Neuroendocrinology Letters Volume 39 No. 3 2018
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Hypophysitis and other autoimmune complications related to immune checkpoints inhibitors´ treatment: Spectrum of imaging appearances

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Submitted: 2018-06-01 *Accepted: 2018-08-12* *Published online: 2018-09-18*

Key words: **MRI; autoimmune; pancreatitis; pneumonitis**

Neuroendocrinol Lett 2018; **39**(3):196–204 **PMID:** 30431741 NEL390318A03 © 2018 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVES: Immune checkpoints inhibitors (ICI) represent a new therapy option for the treatment of several advanced tumors. However, this therapy has been linked to a spectrum of ICI related autoimmune (AI) adverse events. Some may be life threatening and their diagnosis is tricky. The aim of our study was to describe various imaging appearances of ICI related secondary hypophysitis and other coincidental AI diseases.

MATERIAL AND METHODS: We included 28 patients (19 females, 9 men, mean aged 58±13 years), who were consecutively treated mostly for advanced stage melanoma by different ICI. All their CT/MRI records and clinical data were reviewed.

RESULTS: We found 5 (18%) cases of endocrinology proven secondary hypophysitis; 2 cases of panhypopituitarism and 3 cases of central hypocortisolism. Four cases were MRI positive, 1 case was MRI negative. Three cases were accompanied by other AI diseases: 1 by hemorrhagic colitis and mesenterial lymphadenitis, 1 by AI pancreatitis and 1 by pneumonitis. On MRI pituitary gland was swollen in 3 cases, twice enhanced non-homogenously, once homogenously; infundibular enlargement was present in 2 cases. Those 3 cases reacted to glucocorticoid therapy by hypophyseal shrinkage. In 1 case of MRI positive hypophysitis, the pituitary gland was not enlarged, slightly nonhomogeneous with peripheral contour enhancement; no reaction to glucocorticoids was mentioned.

CONCLUSION: Secondary hypophysitis is probably more common ICI related adverse event than reported in the literature. Its MRI appearance is variable. Most of our cases were in coincidence with other AI ICI related events that affected their clinical manifestations.

Abbreaviations:

ACTH	- adrenocorticotropic hormone;
AI	- autoimmune;
FSH	- follicle-stimulating hormone;
CT	- computed tomography;
CTLA-4	- cytotoxic lymphocyte-associated protein 4;
GH	- growth hormone;
ICI	- immune checkpoints inhibitors;
IGF - I	- insulin-like growth factor - I;
IGF- BP-3	- insulin-like growth factor - binding protein;
MRI	- magnetic resonance imaging;
PET/CT	- positron emission tomography - computed tomography
TSH	- thyroid-stimulating hormone;
PD-1	- programmed cell death protein-1.

INTRODUCTION

Immune checkpoints molecules are molecules involved in maintenance of immunologic homeostasis (Zou & Chen, 2008). A number of immune checkpoints molecules have been identified that either activate or inhibit an immune response. The best known and characterized are cytotoxic lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 (PD-1), both inhibitory molecules. Inhibition of CTLA-4 or PD-1 may increase a baseline T cell-specific immune response against tumor (Dunn *et al.* 2002). The knowledge and characterization of immune checkpoints molecules have been recently translated into clinical practice. Immune checkpoints inhibitors (ICI) have been proven for the treatment of advanced solid tumors. Currently 6 different drugs are available for clinical practice (Pardoll, 2012). They include: ipilimumab (the CTLA-4), nivolumab and pembrolizumab (2 PD-1, the programmed cell death protein 1 inhibitors), atezolizumab, avelumab and durvalumab (3 PD-L1, the programmed cell death 1 ligand 1 inhibitors).

In our institution we have experience with the treatment especially by ipilimumab, nivolumab and pembrolizumab. Ipilimumab is a monoclonal antibody that upregulates anti-tumor immunity by blocking CTLA-4 receptors allowing antigen-presenting cells to recognize tumor cells as targets (Fong & Small, 2008). Nivolumab and pembrolizumab are monoclonal antibodies against the PD 1 receptor, which functions to inhibit the down-regulation of the immune system toward tumor cells (Hottinger, 2016). However, disruption of homeostasis of immune checkpoints molecules by ICI can lead to imbalances in immunologic tolerance that may result in exaggerated uncontrolled immune response, which may clinically manifest as inflammatory or autoimmune (AI) adverse events. These types of adverse events may target any normal organ or tissue in the body. Therefore, ICI are associated with unique spectrum of side effects linked to AI adverse events. They include a spectrum of various endocrinology, dermatology, gastroenterology, hepatology diseases and even a spectrum of neurology complications (Hottinger, 2016).

The aim of our study was to describe a spectrum of imaging appearances of the ICI induced AI disease in our cohort of patients who were treated mostly for advanced stage melanoma. We concentrate at the secondary hypophysitis, gastrointestinal tract complications with CT or ultrasound correlations and other AI diseases related to ICI treatment.

