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Paraneoplastic Autoimmune Hypophysitis: An Emerging Concept

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Abstract

Pituitary autoimmunity is one of the principal causes of hypopituitarism. Additionally, hypophysitis is one of the immune-related adverse events associated with immunotherapy. Recent case-oriented research has revealed a novel type of autoimmune hypophysitis, anti-PIT-1 hypophysitis, related to isolated adrenocorticotropic hormone (ACTH) deficiency and immune checkpoint inhibitor-related hypophysitis, as a form of paraneoplastic syndrome. Under these conditions, the ectopic expression of pituitary antigens present in tumors evokes a breakdown of immune tolerance, resulting in the production of autoantibodies and autoreactive cytotoxic T cells that specifically harm pituitary cells. Consequently, an innovative clinical entity of paraneoplastic autoimmune hypophysitis has been purported. This novel concept and its underlying mechanisms provides clues for understanding the pathogenesis of autoimmune pituitary diseases and can be applied to other autoimmune diseases. This review discusses the etiology of paraneoplastic autoimmune hypophysitis and its future.

Keywords

paraneoplastic syndrome, anti-PIT-1 hypophysitis, isolated ACTH deficiency, immune-checkpoint inhibitor-related hypophysitis

Introduction

The pituitary gland regulates the endocrine system by modifying peripheral hormone secretion from the endocrine organs, and comprises the adenohypophysis (anterior lobe) and the neurohypophysis (posterior lobe). Hypopituitarism is defined as the insufficient secretion of the anterior pituitary hormone. The clinical symptoms of hypopituitarism are usually non-specific, but can cause life-threatening events, leading to increased mortality and impairing the quality of life of an individual. Hypopituitarism is classified into two major etiologies: congenital and acquired hypopituitarism. Acquired hypopituitarism is typically caused by organic diseases such as pituitary tumors, surgery, irradiation, infarction, autoimmunity, trauma, infection, hemochromatosis, granulomatous disease, and histiocytosis [1]. However, in 6% of the cases, the etiology of hypopituitarism is unknown [2].

The pathophysiology of autoimmune hypophysitis and isolated adrenocorticotropic hormone (ACTH) deficiency has been contributed to pituitary autoimmunity. Yet, the underlying mechanisms remain unclear. Recently, a new cause of acquired pituitary hormone deficiency in the form of paraneoplastic syndrome has been discovered [3]. In this study, we discuss the clinical characteristics and pathophysiology of this novel concept of "paraneoplastic autoimmune hypophysitis."

A. Hypopituitarism

The anterior pituitary secretes six hormones: ACTH, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), and growth hormone (GH). The posterior pituitary stores the hypothalamic hormones, namely, vasopressin and oxytocin. Hypopituitarism is defined as one or more anterior pituitary hormone deficiency, with or without deficiency of posterior pituitary hormones [4]. Hypopituitarism increases mortality due to cortisol deficiency caused by ACTH deficiency [5]. The onset of

hypopituitarism is classified as either congenital or acquired. The causes of congenital hypopituitarism are mostly associated with mutations in genes that regulate hypothalamus and/or pituitary development and function [6].

One example of a gene associated with pituitary development is pituitary-specific transcription factor 1 (PIT-1, also known as POU1F1). PIT-1 is a pituitary-specific transcription factor that belongs to the POU homeodomain family [7, 8]. PIT-1 is crucial for the differentiation and maintenance of somatotrophs, lactotrophs, and thyrotrophs in the anterior pituitary [9, 10]. Patients with pathogenic variants of the *PIT-1* gene exhibit undetectable levels of GH, PRL, and very low serum TSH levels. PIT-1 R271W, a well-known gene mutation, was the earliest reported cause of congenital hypopituitarism [11]. The R271W mutation leads to dissociation of PIT-1 protein with β-catenin and special AT-rich sequence-binding protein-1 (Satb1), diminishing PIT-1-1-dependent gene activation [12].

Pro-opiomelanocortin (POMC) is the precursor protein for ACTH (the melanocyte-stimulating hormone), β-lipotropin, γ-lipotropin, and endorphins [13]. It is expressed in several tissues, such as the hypothalamus, pituitary gland, skin, and immune system [14]. Therefore, loss-of-function mutations of the POMC gene result in congenital isolated ACTH deficiency accompanied by early onset obesity, hyperphagic obesity, and red hair [15].

The causes of acquired hypopituitarism are vastly diverse. The most common cause of hypopituitarism are pituitary tumors and related treatments such as surgery or radiotherapy [2, 16]. Other causes of acquired hypopituitarism include autoimmune conditions, infection, vascular impairment (including apoplexy), traumatic brain injury, neurosurgery, hemochromatosis, granulomatous disease, and histiocytosis [4]. Pituitary autoimmunity entails not only autoimmune (lymphocytic) hypophysitis, but also IgG4-related hypophysitis, immune checkpoint inhibitor-related hypophysitis, and isolated ACTH deficiency [17].

