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Differential diagnosis of autoimmune pituitary failure and pituitary macroadenoma during nivolumab therapy in an NSCLC patient — a case report

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ABSTRACT

We report a case of patient with non-small-cell lung cancer with expression of PD-L1 molecule on 1% of cancer cells, who was treated with chemotherapy, radiotherapy, and, during disease progression, with nivolumab immunotherapy. In the course of immunotherapy our patient developed symptoms of multi-axis hypopituitarism. Pituitary macroadenoma was diagnosed. In differential diagnosis, autoimmune inflammation of the pituitary gland in the course of nivolumab therapy was considered. After pituitary failure symptoms resolved, the immunotherapy was continued, with two-year remission of the disease.

Key words: non-small-cell lung cancer, immunotherapy, nivolumab, hypopituitarism

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Introduction

Cancer cells have developed mechanisms that allow them to defend against the host immune system. One of the signalling pathways used by cancer cells in this purpose is the interaction between PD-1 (programmed death 1) and PD-L1 (programmed death ligand 1) molecules. Through stimulation of the PD-1 receptor on the surface of lymphocytes their anti-cancer activity toward tumour cells expressing PD-L1 molecule is inhibited. A similar mechanism is the binding of B7-1 or B7-2 molecules on the surface of antigen-presenting cells (APCs) with the CTLA4 (cytotoxic T-lymphocyte-associated antigen 4) molecule on lymphocyte, which also leads to lymphocyte anergy. Due to the discovery of these associations, immune checkpoint inhibitors in the form of anti-PD1 monoclonal antibodies (nivolumab, pembrolizumab), anti-PD-L1 (atezolizumab, durvalumab, avelumab), and anti-CTLA4 (ipilimumab, tremelimumab) were developed.

By blocking these control points, it is possible to activate the destruction of cytotoxic T lymphocytes and cancer cells [1–3].

Development of immunotherapy allowed the extension of the survival time in patients with cancer, including non-small-cell lung cancer (NSCLC) [4]. Immunotherapy is used both in monotherapy and in combination therapy, not only in lung cancer, but also in the treatment of melanoma, kidney cancer, bladder cancer, and others [5]. The mechanism of action of immunological drugs, in addition to the intended therapeutic effects, also causes a number of adverse reactions, including autoimmune and inflammatory reactions defined as immune-related adverse events (irAEs). Skin complications, and gastrointestinal as well as liver and endocrine symptoms are most often observed [6–8]. Endocrinopathies are a group of complications that are usually irreversible [9]. They are mainly connected with the pituitary, thyroid, and adrenal glands [10].

The exact mechanism that causes endocrinopathy is still not fully understood.

Hypopituitarism is the second most frequent endocrine disorder in patients receiving immunotherapy [11, 12]. Among patients with the above-mentioned pathology, a number of cases with enlargement of the pituitary gland revealed in imaging studies have been described. This applies mostly to patients treated with ipilimumab [13]. *Hypopituitarism* was accompanied both by features of enlarged gland and its normal picture with no changes within it. However, tumour metastases to the pituitary gland are extremely rare. Usually they refer to patients with breast and lung cancer [14]. Their symptomatology results mainly from the pressure on surrounding brain structures.

Case report

An 80-year-old woman, a long-time tobacco smoker, was subjected in 2004 to right hand side mastectomy due to breast cancer with subsequent adjuvant chemotherapy. In 2016 a follow-up evaluation was performed for possible recurrence of breast cancer, which showed elevated levels of cancer markers. In chest computed tomography (CT) a tumour in segment 10 of the left lung and lymph node package in left pulmonary hilus (Fig. 1) were visualised.

During bronchoscopy endobronchial biopsy was performed, and in the sections from the left lung tumour non-small-cell cancer not otherwise specified (NOS) was diagnosed. In molecular studies neither mutations in the *EGFR* gene (the most common mutations in exons 18-21 were examined with use of real-time PCR) nor abnormal ALK protein (immunohistochemistry with D5F3 antibody clone) were detected, and the expression of PD-L1 was positive only on 1% of cells cancer (immunohistochemistry with SP263 antibody clone). In March 2016 the patient was qualified for chemotherapy with cisplatin and gemcitabine. Due to grade 4 haematological toxicity, which occurred after the first chemotherapy cycle, treatment was permanently discontinued. In May 2016 the patient underwent chest radiotherapy with a total dose of 20 Gy. In August 2016 positron emission tomography (PET) combined with CT (PET-CT) was performed, which showed the disease progression in the form of osteosclerotic metastases in thoracic and lumbar vertebrae. The patient used radiotherapy of the spine with a dose of 20 Gy and subsequently, in December 2016, was qualified for treatment with nivolumab at a dose of 3 mg/kg of body weight every two weeks within a dedicated extended access program (EAP).