MATERIALS AND METHODS

We included 28 patients (19 females aged 58±12 years and 9 men aged 58±16 years) who were treated for advanced stage melanoma or other dermatology tumors by different ICI, some of them were treated by ICI combinations. Some subjects participated in clinical trials and their specific medication was blinded. All included patients underwent regular clinical, laboratory and imaging follow-ups. Subjects with uncompleted above mentioned follow-ups were not included. We retrospectively reviewed all their available medical records, CT, MRI, ultrasound and X-rays included and looked for signs of possible ICI related complications of the treatment. Pretreatment initial iodine contrast enhanced whole body CT scans including brain scans were available in all patients. All patients underwent regular CT follow-ups in 3 months intervals. The standard whole-body CT protocol was used covering entire head, neck, thorax, abdomen and pelvis. An iodine contrast agent (370 or 400 mg/ml) was administrated intravenously in standard dose 1ml/kg body weight. The arterial phase acquisition was started 15 seconds after the opacification of the abdominal aorta and the venous phase was acquired 20 seconds later. Images of all phases were reconstructed in axial, coronal and sagittal planes (slice thickness 3mm). Patients with neurological or endocrinological symptoms or with positive CT brain scans underwent gadolinium enhanced MRI scans. The standard MRI brain protocol included the following sequences: T2-weighted fast spin echo (slice thickness 4mm), diffusion-weighted imaging (b =1000), T2*-weighted gradient echo (slice thickness 5mm), and T2-weighted fluid-attenuated inversion recovery (slice thickness 4.5mm) in the axial plane, T1-weighted spin echo in the sagittal and/or coronal planes (slice thickness 4mm). A gadolinium-based contrast agent was administrated intravenously; post-contrast sequences included T1-weighted spin echo in sagittal and axial planes (slice thickness 4 and 3 mm, respectively) and T1-weighted 3D gradient echo including multiplanar reconstruction in coronal plane (slice thickness 1mm).

RESULTS

In our group of 28 patients with advanced stage dermatology tumors (mostly melanoma) that were treated by various ICI we found 5 (18%) cases of laboratory and endocrinology proven and clinically manifesting secondary hypophysitis; 2 cases of panhypopituitarism

Tab. 1. Immune checkpoints inhibitors treatment related side effects in our group of patients

Pt	Age/sex	ICI	Clinical manifestation	Coincidence with other AI disease	Laboratory findings	MRI findings	MRI corticoid response
1	33/F	Ipilimumab 3mg/kg	Fatigue, vertigo, malaise,	Mesenterial lymphadenitis; hemorrhagic colitis	Central hypocortisolism	Discrete enlargement, convex proximal margin, homogenous enhancement	Shrinkage
2	48/M	Ipilimumab 10mg/kg	Headache, photophobia	Autoimmune pancreatitis	Panhypopituitarism	Enlargement infundibulum included, nonhomogeneous enhancement	Shrinkage
3	65/F	Pembrolizumab 200mg/per dose	Headache, fever, fatigue, cough, anorexia	Pneumonitis	Panhypopituitarism	Normal size, peripheral enhancement, discreet non-homogeneities	No change
4	49/M	Blinded medication	Headache, fatigue	–	Central hypocortisolism	Hypophyseal and infundibular enlargement, nonhomogeneous enhancement	Shrinkage
5	50/M	Blinded medication	Mineral disbalance, diarrhea, headache, fatigue	–	Central hypocortisolism	Normal	Normal

AI, autoimmune; F, female; ICI, immune checkpoints inhibitors; M, male; Pt, patient.

and 3 cases of central hypocortisolism. Clinical manifestations were variable, most of patients suffered from headache and fatigue (80%), all clinical symptoms are listed in cases below and in the Table 1. Four cases of hypophysitis were MRI positive, in 1 case MRI was normal. Three cases of hypophysitis occurred in combination with other AI diseases related to ICI therapy visible on the follow-up CTs. Two of them with gastrointestinal AI diseases: one with autoimmune pancreatitis and one with hemorrhagic colitis with remarkable mesenterial lymphadenopathy. In one case hypophysitis was in combination with pneumonitis. Our findings are summarized in the Table 1 and detailed clinical and imaging information are given below in the series of cases.

We also noticed several cases of clinical manifesting colitis/enteritis without imaging findings on CT, MRI or US. We did not include these cases in this paper, as well as the cases of other adverse effects as dermatology or rheumatology complications without graphical appearances on imaging methods such as CT, MRI or ultrasound.