Based on its etiology, hypophysitis is classified into two groups: primary and

secondary [18]. Primary hypophysitis is classified into several histological diagnoses, including lymphocytic (also known as autoimmune), granulomatous, xanthomatous, and necrotizing hypophysitis [19]. Pituitary biopsy is the most helpful way to differentiate between neoplastic and inflammatory conditions and ideally results in a definite diagnosis. Histological findings of lymphocytic hypophysitis generally show infiltration of polyclonal lymphocytes without a dominant subset [20]. In addition to lymphocytes, the immune infiltrate comprises other cells such as plasma, eosinophils, macrophages, histiocytes, and neutrophils [21]. Endocrine abnormalities in lymphocytic hypophysitis are often associated in the following order (although not definitive): ACTH > LH/FSH = TSH > GH = PRL [17].

Secondary hypophysitis is caused by a spread of a nearby inflammatory lesion (such as Rathke's cleft cyst and germinoma), or as part of systemic diseases such as IgG4-RD, granulomatous with polyangiitis, sarcoidosis, Langerhans cell histiocytosis, and systemic lupus erythematosus [18]. This category also includes immune checkpoint inhibitor-related hypophysitis, as described in our other review series titled "Immune Checkpoint Inhibitor-Related Hypophysitis".

Several reports have demonstrated the presence of circulating autoantibodies in autoimmune hypophysitis, including GH1 or GH2 [22], α-enolase [23], pituitary gland specific factors 1a and 2 [24], and secretogranin-2 [25]. Autoantibodies directed against lactotroph have rarely been reported [26]. Evidently, autoantibodies against Rabphilin-3A can be used as markers of lymphocytic infundibuloneurohypophysitis [27, 28]. Generally, the specificity of these antibodies directed against pituitary cells/tissue is not high, as they have been found in various diseases such as Cushing's disease [29] and pituitary adenomas [30]. Therefore, it is speculated that most of these antibodies are produced due to pituitary tissue disruptions and can be utilized as disease markers.

B. Classic paraneoplastic endocrine syndromes

Paraneoplastic syndrome refer to symptoms or signs resulting from damage to organs or tissues that are isolated from the site of a malignant neoplasm or its metastases [31]. One important cause of paraneoplastic syndrome is the secretion of bioactive substances, such as hormones and cytokines, from the tumor. In contrast, most paraneoplastic neurological syndromes are caused by the antigen mimicry mechanism between tumor and normal tissues, causing autoimmune tissue damage. Historically, "classic" paraneoplastic endocrine syndrome has been associated with ectopic expression of various hormones. Malignant tumors occasionally secrete hormones or bioactive peptides, leading to the manifestation of these hormones, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH) and ectopic Cushing syndrome (Table 1) [32, 33]. These conditions are caused by ectopic production of hormones or peptides from malignant tumors; thus, the direct effect of these hormones or peptides causes systemic symptoms. Successful treatment of the underlying tumor, namely, reducing the amount of ectopic hormones or peptides, occasionally improves these symptoms. For example, although the prognosis of ectopic ACTH syndrome with small cell lung cancer is generally ominous, it has been reported that successful treatment with immune-checkpoint inhibitors of small cell lung cancer resolved Cushing’s syndrome [34].

Immune cross-reactivity between malignant and normal tissues also causes symptomatic paraneoplastic syndromes, which are frequently associated with paraneoplastic neurological syndromes. The tumor ectopically expresses various autoantigens and evokes autoimmunity against host tissues due to cross-reactivity. Dendritic cells phagocytose the antigen-expressing apoptotic tumors and activate antigen-specific lymphocytes. B cells and plasma cells produce antibodies against the antigens. An immune attack by the antibodies and/or cytotoxic T lymphocytes (CTLs) may prevent tumor growth. However, autoimmunity directed towards tumors can also react with normal tissues expressing similar antigens, leading

to their damage and/or dysfunction. The relative roles of antibodies and cytotoxic T lymphocytes (CTLs) in paraneoplastic syndrome depend on each individual pathological condition. Various autoimmune paraneoplastic syndromes have been reported, especially in neurologic, dermatologic, and rheumatologic paraneoplastic diseases (Table 2) [32, 35]. Generally, symptomatic paraneoplastic syndromes are rare, except for the Lambert–Eaton myasthenic syndrome in 3% of small-cell lung cancer [36], myasthenia gravis in 15% of patients with thymoma [37], and demyelinating peripheral neuropathy in 50% of patients with osteosclerotic plasmacytoma [31, 38].

Recent research has elucidated an increasing number of autoantigens and the identification of tumoral factors associated with paraneoplastic syndromes. Autoantibody detection in the serum of patients with paraneoplastic syndrome suggests that the etiology of paraneoplastic syndrome is autoimmunity. The etiology has been classified into two groups based on the characteristics of the autoantibody epitopes. These are as follows:

1) Autoantigens are intracellular proteins shared by tumors and normal tissues. Autoantibodies, although thought to be valuable diagnostic markers, are not pathogenic [39]. The primary etiology of tissue degeneration are the antigen-specific CTLs. One such example is cancer-associated retinopathy. The epitopes of recoverin, the antigen of cancer-associated retinopathy, were detected in malignant tumor tissues. Anti-recoverin antibody is detected in the serum of patients with cancer-associated retinopathy [40]. However, antitumor CTLs recognize recoverin epitopes, causing the disease [41]. For example, Yo-specific or Hu-specific T cells have been reported in patients with paraneoplastic cerebellar degeneration and limbic encephalitis [42, 43].

