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Case Report

Case Report

Two Cases of anti–PIT-1 Hypophysitis Exhibited as a Form of Paraneoplastic Syndrome not Associated With Thymoma

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Abbreviations: ACTH, adrenocorticotropin; anti–PIT-1, anti–pituitary-specific transcription factor; anti–PIT-1 hypophysitis, anti–PIT-1 antibody syndrome; CTLs, cytotoxic T cells; DLBCL, diffuse large B-cell lymphoma; ELISPOT, enzyme-linked immunospot; FSH, follicle-stimulating hormone; FT4, free thyroxine 4; GH, growth hormone; HRP, horseradish peroxidase; IgG, immunoglobulin G; LH, luteinizing hormone; PBMC, peripheral blood mononuclear cell; POMC, proopiomelanocortin; PRL, prolactin, TSH, thyrotropin.

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Abstract

Anti–pituitary-specific transcription factor 1 (PIT-1) hypophysitis (anti–PIT-1 antibody syndrome) is a thymoma-associated autoimmune disease characterized by acquired growth hormone (GH), prolactin (PRL), and thyrotropin (TSH) deficiencies due to autoimmunity against PIT-1. Ectopic expression of PIT-1 in the thymoma plays a causal role in development of the disease. Here, we report 2 cases of anti–PIT-1 hypophysitis exhibiting as a form of paraneoplastic syndrome with conditions other than thymoma. A 79-year-old woman (case 1) and an 86-year-old man (case 2) were referred with a suspicion of anti–PIT-1 hypophysitis because of acquired GH, PRL, and TSH deficiencies. Case 1 was complicated by diffuse large B-cell lymphoma (DLBCL) of the bladder and case 2 was diagnosed with malignancy with multiple metastases of unknown origin. Because circulating anti–PIT-1 antibody was detected, both patients were diagnosed with anti–PIT-1

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hypophysitis. Circulating PIT-1–reactive T cells were detected in case 1 via enzyme-linked immunospot (ELISPOT) assay. Interestingly, the PIT-1 protein was ectopically expressed in the DLBCL cells of case 1, whereas DLBCL tissues derived from patients without anti–PIT-1 hypophysitis were negative for PIT-1. In case 2, the materials were not available because of best supportive care was under way. These data show that anti–PIT-1 hypophysitis is associated not only with thymoma but also with other malignancies. Additionally, the ectopic expression of PIT-1 in the DLBCL tissues and presence of PIT-1–reactive T cells suggested that the underlying mechanisms were similar to those observed in thymoma. Thus, anti–PIT-1 hypophysitis is defined as a form of paraneoplastic syndrome.

Key Words: autoimmunity, hypopituitarism, anti–PIT-1 hypophysitis, anti–PIT-1 antibody syndrome, paraneoplastic syndrome

Anti–PIT-1 hypophysitis (anti-PIT-1 antibody syndrome) is characterized by acquired growth hormone (GH), prolactin (PRL), and thyrotropin (TSH) deficiencies associated with autoimmunity to PIT-1 [1, 2]. The condition of thymoma has been found to be complicated in patients with anti–PIT-1 hypophysitis. Additionally, previous studies have also demonstrated that thymoma tissues ectopically expressed PIT-1 that broke immune tolerance, resulting in the production of circulating anti–PIT-1 antibody and PIT-1–reactive cytotoxic T cells (CTLs) [2].

The term *paraneoplastic syndrome* refers to symptoms and signs resulting from damage to organs or tissues that are remote from the site of a malignant neoplasm or its metastasis. In particular, most paraneoplastic neurological syndromes are immune mediated and are associated with ectopic antigen presentation in the tumor that induces humoral and/or cellular autoimmune responses. Various tumors are known to cause paraneoplastic neurological syndromes [3]. A recent study reported the association of lung cancer with a case of isolated adrenocorticotropin (ACTH) deficiency related to paraneoplastic syndrome. Lung cancer ectopically expressed proopiomelanocortin (POMC), which in turn promoted the production of POMC-specific CTLs [4]. These results suggested that pituitary injury can also occur as a form of paraneoplastic syndrome in addition to neuronal injury.

We previously described a case of anti–PIT-1 hypophysitis with diffuse large B-cell lymphoma (DLBCL) briefly in the review literature [5]. In this study, we present the details of this case with further investigation for pathophysiology along with another novel case of malignancy and discuss a new definition of this disease.

Case Presentation

Case 1

A 79-year-old woman, hospitalized for the evaluation of chronic kidney disease, was diagnosed with central hypothyroidism. Endocrinological evaluation revealed extremely low basal levels and blunted responses to the provocative stimuli of GH, PRL, and TSH. However, the secretion of other anterior pituitary hormones was not impaired (Table 1). Pituitary magnetic resonance imaging revealed mild atrophy of the anterior pituitary (Fig. 1A). The patient was diagnosed with anti–PIT-1 hypophysitis by the detection of circulating anti–PIT-1 antibody (Fig. 2). Thereafter, she was treated with levothyroxine. At age 82 years, macroscopic hematuria and bladder tumors were detected. A biopsy of the tumor revealed the diagnosis of DLBCL. Computed tomography (CT) imaging revealed no evidence of thymoma (Fig. 1B) but multiple bilateral cervical, axillary, para-aorta, and internal and external periiliac lymphadenopathies (data not shown). Therefore, the patient was diagnosed with stage IV DLBCL and systemic chemotherapy was performed.