Case 1: 33 years old woman with facial Merkel-cell carcinoma

In September 2016 she underwent non-radical operation of Merkel-cell carcinoma on the face with reoperation and cervical lymph nodes dissection 2 weeks later. The treatment by ipilimumab was indicated with the total dose of 3mg/kg in 4 administrations. The treatment finished in February 2017. One week after the last dose of ipilimumab she started to suffer from abdominal pain, diarrhea, vomitus and fever and she was treated by antibiotics. The therapy did not lead to improvement; therefore, she was admitted to the gastroenterology ward for hemorrhagic colitis. On ultrasonography painful mesenterial lymphadenopathy was apparent. Infection was excluded, Campylobacter and Yersinia cultivations were negative. ICI related colitis and mesenterial lymphadenitis was considered and glucocorticoid therapy was started (1mg/kg of prednisone) in decreasing dose. After the discharge from hospital, PET/CT and neck MRI were performed, both with negative results. However, on the neck MRI the skull base and the pituitary gland was visible. It was not generally enlarged: it measured 8mm craniocaudally, postcontrast enhancement was nearly homogenous; however, its cranial margin was convex. We did not mention this appearance as pathological. Glucocorticoid therapy was finished in August 2017. In that time, her overall medical status worsened. She suffered from strong fatigue, vertigo and malaise. The laboratory tests were performed with remarkable decreased serum cortisol (less then 13nmol/l) and ACTH (less than 0.22 pmol/L). The level of serum thyroxin was also lower (10.75 pmol/L), TSH was discreetly higher 4.66 mIU/L. From the clinical point of view, the secondary hypophysitis was sus-

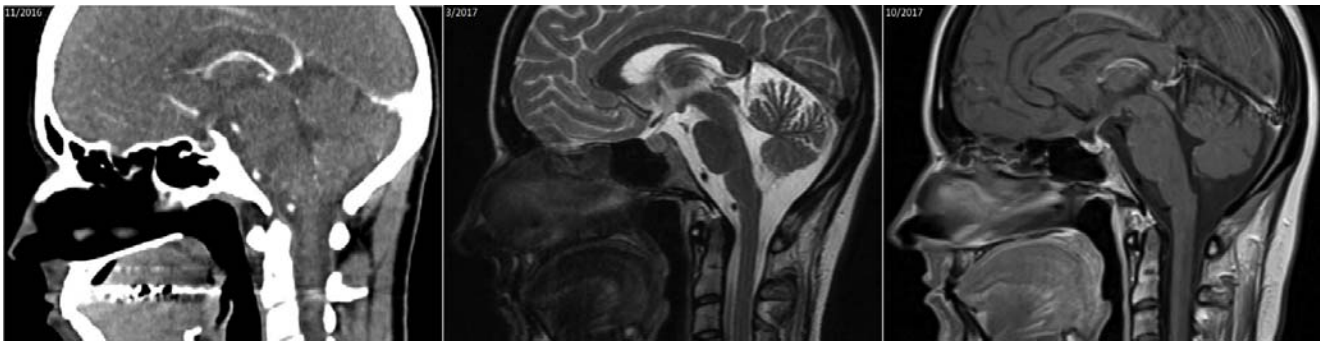

Fig. 1. Secondary hypophysitis: hypophyseal appearance development on different imaging methods (Case 1)
On PET/CT provided in November 2016 the pituitary gland was not enlarged. Five months later in March 2017 the pituitary gland was clearly larger than on previous PET/CT. In October 2017 after corticosteroid therapy the pituitary gland shrunk to the normal size again. (The left picture: PET/CT with sagittal multiplanar CT reconstruction; the middle picture: MRI, fast spin echo T2 weighted sagittal scan; the right picture: MRI, gadolinium contrast enhanced spin echo T1 weighted sagittal scan)

pect. However, on the recent brain MRI, the pituitary gland was of completely normal size and appearance. We revised all CT and MRI scans and found remarkable findings, which we did not mention before. On PET/CT performed before ipilimumab treatment, the pituitary gland was small with the craniocaudally diameter of 4 mm. In March 2017, during the treatment for AI hemorrhagic colitis and mesenterial lymphadenitis, the appearance of the pituitary gland was clearly different, it was slightly enlarged with convex proximal margin as described above. However, on the last brain MRI the hypophysis was the same size as on the initial PET/CT. Apparently changing development of hypophyseal appearance on different imaging methods during the time is documented on Figure 1. We came to conclusion that the patient suffered the secondary hypophysitis with central hypocortisolism. The cortisol replacement therapy was initiated and her medical status dramatically improved.

Case 2: 48 years old man with melanoma

In June 2015 the patient underwent surgery for melanoma on the back (Breslow 3.2 mm, T3a, N0, M0, stage IIA) followed by the adjuvant immunotherapy by interferon alfa 2a. However, in July 2016, the right axillary lymphatic metastases were proven histologically. No other metastases were found on CT and PET/CT. In September 2016, the therapy by ipilimumab with the total dose of 10mg/ kg was initiated. The treatment was complicated by lymphangitis and thrombophlebitis of the right arm. In November 2017 he complained for headache and photophobia. He was treated by common analgesics. However, the standard analgesic therapy was not successful; moreover, he suffered with dyspepsia, nausea, vomitus and abdominal pain. Symptoms had been progressing, he lost weight. The abdominal CT scan was indicated, where the signs of acute pancreatitis were present. The pancreas was enlarged, swollen with edema of surrounded fat and multiple mesenterial lymph nodes were present (Figure 2). The pancreatic duct was not dilated. There were no signs of choledocholithiasis and cholecystolithiasis. The laboratory tests showed expected elevation of serum amylases with remarkable decrease in serum cortisol (38 nmol/l), serum testosterone (less than 0.24 nmol/l), serum FSH (1.19 U/l), serum free thyroxin (6.15 pmol/l), serum triiodothyronine (2.95 pmol/l), IGF-I (37.9 up/l) and IGF- BP-3 (1.1 mg/l). Level of GH was on the lower limit (0.431 mU/l) as well as LH (1.19 U/l) and prolactin (2.7 ug/l). Described findings were interpreted as AI pancreatitis and secondary hypophysitis (due to the laboratory signs of panhypopituitarism). MRI confirmed the diagnosis. The pituitary gland was enlarged (when compared with previous CT several months earlier, where the pituitary gland was small; the craniocaudal diameter of 4 mm), the craniocaudal diameter