2) Autoantibodies recognize cell-surface functional molecules, such as channels or receptors, and cause the symptom. The well-established examples are autoantibodies against the voltage-gated calcium channel (VGCC) and acetylcholine receptor (AchR).

These antibodies are associated with Lambert-Eaton myasthenia syndrome and myasthenia gravis, respectively [44, 45]. These antibodies interfere with channels or receptors, resulting in functional dysfunction of these molecules. In addition, the anti-AchR antibody attached to nerve cell receptors also initiates an inflammatory reaction by complement activation with the formation of membrane attack complexes, resulting in cell injury. Moreover, antigenic modulation by an anti-AchR antibody causes the internalization and degradation of surface AChRs [46]. In other words, antibodies attached to surface proteins can play a pathological role.

C. Novel clinical entity: Paraneoplastic autoimmune hypophysitis

One of the underlying mechanisms in paraneoplastic syndrome is the ectopic expression of various proteins in tumors. The direct effect of ectopic production of hormones or bioactive peptides causes "classic" paraneoplastic endocrine syndrome whereas the occurrence of autoimmunity-related paraneoplastic endocrine syndrome is rare. Recently, new autoimmunity-related paraneoplastic endocrine syndrome has been reported in three conditions: anti-PIT1 hypophysitis, isolated ACTH deficiency, and immune checkpoint inhibitor-related hypophysitis (Table 3) [47].

1) Anti-PIT-1 hypophysitis

History and pathophysiology

The account of anti-PIT-1 hypophysitis (anti-PIT-1 antibody syndrome) started from a medical case presented with acquired and specific GH, PRL, and TSH deficiency in a middle-aged man. Endocrinological abnormalities were similar to those in patients with *PIT-1* mutations, but as the condition developed, no mutation in the *PIT-1* gene was detected [48]. Thereafter, two additional medical cases with similar symptoms were identified. Interestingly, circulating anti-

PIT-1 antibody was detected, indicating the presence of autoimmunity directed against PIT-1, which could explain the pituitary hormone abnormalities. Immunohistochemistry of the pituitary gland from the patient's autopsy revealed that not only GH-, PRL-, and TSH-positive cells were absent, but also PIT-1 positive cells, despite the presence of ACTH-, LH-, and FSH-positive cells. Additionally, histological analysis of other tissues (i.e., gastric mucosa, pancreas, adrenal gland, liver, and thyroid) revealed lymphocyte infiltration and disrupted tissue structure. From these observations, we initially defined "anti-PIT-1 antibody syndrome" as: 1. Acquired combined pituitary hormone deficiency (CPHD) characterized by specific GH, PRL, and TSH deficiencies, 2. The presence of circulating anti-PIT-1 antibodies, and 3. Various autoimmune endocrinopathies, including insulitis, thyroiditis, and adrenalitis, suggest that this syndrome may be associated with autoimmune polyglandular syndrome (APS) [48, 49]. However, we later redefined this syndrome and renamed it "anti-PIT-1 hypophysitis" due to the clarification of the pathophysiology.

Additional investigation revealed a further in-depth pathophysiology of this disease. In several autoimmune diseases such as Graves' disease [50], hypoparathyroidism [51], and myasthenia gravis [52], the circulating autoantibodies are known to play a causal role in the pathogenesis. In anti-PIT-1 hypophysitis, the serum of the patient did not exhibit inhibitory effects on the pituitary cells and complement-dependent cytotoxicity was not detected. Conversely, Enzyme-Linked ImmunoSpot (ELISpot) assay revealed that the patient lymphocytes react specifically toward PIT-1 protein. The infiltration of clusters of differentiation (CD) 8-positive cells (meaning CTLs) was observed in the pituitary gland. These results strongly suggest that CTL-mediated autoimmunity plays a pivotal role in anti-PIT-1 hypophysitis development [53]. Based on these observations, the anti-PIT-1 antibody is a diagnostic marker and the pathological findings in the pituitary indicate that this is an autoimmune-based inflammatory disease such as lymphocytic hypophysitis with a targeted

injury of specific pituitary cells, we renamed this syndrome "anti-PIT-1 hypophysitis." A similar mechanism is used in type 1 diabetes mellitus [54]. The anti-GAD antibody is widely used for the diagnosis of type 1 diabetes mellitus. However, this autoantibody is a disease marker, and CTLs play an essential role in disease development. Additional studies have demonstrated that PIT-1 protein is processed in the antigen presentation pathway, and its epitopes are presented with major histocompatibility complex (MHC)/ human leukocyte antigen (HLA) class I molecules on the cell surface of anterior pituitary cells, supporting the hypothesis that PIT-1-reactive CTLs caused cell-specific damage [55]. Interestingly, a disease model using patient-derived induced pluripotent stem cells showed that the number of PIT-1 epitope presentation was similar to that in control subjects, suggesting that the pituitary condition was not responsible for the disease, although it cannot be ruled out as there were differences in of antigen presentation quality and there was a promotion factor for antigen presentation at the onset in the patients.