After two months of treatment, stabilisation of lesions in the lungs was observed, followed by partial remission (PR). Immunotherapy was well tolerated for 11 months. In November 2017, the 22nd nivolumab treatment cycle began. Then the patient reported



Figure 1. Computer tomography image from January 2016

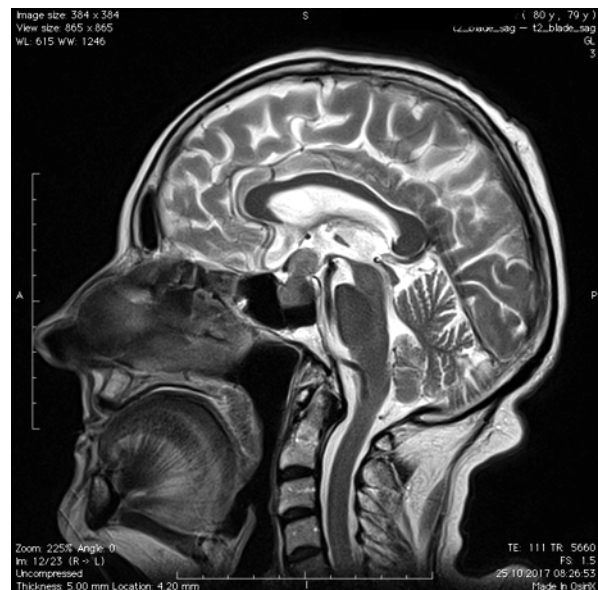


Figure 2. Magnetic resonance image of the head suggesting pituitary tumour of macroadenoma character with dimensions 26 × 16 × 14 mm (October 2017)

difficulties in reading, weakness, worse well-being, and weight loss. Hyperkalaemia and hyponatraemia have been reported in laboratory studies. In a previous magnetic resonance examination of the head (October 2017) in the area of the sella turcica and suprasellar cisterns, a tumour filling the entire sella turcica and suprasellar cistern with dimensions of 26 × 16 × 14 mm was revealed. This lesion showed heterogeneous contrast enhancement. The image suggested the presence of pituitary tumour with the features of macroadenoma (Fig. 2).

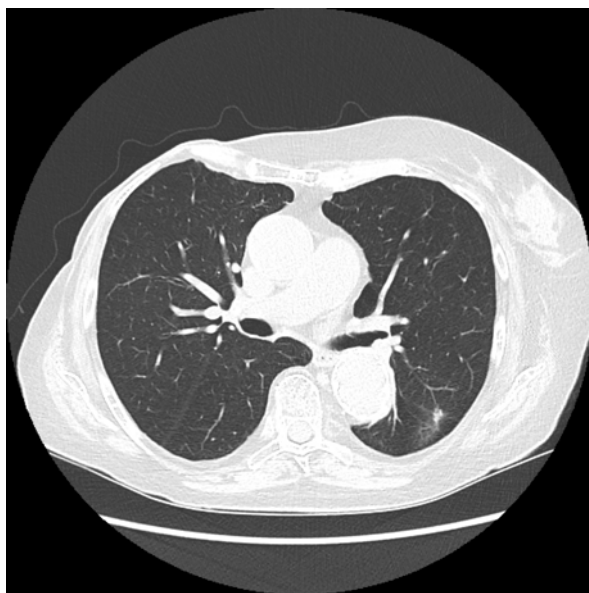


Figure 3. Partial remission of the disease in March 2018

Laboratory tests showed decreased gonadotropins (LH < 0.10 mIU/mL, FSH 0.11 mIU/mL) and growth hormone (0.579 ng/mL) levels, elevated prolactin concentration (48.50 ng/mL), and reduced thyrotropin (0.205 mIU/L), free triiodothyronine (1.50 pg/mL), and free thyroxine (0.96 ng/dL) levels. The concentration of adrenocorticotropic hormone (ACTH) was 1.15 pg/mL, while cortisol was 9.7 µg/dL. Based on available results, hypopituitarism in the hypothalamic–pituitary–adrenal axis with accompanying secondary hypothyroidism and secondary adrenal insufficiency were diagnosed. Due to the patient's condition, the 23rd administration of nivolumab was postponed. After endocrinology consultation, levothyroxine treatment was used in a substitution dose — initially 12.5 µg for three days, followed by 25 µg and hydrocortisone in a daily dose of 40 mg. After finding an inadequate substitution of L-thyroxine, the dose was increased to 50 µg and autoimmune thyroid disease was excluded. Then, the hydrocortisone doses were reduced to 20 mg per day. After stabilisation of the patient's general condition and improvement of the results of laboratory tests, it was decided in January 2018 to continue the immunotherapy and the 23rd dose of nivolumab was administered. The interval in the use of nivolumab was 1.5 months. Resolution of endocrine symptoms during a long break in immunotherapy suggested an autoimmune background of pituitary gland inflammation. Chest CT performed in March 2018 showed a further regression of lesions in the lungs (Fig. 3).