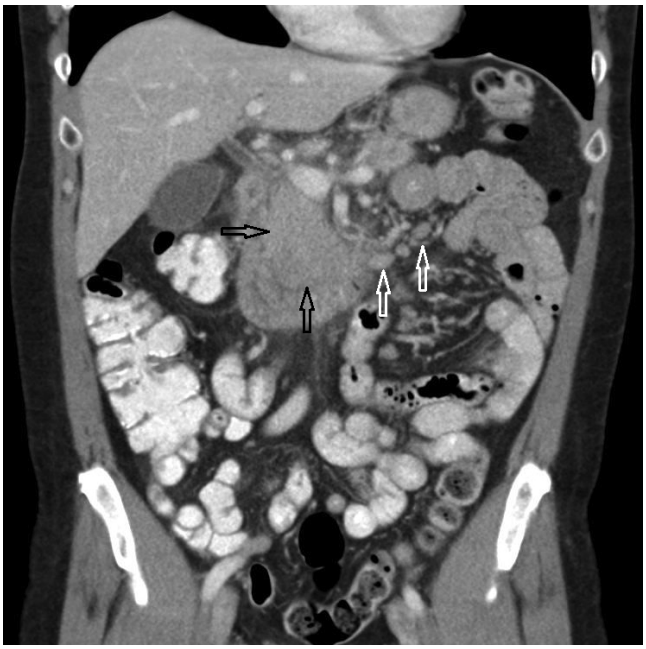

Fig. 2. Acute autoimmune pancreatitis (Case 2)
The pancreas was swollen (black arrows) with edema of surrounded fat, multiple mesenterial lymph nodes were present (white arrows).
(Contrast enhanced CT, multiplanar coronal reconstruction)

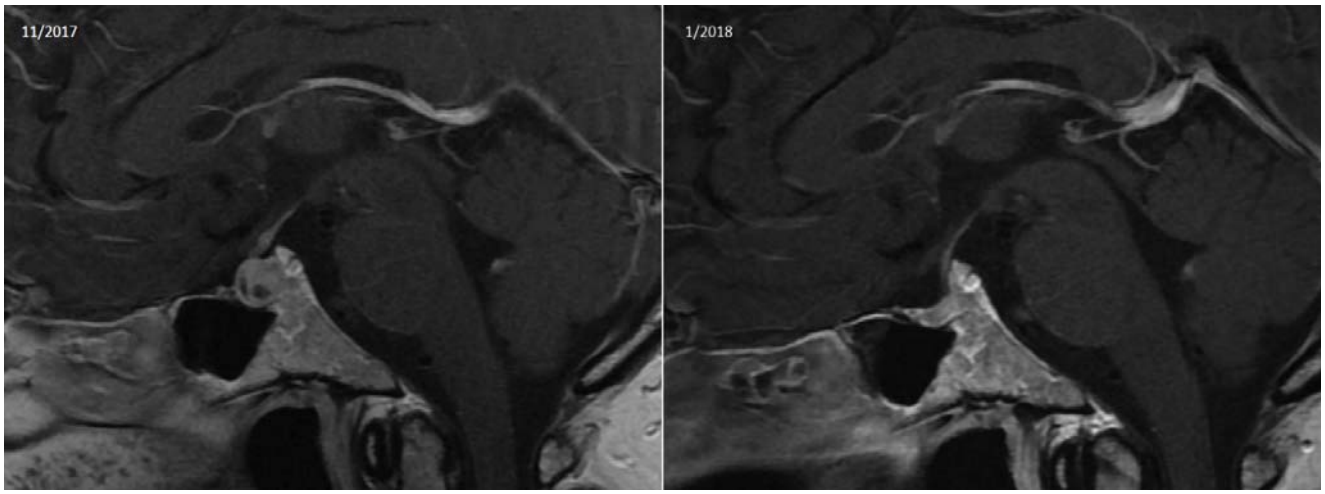

Fig. 3. Secondary hypophysitis (Case 2)
In November 2017 the pituitary gland was enlarged, nonhomogeneous with focal irregular hypointensities, the infundibulum was irregularly thickened. In January 2017 after glucocorticoid replacement therapy, shrinkage of the gland and infundibulum was apparent. (MRI, gadolinium contrast enhanced spin echo T1 weighted sagittal scans)