In the first three cases of anti-PIT-1 antibody syndrome, thymoma was diagnosed, and thymoma tissue showed ectopic expression of PIT-1 in the neoplastic cortical thymic epithelial cells, suggesting that thymoma plays a role in the pathogenesis of this syndrome. Interestingly, after thymectomy, the titer of anti-PIT-1 antibody decreased, and CTLs reacting with PIT-1 protein diminished. Based on this evidence, we defined this syndrome as a novel thymoma-associated disease [56]. It was speculated that the ectopic expression of PIT-1 as a self-antigen and impaired negative selection of autoreactive T cells in the thymoma was the etiology of this disease.

This clinical concept has been further developed recently. Subsequently, we have encountered more cases of this disease, in which thymoma was undetected; other malignancies, however, were complicated [57]. A case was diagnosed as anti-PIT-1 hypophysitis with a typical feature of endocrine abnormalities and exhibited diffuse large B-cell lymphoma

(DLBCL) in the bladder. Interestingly, DLBCL cells ectopically expressed PIT-1 protein, as observed in thymomas in previous cases. ELISpot assay revealed that the patient's lymphocytes recognized the PIT-1 protein. Additional cases with malignant non-thymic tumors also showed GH-, PRL-, and TSH-deficiencies that matched the definition of this syndrome [57, 58]. Based on our study involving multiple medical cases, it is now considered that ectopically expressed PIT-1 protein in the tumor tissues – complicated malignant tumors which are not necessarily thymoma–evokes the breakdown of immune tolerance for PIT-1, resulting in autoimmunity against PIT-1. Hence, we recognized that anti-PIT-1 hypophysitis is a form of paraneoplastic syndrome and defined the following new diagnostic criteria [3].

Criterion 1: Acquired specific GH, PRL, and TSH deficiency.

Criterion 2: Presence of anti-PIT-1 antibody or PIT-1-reactive T cells in circulation

Criterion 3: Coexistence of thymoma or malignant neoplasm.

A probable diagnosis would meet criterion 1. A definite diagnosis would need to meet criteria 1 and 2. Criterion 3 is an auxiliary diagnostic demand, because, as with other paraneoplastic syndromes, endocrine abnormalities tend to proceed with the diagnosis of causal malignancies, and malignancies can be occult tumors.

Unsolved issues in anti-PIT-1 hypophysitis

Although accumulating medical cases of this disease have unveiled new discoveries about the pathophysiology, there are many unresolved issues. One enigma is the type of malignancy associated with this syndrome. We have reported cases with anti-PIT-1 hypophysitis that accompanied with thymoma, DLBCL, bladder cancer, and multiple metastases of unknown origin malignancy [57]. PIT-1 is highly specific for pituitary expression. However, there are several reports showing ectopic PIT-1 expression in malignancies. For example, PIT-1 is expressed in breast cancer and is associated with tumor aggressiveness via the CXCL12-

CXCR4 axis [59, 60]. A previous study showed that PIT-1 protein functions to enhance cell proliferation in a mammary gland cancer cell line, suggesting that PIT-1 expression plays a role in the development of these tumors. Still, the underlying mechanisms of ectopic PIT-1 expression in malignant tumors need to be clarified. With regard to thymoma, it has been reported that various genes associated with DNA methylation regulation are mutated in thymic carcinoma [61, 62], and epigenetic abnormalities are common in thymoma [63, 64]. Given that many malignancies exhibit abnormal epigenetic regulation [65], it is plausible that these altered epigenetic modifications result in ectopic PIT-1 expression. Although we analyzed the methylation status of the regulatory region of the *PIT-1* gene in thymoma, we are yet to detected methylation abnormalities (data not shown).

Another query that came up due to this study is the prevalence of anti-PIT-1 hypophysitis in patients with neoplasms, including thymoma. Thymoma is a rare neoplasm with a prevalence of 0.13 per 100,000 person-years [66]. It is well known that thymoma is often complicated with autoimmune diseases such as myasthenia gravis and pure red cell anemia [67]. Myasthenia gravis are reportedly observed in 30% to 45% of thymoma cases [68]. It remains unknown how often anti-PIT-1 hypophysitis is complicated. Additionally, the prevalence of anti-PIT-1 hypophysitis in other malignancies also needs to be clarified. GH and TSH deficiencies can cause general fatigue and impaired quality of life. These symptoms are sometimes indistinguishable from malignancy symptoms. Therefore, the complication of anti-PIT-1 hypophysitis in various malignancies may be underestimated.

