F, Tayfun C, Uçöz T, et al. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. AJNR Am J Neuroradiol 2003;24(2):225–33.