was 11mm with cranial convex margin. After the gadolinium contrast administration, the texture of the gland was nonhomogeneous with focal irregular hypointensities, the infundibulum was nodulary enlarged. On MRI brain metastases were excluded. The therapy by ipilumumab was terminated in December 2017 and hormone replacement therapy was initiated. In January 2018 there was remarkable regression of signs of hypophysitis on the brain MRI follow-up; the pituitary gland had nearly normal appearance. The development of hypophyseal appearance is demonstrated on the Figure 3. We must also admit the fact, that MRI findings were misinterpreted at first. Initially the MRI scan was assessed as 2 microadenomas. The correct diagnosis was done later, from the second reading at the oncology multidisciplinary board.

Case 3: 65 years old woman with advanced metastatic melanoma

The patient was diagnosed with melanoma of the right breast (Breslow 4,7 mm, T4a, N2a, M0, stage IIIC) with axillary lymph nodes metastases in 2012. Three years later the solitary metastasis in the right breast was discovered and the patient underwent mastectomy. Since March 2017 she was treated by pembrolizumab 200 mg/dose. Since June 2017 she had suffered from headache, fever, fatigue, cough and anorexia. On CT scans a solitary brain metastasis in the left temporal lobe was depicted and she was treated by stereotactic radiotherapy by Leksell Gamma Knife. The lung CT also showed signs of pneumonitis (Figure 4). Laboratory tests revealed decreased serum levels of TSH (0.049mU/l), LH (0.9U/l), FSH (19.5U/l), cortisol (37nmol/l) and ACTH (0.98 pmol/l). She had clinical signs of secondary hypophysitis. On MRI scans the pituitary gland was not enlarged or swollen; however, we found discrete non-homogeneities inside the gland, and discrete peripheral enhancement (Figure 5). Corticosteroid therapy at immunosuppression doses was initiated (1mg/kg of prednisone). In July 2017 the treatment of pembrolizumab was terminated for above described side effects. In December 2017 on the CT follow-up the lung metastases were found and the treatment by pembrolizumab was re-initiated. In January 2018 she suffered seizure and was scheduled for the brain MRI with the finding of the new metastasis in the right basal ganglia; she was again treated by stereotactic radiotherapy by Leksell Gamma Knife. In March 2018 she visited emergency ward and complained with fever, cough and dyspnea. The lung CT revealed signs of severe pneumonitis with consolidation patterns on lung CT scans. She was treated by glucocorticoids (1mg/kg of prednisone) and antibiotics. Therapy was complicated by Clostridium colitis. In April the brain MRI follow-up found 2 new brain metastases, enhancement of both vestibulocochlear nerves was evident without signs of mass effect. The next new finding was smooth widening of the infundibulum; the hypophyseal size

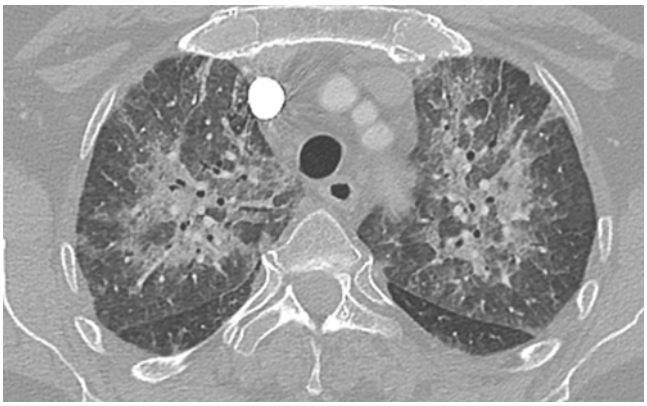

Fig. 4. Autoimmune pneumonitis (Case 3)
The bilateral pulmonary consolidation on CT scan.