Regarding endocrine disease, anti-PIT-1 hypophysitis is one of the causes of adult GH deficiency. Adult GH deficiency symptoms include metabolic abnormalities associated with visceral obesity, reduced muscle and bone mass, and impaired QOL [69]. GH replacement therapy effectively improves these clinical features. However, GH replacement therapy is contraindicated in patients with active malignancies because the GH/insulin-like growth factor

(IGF-I) axis is generally considered to promote tumor progression in certain malignancies. However, many clinical studies have shown that GH replacement therapy does not increase the incidence of malignancies in patients with adult GH deficiency [70]. In anti-PIT-1 hypophysitis, the possibility of a complicated tumor must be considered when performing GH replacement therapy.

2) Paraneoplastic autoimmune isolated ACTH deficiency

Isolated ACTH deficiency (IAD) is a disorder that results from impaired secretion of ACTH and can occasionally cause life-threatening events due to adrenal crisis [71]. Various autoimmune diseases, especially autoimmune thyroid diseases, frequently accompany acquired IAD. Therefore, autoimmunity against corticotrophs, which are ACTH-producing cells, has been suggested as the pathogenesis of IAD. In fact, anti-pituitary antibodies, such as anti-corticotroph antibodies, were detected in the serum of patients [72, 73]. Interestingly, autoantibodies against S100β-positive cells were detected in some patients with IAD, suggesting the presence of autoimmunity against folliculo-stellate cells, indicating that autoimmune pathogenesis of IAD is heterogeneous [74]. Yet, the underlying mechanism of IAD remains largely unknown.

Recently, a case of acquired IAD with large cell neuroendocrine carcinoma (LCNEC) in the lung was reported [75]. The 42-year-old woman was diagnosed with LCNEC 3 years after being diagnosed with acquired IAD. Interestingly, immunostaining revealed ectopic ACTH expression in LCNEC tissue. In addition, infiltration of lymphocytes, particularly CTLs and B cells, was observed in the tumor. Immunofluorescence analysis using the pituitary gland of a mouse showed that the patient's IgG recognized POMC protein, suggesting that autoimmunity against POMC protein was present. The patient’s IgG did not exhibit any impairment of cell proliferation and viability of AtT20 cells (a mouse POMC-expressing cell

line). However, the ELISpot assay revealed that the patient's lymphocytes specifically reacted with the POMC protein. Collectively, these data suggest that the anti-POMC antibody is a disease marker and that POMC-reacting CTLs play a pivotal role in the pathogenesis of anti-PIT-1 hypophysitis in this case.

Several medical cases of acquired IAD accompanied by malignant tumors have been reported, such as gastric cancer [76, 77] and acute lymphoblastic leukemia [78], ectopic expression of POMC has not been examined in these cases. Interestingly, it has been reported that 48% of non-small cell lung cancers show silent POMC expression without clinical symptoms of Cushing's syndrome [79], and carcinoid tumors express POMC even in the absence of ectopic ACTH syndrome [80]. These data suggest that the prevalence of tumors that ectopically express POMC and have IAD causing potential may be underestimated. It has been reported that malignancies are often occult tumors in patients with paraneoplastic syndromes because of the tumor immunity activation. Thus, it is speculated that in patients with idiopathic acquired IAD, occult tumors may be present.

Collectively, the case of IAD associated with LCNEC suggested that IAD was caused as a form of paraneoplastic syndrome. Several reported cases of acquired IAD complicated with malignancies have been reported, although a causal relationship has not been determined [75-78, 81]. Therefore, it is important to clarify the prevalence of paraneoplastic autoimmune IAD and the profile of potential cancers.

3) Immune-checkpoint inhibitor-related hypophysitis as a paraneoplastic autoimmune hypophysitis

Recently, immune-checkpoint inhibitor (ICI)-related hypophysitis has emerged as the development of cancer immunotherapy has expanded. The thyroid and pituitary glands are the organs majorly involved in immune-related endocrine adverse events [82]. Although the

underlying mechanisms of ICI-related hypophysitis are largely unknown, it has been reported that the expression of anti-cytotoxic T-lymphocyte antigen-4 (CTLA4) plays a role in CTLA-4 inhibitor-related hypophysitis. Lactotroph and thyrotroph express CTLA-4, and the direct interaction of anti-CTLA-4 antibodies with these cells induces complement-dependent cytotoxicity to the pituitary gland [83]. However, the underlying mechanisms of programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitor-related hypophysitis remain unclear. Furthermore, the pattern of impaired pituitary hormones and clinical features are different between CTLA-4 inhibitor- and PD-1/PD-L1 inhibitor-related hypophysitis, suggesting that the underlying mechanisms are different.