Follow-up brain NMR performed in April 2018 showed the regression of lesion in the sella turcica area, mainly at the level of the pituitary stalk (infundibulum), up to 16 × 10 × 15 mm. The lesion in

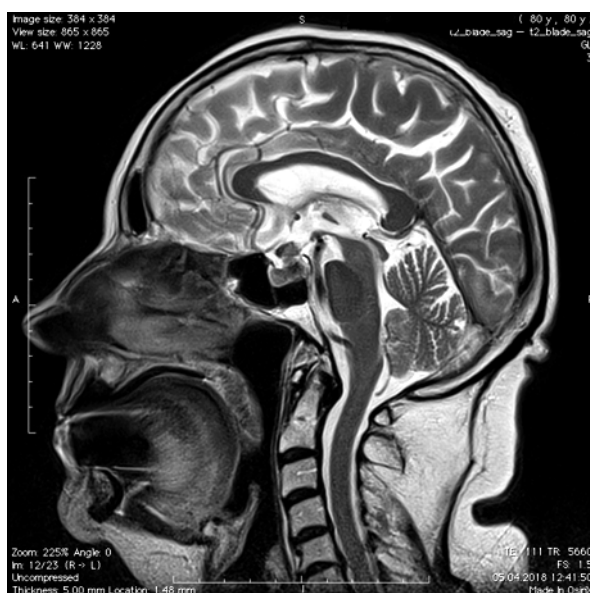


Figure 4. Control magnetic resonance examination of the head showing regression of pituitary tumour to dimensions 16 × 10 × 15 mm (April 2018)

CNS showed a heterogeneous contrast enhancement, and its character was not entirely clear, considering the regression of its dimensions as well as its oncological history and the use of immunotherapy (Fig. 4). In July 2018, the patient was admitted in order to administer the 35th dose of nivolumab; however, the treatment was postponed due to herpes zoster diagnosis. During the next hospitalisation, despite visible infected, residual herpes zoster-related skin lesions, it was decided that nivolumab would be given.

The patient is still being treated with nivolumab (for 23 months, the last hospitalisation was in September 2018). In the last control chest CT performed in September 2018, there was continuous regression of cancer lesions in the left lung (Fig. 5). In addition, the patient continues to receive hydrocortisone in a dose 20 mg daily and levothyroxine 50 µg daily for the treatment of endocrine complications during nivolumab therapy.

Literature review

The phase III CheckMate 057 and CheckMate 017 clinical trials compared the effectiveness of nivolumab and docetaxel in the second-line treatment in NSCLC patients. Among the immune-related endocrinopathies no pituitary complication was found [15].

Faje et al. reported a group of 17 patients with hypopituitarism, out of 154 melanoma patients treated with ipilimumab. In all patients, enlargement of the pituitary gland was revealed in brain NMR. The most frequently

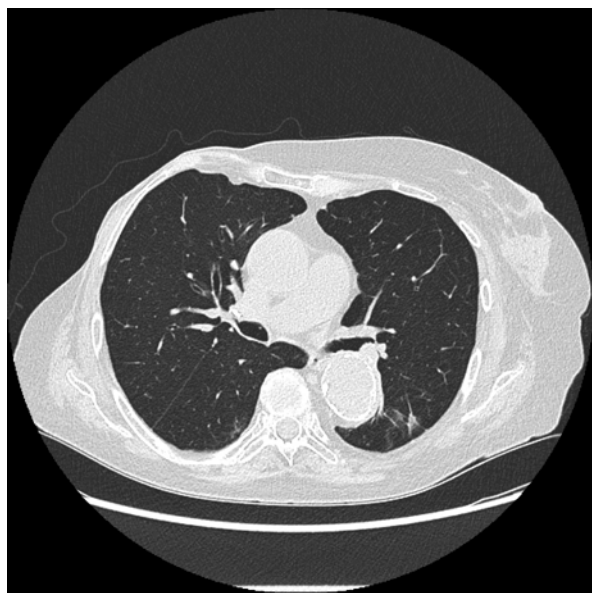


Figure 5. Control computed tomography of the chest (September 2018). Persistent regression of neoplastic lesion in left lung