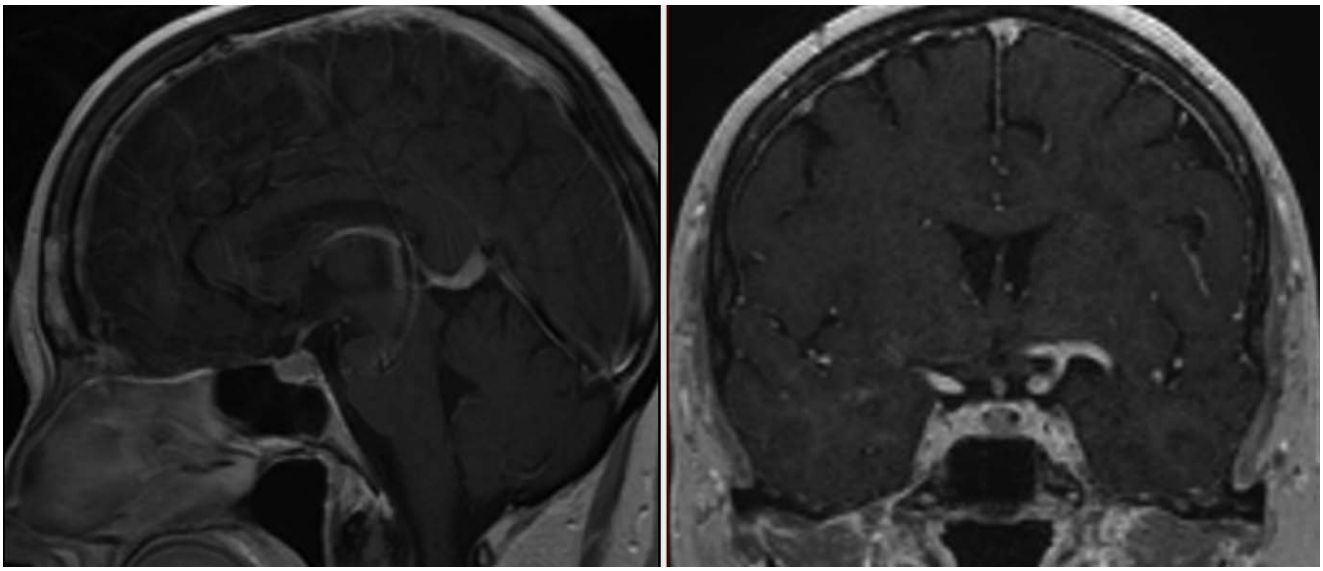

Fig. 5. Secondary hypophysitis (Case 3)
The pituitary gland is not generally enlarged; discrete non-homogeneities and peripheral contour enhancement was present. (MRI, gadolinium contrast enhanced spin echo T1 weighted sagittal scan and gradient echo T1 weighted coronal scan)

and appearance were not changed. Laboratory tests did not reveal decreases in serum hormonal levels. On the one-month MRI follow-up progression of the infundibular mass and cranial nerves enhancement was present, we consider those findings as carcinomatosis and the infundibular metastasis.

Case 4: 49 years old man who suffered melanoma metastases 13 years after melanoma excision

In 2004 the patient in his age of 36 years underwent surgery for melanoma of the right thigh (Breslow 0.52mm, Clark II). Thirteen years later inguinal metastases were found. Since November 2017 he was treated by ICI in the clinical trial (ipilimumab plus nivolumab versus nivolumab), his medication was blinded. The last infusion was administrated in January 2018. In that time, he complained for headache and fatigue. The brain MRI was indicated. The pituitary gland was enlarged (11mm craniocaudally) with the cranial convex margin and irregular infundibular enlargement, the gland was only slightly non-homogenous after the gadolinium contrast administration. Laboratory tests revealed central hypocortisolism (the serum cortisol level was under 13 nmol/l, ACTH was 1.54 pmol/l; TSH was also apparently decreased to 0.030 mU/l); however, serum levels of thyroxin and triiodothyronine were not affected. The replacement therapy was initiated (hydrocortisol 30 mg/per day). One month later the brain MRI follow-up showed remarkable regression of hypophysitis signs with nearly normal hypophyseal appearance. The Figure 6 demonstrates the graphical development of the hypophyseal appearance.

Case 5: 50 years old man with metastatic melanoma with ICI related hypophysitis without MRI graphical correlation

50 years old man with melanoma on the back (Breslow 5,1 mm, T4b, N0, M0, stage IIC), that was diagnosed in January 2015. In March 2017 the satellite skin metastasis was extirpated. In July 2017 axillary metastases were found. The patient was indicated for the ICI treatment and was included in the clinical trial (nivolumab versus ipilimumab plus nivolumab), his medication was blinded. ICI treatment was initiated in November 2017. In April 2018 he came with strong fatigue, diarrhea and headache. Laboratory tests revealed hyponatremia and hypochloremia. The serum cortisol level was very low (under 13 nmol/l), ACTH level was also apparently decreased (0.52 pmol/l). Other hormonal levels were normal. Glucocorticoid therapy by hydrocortisone in the cumulative dose 350mg during 3 days was initiated, then therapy by hydrocortisone 30mg per day continued. Both initial brain MRI and MRI follow-up one month later revealed completely normal hypophyseal appearance.

DISCUSSION

ICI have been revolution in the treatment of advanced melanoma and other advanced malignant tumors as squamous cell lung cancer, renal cell carcinoma or classical Hodgkin lymphoma. However, the ICI treatment also brings a novel set of adverse effects that require early recognition and careful management. It is believed the adverse effects are due to the general activation of