The new concept of "paraneoplastic autoimmune hypophysis" and "paraneoplastic autoimmune IAD" has further developed to understand the pathophysiology of ICI-related hypophysitis. As formerly mentioned, although ectopic ACTH syndrome is rare, malignant tumors often express POMC silently. Intriguingly, in PD-1/PD-L1 inhibitor-related hypophysitis, most cases exhibit IAD [84, 85]. We detected anti-corticotroph antibodies in two out of 20 patients (10%) with PD-1/PDL-1 inhibitor-related hypophysitis. Remarkably, the tumor tissues of these cases exhibited ectopic expression of POMC, suggesting that immune tolerance for POMC was broken by the ectopic expression of POMC in the tumor. Furthermore, the pituitary gland expresses PDL-1 [86] and it is possible that PD-1/PDL-1 inhibitors directly enhance autoimmunity against the pituitary. Collectively, these data clearly show a common underlying mechanism between "paraneoplastic autoimmune hypophysitis" and PD-1/PD-L1 inhibitor-related hypophysitis, and some of PD-1/PD-L1 inhibitor-related hypophysitis is caused by these mechanisms. It is also suggested that in patients with cancers that silently and ectopically expressed POMC, ICI use can promote the autoimmune reaction and develop hypophysitis, resulting in IAD.

D. Future perspective

Presently, a novel clinical entity, "paraneoplastic autoimmune hypophysitis," includes anti-PIT-1 hypophysitis, paraneoplastic IAD, and PD-1/PD-L1-related hypophysitis (Table 2). Ectopic hormone expression in tumors can generally be diagnosed when the symptoms associated with hormone excess manifest. Clinically relevant ectopic hormone production is generally rare. However, "silent" ectopic expression of hormones may not be rare, as shown in the silent ACTH expression [79]. Epigenetic dysregulation is commonly observed in many malignant tumors, resulting in ectopic expression of various proteins [87]. In addition, even if the expression is silent, it can be an antigen and may cause autoimmunity. Therefore, attention should be paid to concurrent malignant tumors in patients with acquired hypopituitarism. It is important to be cautious that symptoms related to autoimmunity sometimes proceed to diagnose malignancies such as paraneoplastic syndromes, dermatomyositis, and Leser-Trélat syndrome [88]. Indeed, many occult tumors that cause paraneoplastic syndrome and tumors associated with paraneoplastic syndrome show a slow progression, likely due to tumor immunity [31]. Therefore, it may be challenging to find occult tumors in patients with paraneoplastic hypopituitarism.

Although the prevalence of acquired IAD is rare (3.8 to 7.3 per 100,000 people [89]), it is the most prevalent among the anterior pituitary hormones. Interestingly, the prevalence of ectopic ACTH syndrome is also the most prevalent among the anterior pituitary hormones [90-94]. These data suggest that although the reasons remain unknown, POMC tends to be ectopically expressed in various tumors. These data can also explain the reason for IAD is observed in PD-1/PD-L1-related hypophysitis [81] (Figure 1).

Another issue is the significance of ectopic expression of these proteins in tumors. PIT-1 is reportedly expressed in several malignant tumors, such as breast cancer [60] and acute myeloid lymphoma [95]. A recent study revealed that PIT-1 expression leads to tumor

progression and metastasis in breast cancer-induced metabolic reprogramming [96, 97]. These data suggest that ectopically expressed molecules, including hormones, play a role in tumor progression and can be targets for treatment strategies.

The emerging concept, "paraneoplastic autoimmune hypophysitis," has allowed for the furthering of research in multiple areas. First, this concept clearly indicates that a part of the paraneoplastic endocrine syndrome is caused by autoimmunity, which is commonly observed in paraneoplastic neurological syndromes. Second, not only oncology but also immunology and endocrinology need to be united in understanding the pathophysiology, indicating the importance of the new field of onco-immuno-endocrinology. Finally, this concept can be applied to various autoimmune conditions related to malignancies to understand the underlying mechanisms.

Summary

Novel clinical entities related to hypophysitis caused by pituitary autoimmunity have recently emerged due to the continued study of this area. These entities include anti-PIT-1 hypophysitis, paraneoplastic autoimmune isolated ACTH deficiency, and immune checkpoint inhibitor-related hypophysitis. In these conditions, ectopic expression of pituitary transcription factors or hormones in complicated tumors evokes autoimmunity against pituitary cells, leading to the production of autoantibodies and auto-reactive cytotoxic T cells. These mechanisms resemble those of the paraneoplastic neurologic syndrome. In most paraneoplastic neurologic syndromes, autoantibodies against self-antigens expressed in the tumor play a pivotal role in the development of the disease, and cellular immunity plays an essential role in hypophysitis. These conditions clearly support our newly presented concept of "paraneoplastic autoimmune hypophysitis." These data clearly indicate the significance of the interplay between tumors and the immune and endocrine systems, suggesting the importance of new disciplinarily in onco-

immuno-endocrinology.

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Conflict of Interest

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Figure Legend

Figure 1. Pathogenesis of paraneoplastic autoimmune hypophysitis.

Malignant tumors ectopically express ACTH/POMC. Dendric cells phagocytize tumor cells, leading to the generation of ACTH/POMC-reactive cytotoxic T lymphocytes (CTLs). ACTH/POMC-reactive CTLs destroy corticotrophs in the pituitary gland.