reported symptoms were headache and fatigue. In laboratory tests, hyponatraemia, features of hypothyroidism (decreased ft_4 and TSH level in the lower normal range), and secondary adrenal insufficiency (decreased cortisol and ACTH levels) were observed. LH and FSH were also in the lower normal range. In eight patients with brain metastases, radiotherapy of the central nervous system was performed before diagnosis of pituitary pathology. During follow-up, after substitution treatment with prednisone, a relatively fast regression of the enlarged pituitary gland was observed. The authors suggest that persistent enlargement of the pituitary gland after treatment initiation, without visible regression, argues in favour of another process, e.g. metastatic. However, the resolution of changes in the pituitary gland after substitution treatment results rather from the autoimmune process associated with immunotherapy [13].

Kastrisiou et al. published a case of a patient treated with nivolumab due to lung adenocarcinoma, in whom pituitary hypoplasia occurred, but without enlargement of the gland. After administration of 11 cycles of nivolumab, the patient presented symptoms such as dizziness, gait disturbances, cachexia, and confusion. In the CT scan of the head, metastatic lesions were excluded. Based on laboratory tests, hypothyroidism was diagnosed. Treatment with levothyroxine and liothyronine was used; additionally, it was decided to discontinue nivolumab therapy. After six weeks of treatment, TSH levels normalised; however, the patient's general condition deteriorated — fatigue, loss of appetite, joint stiffness, nausea, and abdominal pain intensified. Physical

examination revealed exfoliative keratolysis, dehydration, and low blood pressure. The symptoms indicated adrenal insufficiency, and laboratory tests showed low cortisol and ACTH plasma levels. In the next imaging of the head, no metastatic lesions and enlargement of the pituitary gland were observed, the concentration of all hormones normalised under the influence of substitution treatment, and resolution of previously seen symptoms was observed. The adrenocortical insufficiency induced by hypopituitarism as a complication of anti-PD-1 antibody treatment was hypothesised [16].

In a publication by Kitajima et al. two cases of patients treated with nivolumab due to melanoma and with isolated ACTH deficiency were presented. The first case, a male patient, at the 13th administration of nivolumab reported malaise with low levels of cortisol and ACTH and no changes in brain NMR. In the next case, after 13 cycles of therapy nivolumab was changed to ipilimumab due to occurrence of lung metastases. After the second administration of ipilimumab, fever, asthenia, and dizziness were observed. The laboratory tests indicated a decrease in ACTH and cortisol concentrations and a normal magnetic resonance image of the head [17].

Okano et al. described the case of a male patient treated with nivolumab due to melanoma, who presented symptoms of hypopituitarism with visible moderate enlargement of the gland in an imaging test [18].

In 2017, Mengoli et al. published a paper describing the first case of a female patient with lung adenocarcinoma with *ALK* gene rearrangement and with known metastasis to the pituitary gland. Initially the patient was admitted to the neurology department due to vision disorders and polydipsia. Magnetic resonance of the head revealed a change in the pituitary gland area. Initially, it was thought that it was a pituitary adenoma pressing on the optic nerve. A partial resection was performed showing the rearrangement of *ALK* gene in tumour cells. The chest CT scans and pathomorphological examination revealed an adenocarcinoma of the left lung. Chemotherapy was initiated; however, after the progression of the lesion in the pituitary gland immunotherapy (without the intended effect) and radiotherapy were introduced, leading to regression of the lesion. Stabilisation of the disease was obtained only after the introduction of crizotinib [19].

In the present case, features of hypopituitarism were found during treatment with anti-PD-1 antibody — nivolumab. In magnetic resonance imaging of the head, enlargement of the pituitary gland was detected, possibly corresponding to macroadenoma. After the implementation of hormonal substitution treatment, a control head NMR was performed, showing regression of pituitary lesion. On the basis of the available literature, the most likely mechanism responsible for

the development of the pathology described above and its regression is hypothyroidism and autoimmune inflammation of pituitary gland during immunotherapy. Radiological differentiation included the presence of adenoma and metastatic lesions. Pituitary adenomas most often exhibit different characteristics of endocrine disorders, while metastatic lesions usually have no hormonal activity and are extremely rare. Also, a quite fast regression during substitution treatment contradicts the possible concept of adenoma or metastatic lesion.

Therefore, the syndrome of hormonal and structural disorders related to the pituitary gland described by the authors should be associated with the adverse effect of immunotherapy with nivolumab. It should be noted that this is one of the few descriptions in which hormonal disorders were accompanied by an enlarged pituitary gland. The presented case report is also further proof of the possibility of obtaining a response to treatment with nivolumab in patients with very low PD-L1 expression on tumour cells.

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