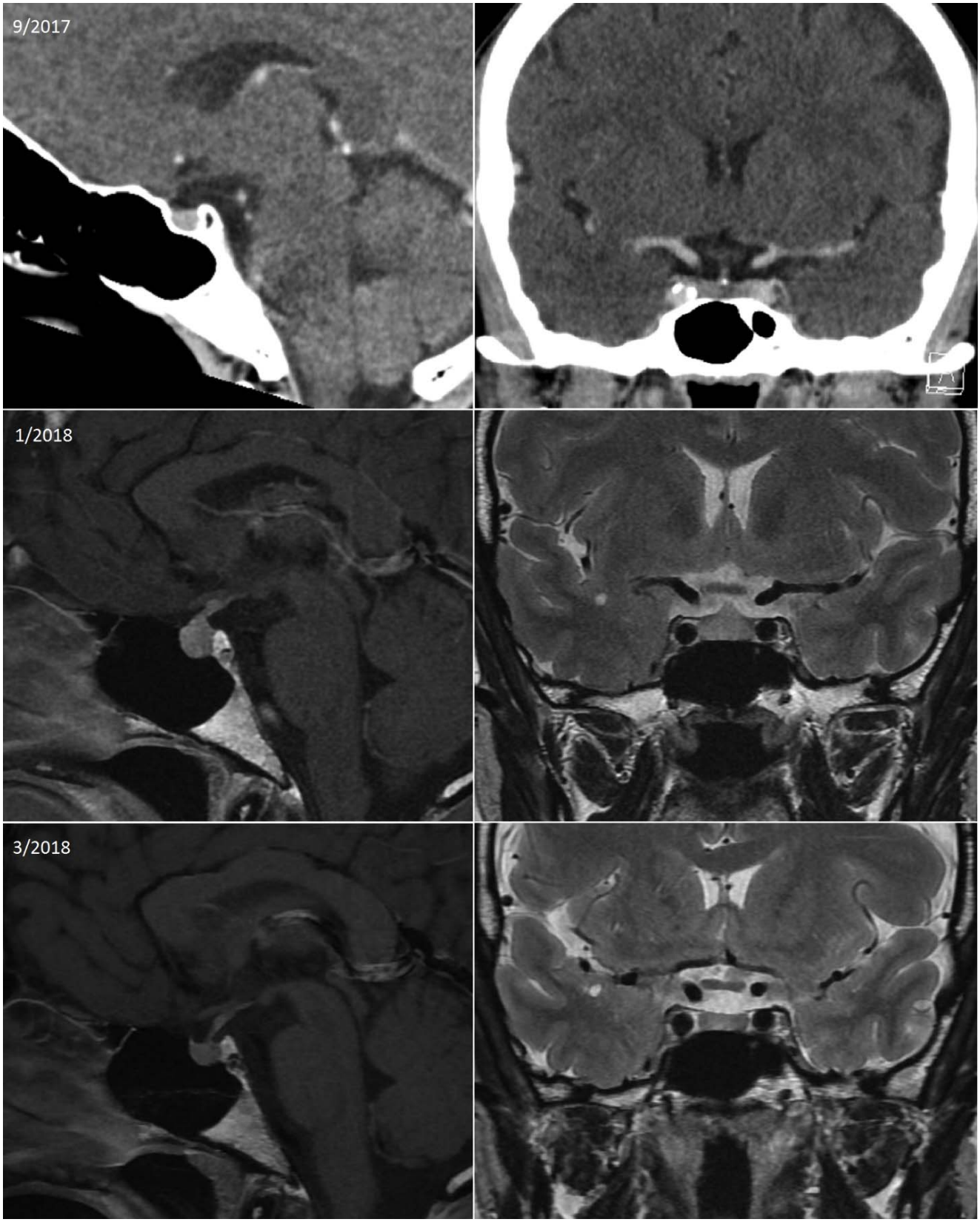

Fig. 6. Secondary hypophysitis: development of hypophyseal appearance (Case 4)
The upper picture: Normal size of the pituitary gland in September 2017 (CT sagittal and coronal multiplanar reconstructions).
The middle picture: In January 2018 the pituitary gland was swollen with irregular infundibular thickening; the gland was only slightly non-homogenous after the gadolinium contrast administration (MRI; contrast enhanced spin echo T1 weighted sagittal and fast spin echo T2 weighted coronal scan).
The lower picture: In March 2017 after glucocorticoid replacement therapy, the pituitary gland had normal gland appearance (MRI; contrast enhanced spin echo T1 weighted sagittal and fast spin echo T2 weighted coronal scan).

immune system. In the treatment of ipilimumab overall adverse effects grade 3-4 are observed in 22-24% of treated subjects (O´Day *et al.* 2010). In the treatment of PD-1 inhibitors side effects grade 3-4 are observed in 5-10% of cases (Weber *et al.* 2015). In the case of combined therapy of ipilimumab and nivolumab or ipilimumab and pembrolizumab the rate of serious adverse effects increases to 55% (Larkin *et al.* 2015; Robert *et al.* 2015).

In our group of patients, we diagnosed clinically manifesting secondary hypophysitis in 18% of cases. The secondary hypophysitis is a typical immune - related toxicity, it is a life-threatening disease due to the risk of secondary hypoadrenalism. According to the literature data, the secondary hypophysitis occurs up to 5% as a complication of the combined ICI treatment (Corsello *et al.* 2015). However, in case of CTLA-4 inhibitors, the secondary hypophysitis is reported in 3.2% and in case of PD-1 inhibitors in 0.4% (Barroso-Sousa *et al.* 2018). In comparison with the literature data the incidence of hypophysitis in our group of patients was remarkable higher, although in some patients the medications were blinded and the group of reviewed patients was very small. Despite this fact, it seems that hypophysitis is more common ICI related adverse event than it is expected and reported in the literature. We must also stress on the fact that this study was aimed to MRI/CT appearances of ICI related adverse events and should bring the information about imaging variability of this group of diseases to radiologists.