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Table 1. "Classical" paraneoplastic endocrine syndromes

Syndrome/Symptom	Hormone(s)	Neoplasma
SIADH	Vasopressin	Small cell lung cancer, mesothelioma, bladder cancer, ureteral cancer, endometorial cancer, prostate cancer, esopharingial cancer, thymoma, lymphoma, Ewing sarcoma, brain tumors, gastrointestinal tumors, breast cancer, and adrenal carcinoma
Cushing syndrome	ACTH	Small cell lung cancer, bronchial carcinoid, thymoma, medullary thyroid cancer, gastrointestinal tract tumors, pancreatic cancer, adrenal carcinoma, and ovarian cancer
Hypoglycemia	IGF-II, insulin	Mesothelioma, sacroma, lung cancer, and gastrointestinal cancer
Hypercalcemia	PTHrP	Breast cancer, multiple myeloma, renal cell carcinoma, squamous cell cancer, malignant lymphoma, ovarian cancer, and endometrial carcinoma
Carcinoid syndrome	Serotonin, tachykinins, histamine, kallikrein, prostaglandins	Neuroendocrine tumor (lung, liver, pancreas, stomach, small intestine, appendix, colon, and rectum)

SIADH: syndrome of inappropriate secretion of ADH, ADH: antidiuretic hormone, ACTH: adrenocorticotropic hormone, IGF-2: Insulin-like growth factor 2, PTHrP: parathyroid hormone-related protein

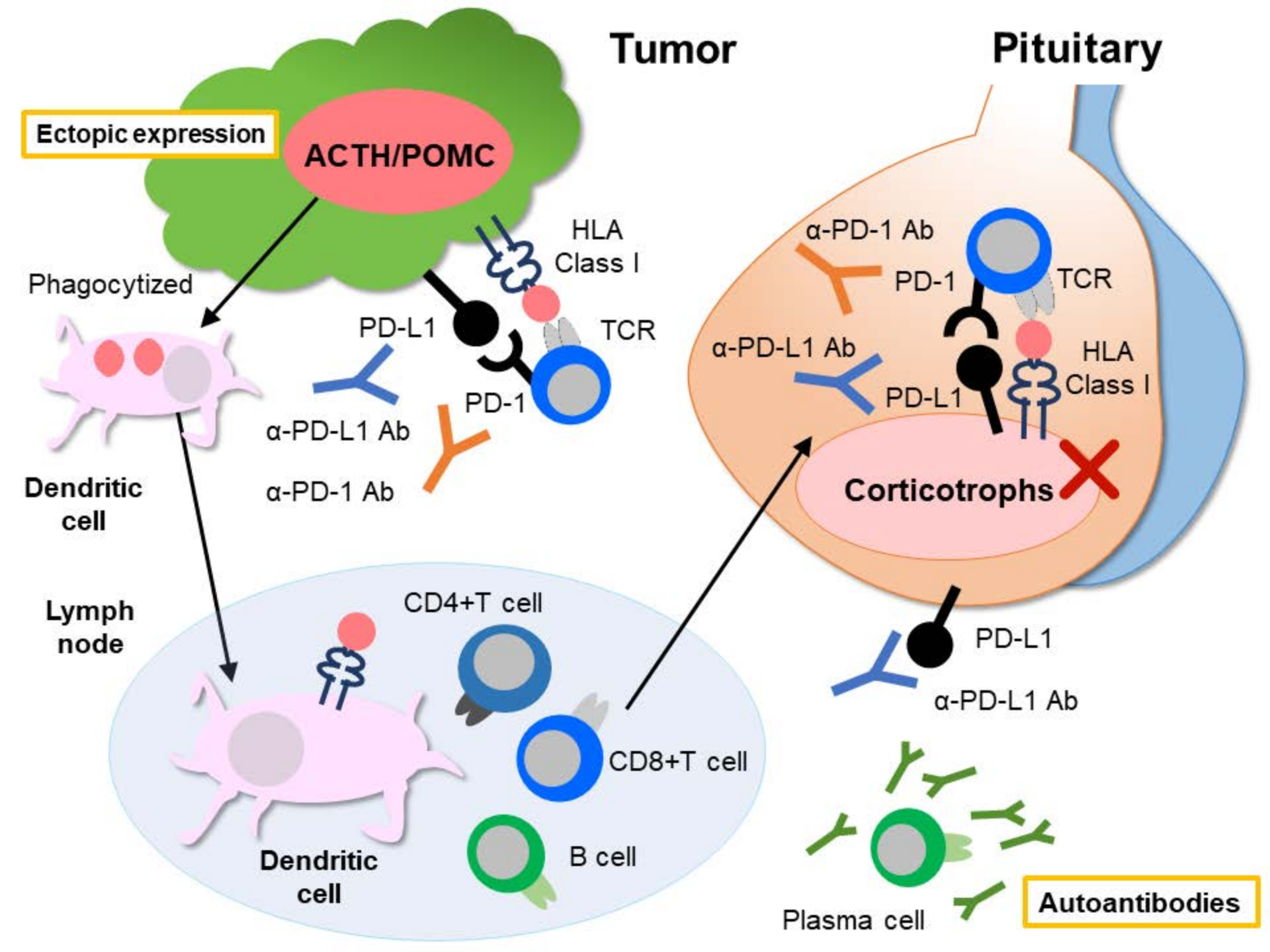
Table 2. Underlying mechanisms paraneoplastic syndrome