The MRI findings of hypophysitis were not uniform. The mild enlargement caused by hypophyseal swelling was seen in 60% of cases, in 2 of 5 cases the infundibulum was slightly irregularly thickened. In 3 of 5 cases hypophyseal enhancement was nonhomogeneous. In one case hypophysis was normal sized; however, slightly non-homogenous with thin peripheral enhancement. In one case the brain MRI was completely negative as well as all previous CT brain scans. During the corticosteroid treatment or during cortisol replacement therapy we encountered hypophyseal shrinkage in the most of cases that was relatively prompt. Thus, in case of corticosteroid therapy the hypophyseal MRI may be normal and normal size and hypophyseal appearance does not exclude the diagnosis of hypophysitis. We believe that this is an explanation of our MRI negative case. Our results are in confidence with other published data (Carpenter *et al.* 2009; Faje, 2016). However, we must admit the fact, that in the first 2 cases, the correct MRI diagnosis was not established by the radiologist who first read the MRI scans. In the first case, the hypophysis was considered as normal variant in the young woman. In the second case, the MRI was assessed as multiple adenomas. In both cases the comparison with the previous CT/MRI was helpful.

The most of our reported hypophysitis cases (3 of 5 cases) were coincidental with other AI side effects. In one case of the patient who was treated by ipilimumab, we found the coincidence of hypophysitis and hemorrhagic colitis and mesenterial lymphadenitis. Gastrointestinal complications of CTLA-4 inhibitors treatment are common, diarrhea after the ipilimumab treatment is reported up 33% of cases (Hodi *et al.* 2010). In the second case, we described the coincidence of secondary hypophysitis and acute AI pancreatitis. Acute AI pancreatitis is not common ICI therapy related event (Friedman *et al.* 2016). For proper diagnosis of AI pancreatitis, the revised Atlanta Classification criteria must be met. They included abdominal pain, CT positivity for pancreatitis and the elevation of serum amylase and lipase. The elevation of serum lipase and amylase is relatively often finding in patients treated by ICI and their isolated elevation should not be considered as pancreatitis. Friedman *et al.* in retrospective analysis of 119 subjects treated by the combination of nivolumab and ipilimumab found the elevation of serum lipase (grade 3 and 4) nearly in 27% of cases and the elevation of serum amylase in about 8% of cases. However, acute pancreatitis that met the revised Atlanta criteria was reported only in 1.7% (Friedman *et al.* 2016). In the third case we found the coincidence hypophysitis and AI pneumonitis. ICI related pneumonitis is less frequent adverse event of ICI therapy. However, pneumonitis grade 3-4 is a life-threatening event with incidence under 1%. Pneumonitis could lead to hypoxia, limiting self-care, oxygen requirements, and respiratory compromise requiring urgent intervention. Immunotherapy should be permanently discontinued (Villadolid & Amin, 2015).

Clinical manifestations of hypophysitis in our group of patients were variable and affected by the coincidental AI disease. The most common clinical findings were unspecific, headage and fatigue.

Our study has several important limitations. The first limitation is retrospective design of the study. Moreover, the study group was small and subjects were treated by different ICI, some in combination. Patients were not scheduled for MRI follow-ups on regular basis, only whole-body CT follow-ups were scheduled and the MRI was indicated just in case of new symptoms.

CONCLUSION

Secondary hypophysitis is probably not uncommon ICI treatment related adverse event. Its MRI appearance is variable and negative MRI do not exclude the diagnosis. To make an early diagnosis we recommend monitoring the size of the pituitary gland on imaging methods with careful previous exams comparison. Lack of knowledge of those ICI related adverse events leads to misdiagnosis or misinterpretation of CT and MRI findings as we demonstrated in our cases. Moreover, most of our cases were in coincidence with other AI ICI related events that remarkable affected clinical manifestation.

ACKNOWLEDGEMENTS

This work was supported by the Charles University research program PROGRES Q 28 (Oncology).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients provided written informed consent to treatment including diagnostic procedures (all patients provided written informed consent to enhanced MRI and CT) and agreed to the publication of medical data and images in an anonymous form. The informed consent forms are maintained on files. This retrospective study conforms to the Declaration of Helsinki and was approved by local Ethics committee of Faculty Hospital Kralovske Vinohrady. Trial registration for this retrospective study was not required.

AVAILABILITY OF DATA AND MATERIALS

The raw MRI and CT data are stored in the digital form at the Radiology Department of our institution.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work and none of the authors have any competing interests in the manuscript.

AUTHOR CONTRIBUTIONS

All authors collected and analyzed data, participated in manuscript preparation, read and approved the final manuscript.

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