Paraneoplastic syndrome	Antigen	Mechanism of cell injuery	Neoplasma
Inflammatory myopathies (polymyositis/dermatomyositis) Interstitial pneumonia	Aminoacyl transfer RNA synthetase (ARS)	Unknown (unlikely for the autoantibodies to have a direct pathogenic role)	Ovarian cancer, breast cancer, prostate cancer, lung cancer, colorectal cancer, nasopharyngeal cancer, and non-Hodgkin lymphoma
Lambert-Eaton myasthenia syndrome	Voltage-gated calcium channel (VGCC) complex	Autoantibody	Small cell lung cancer (SCLC), prostate cancer, cervical cancer, and lymphomas
Limbic encephalitis	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor(AMPAR)	Autoantibody	Lung cancer, breast cancer, and thymic cancer
Limbic encephalitis	Gamma-aminobutyric acid B receptor ($GABA_BR$)	Autoantibody	SCLC
Limbic encephalitis	metabotropic glutamate receptor (mGluR) 5	Autoantibody	Hodgkin lymphoma
Limbic encephalitis	N-Methyl-D-Aspartate receptor (NMDAR)	Autoantibody	Teratoma
Limbic encephalitis Encephalomyelitis	Ma1/2	Unknown	Germ-cell tumors of testis
Limbic encephalitis Encephalomyelitis Paraneoplastic cerebellar degeneration Autonomic neuropathy	Hu	Cytotoxic T lymphocyte	SCLC
Limbic encephalitis Paraneoplastic cerebellar degeneration	Collapsin response mediator protein 5 (CRMP5)	Cytotoxic T lymphocyte	SCLC and thymoma
Limbic encephalitis Paraneoplastic cerebellar degeneration Autonomic neuropathy	Amphiphysin	Autoantibody	Breast cancer and SCLC
Limbic encephalitis Progressive encephalomyelitis with rigidity and myoclonus (PERM)	Glycine receptor (GlyR)	Autoantibody	Thymoma
Myathenia gravis	Acetylcholine receptor (AchR)	Autoantibody	Thymoma
Myathenia gravis	LDL receptor related protein 4 (LRP4)	Autoantibody	Thymoma
Myathenia gravis	Muscle-specific tyrosine kinase (MuSK)	Autoantibody	Thymoma
Myathenia gravis	Titin	Unknown (unlikely for the respective autoantibodies to have a direct pathogenic role)	Thymoma
Paraneoplastic autoimmune hypophysitis	Pituitary-Specific Positive Transcription Factor 1 (PIT-1), and pro-opiomelanocortin (POMC)	Cytotoxic T lymphocyte	Thymoma, malignant lymphoma, bradder cancer, unknown malignancy, large cell neuroendocrine carcinoma (LCNEC), malignant melanoma, and renal cell carcinoma
Paraneoplastic cerebellar degeneration	mGluR1	Autoantibody	Hodgkin lymphoma
Paraneoplastic cerebellar degeneration	Yo	Cytotoxic T lymphocyte	Ovarian cancer, uterus cancer, and breast cancer

Table 3. Paraneoplastic autoimmune hypopituitarism

	Anti-PIT-1 hypophysitis	Paraneoplastic isolated ACTH deficiency	Immune checkpoint inhibitor (PD-1/PD-L1)-related hypophysitis
Affected pituitary hormone(s)	GH, PRL, TSH	ACTH	ACTH
Antigen	PIT-1	POMC	POMC
Associated tumors	Thymoma, diffuse large B cell lymphoma,and unknown origin	Large cell neuroendocrine carcinoma (LCNEC) in the lung, gastric cancer*, and acute lymphoblastic leukemia*	Malignant melanoma and renal cell carcinoma

ACTH; adrenocorticotropic hormone, GH; growth hormone, TSH; thyroid-stimulating hormone, PD-1; Programmed cell death 1, PD-L1; Programmed death ligand 1, PIT-1; pituitary-specific transcription factor 1, POMC; pro-opiomelanocortin, PRL; prolactin, *; unproven


Tumor
Pituitary
Ectopic expression
ACTH/POMC
Phagocytized
HLA
Class I
PD-L1
TCR
PD-1
α-PD-L1 Ab
α-PD-1 Ab
Dendritic
cell
α-PD-1 Ab
PD-1
TCR
α-PD-L1 Ab
PD-L1
HLA
Class I
Corticotrophs
Lymph
node
CD4+T cell
CD8+T cell
B cell
Dendritic
cell
PD-L1
α-PD-L1 Ab
Plasma cell
Autoantibodies