Case 2

An 84-year-old man was hospitalized for evaluation of immunoglobulin A nephropathy. At age 86 years, he manifested cold intolerance and was diagnosed with central hypothyroidism. Endocrinological evaluation revealed extremely low basal levels and blunted responses to the provocative stimuli of GH, PRL, and TSH (Table 1); however, the secretion of ACTH and luteinizing hormone (LH)/follicle-stimulating hormone (FSH) was preserved (see Table 1). Pituitary magnetic resonance imaging revealed no obvious abnormalities in the anterior pituitary (Fig. 1D). CT imaging showed no evidence of thymoma (Fig. 1E), para-aortic and para-gastric lymphadenopathies (Fig. 1F), and vertebral body infiltrates (Fig. 1F). Although no pulmonary nodules were detected on chest CT, serum levels of progastrin-releasing peptide (143 pg/mL; 0-81 pg/mL) and squamous cell carcinoma antigen (1.5 ng/mL; 0-1.5 ng/mL) levels were elevated. Taken together, the patient was diagnosed with malignancy with multiple metastases with

Table 1. Endocrinological data of cases 1 and 2

		Case 1	Case 2	Normal range	Unit of measure
GH	Basal	0.01	< 0.03		ng/mL
	Peak	0.01	< 0.03		ng/mL
ACTH	Basal	13.9	7.4	7.4-63.1	pg/mL
	Peak	93.2	39.4		pg/mL
Cortisol	Basal	13.2	14.2		μg/dL
	Peak	24.6	23.1		μg/dL
TSH	Basal	0.03	0.2	0.4-5.0	μIU/mL
	Peak	0.03	0.3		μIU/mL
PRL	Basal	0.3	0.2	3.6-12.8	ng/mL
	Peak	0.3	0.2		ng/mL
LH		33.9	10.1	0.8-5.7	μIU/mL
FSH		161.9	23.7	0.7-1.5	μIU/mL
IGF-1		66.0	18.0		ng/mL
FT4		0.4	0.4	0.7-1.5	ng/dL
TPOAb		Negative	Negative		IU/mL
TgAb		Negative	Negative		ng/mL
TRAb		Negative	NA		IU/L
GADAb		Negative	NA		U/mL

Endocrinological examination demonstrated a specific defect in GH, TSH, and PRL secretion. FT4 and IGF-1 were evaluated at the first visit before replacement therapy, including levothyroxine.

Abbreviations: ACTH, adrenocorticotropin; FSH, follicle-stimulating hormone; FT4, free thyroxine; GADAb, antiglutamic acid decarboxylase antibody; GH, growth hormone; IA2Ab, anti-insulinoma–associated protein-2 antibody; IGF-1, insulin-like growth factor-1, LH, luteinizing hormone; NA, not applicable; PRL, prolactin; TgAb, antithyroglobulin antibody; TPOAb, antithyroid peroxidase antibody; TRAb, thyrotropin receptor antibody, TSH, thyrotropin.

unknown origin. He refused further examinations and only irradiation therapy for the vertebral lesion was performed for palliative care. The patient was diagnosed with anti–PIT-1 hypophysitis by the detection of circulating anti–PIT-1 antibody (Fig. 2). Cold intolerance improved by following levothyroxine replacement.

Circulating pituitary-specific transcription factor 1–reactive T cells detected in case 1

ELISPOT assay using peripheral blood mononuclear cells (PBMCs) derived from case 1 demonstrated the presence of circulating PIT-1–reactive T cells, whereas these cells were not detected in PBMCs derived from control individuals (Fig. 3A and 3B). The number of reactive T cells was comparable with that in a previously described case with anti–PIT-1 antibody [1].

Ectopic expression of pituitary-specific transcription factor 1 in diffuse large B-cell lymphoma cells

In previous cases of anti–PIT-1 hypophysitis associated with thymoma, ectopic expression of PIT-1 was observed in the tumor tissue [6]. Therefore, we examined the DLBCL tissue in case 1. Interestingly, the lymphoma cells clearly showed ectopic PIT-1 expression; however, the DLBCL tissues derived from other patients without anti–PIT-1 hypophysitis did not (Fig. 4). The expression of PIT-1 in the DLBCL was also detected using the serum obtained from the patient with anti–PIT-1 hypophysitis containing anti–PIT-1 antibody [1].

Materials and Methods

Patients

This study was approved by the ethics committee of the Kobe University Graduate School of Medicine. All methods were performed in accordance with the guidelines of the approved protocol (reference No.: 29–62). Written informed consent was obtained from all the patients involved in this study.

Hormone assay

We measured the basal levels of pituitary and peripheral hormones to screen for hypopituitarism [7]. Hormone provocation tests were performed to achieve a definitive diagnosis [8]. Provocative tests were performed using corticotropin-releasing hormone (100 μg), thyrotropin-releasing hormone (200 μg), and GH-releasing peptide-2 (100 μg) to assess pituitary function [8, 9]. Plasma TSH [10], free thyroxine 4 (FT4) [11], cortisol [12], LH [13], and FSH [14] levels were measured by chemiluminescent

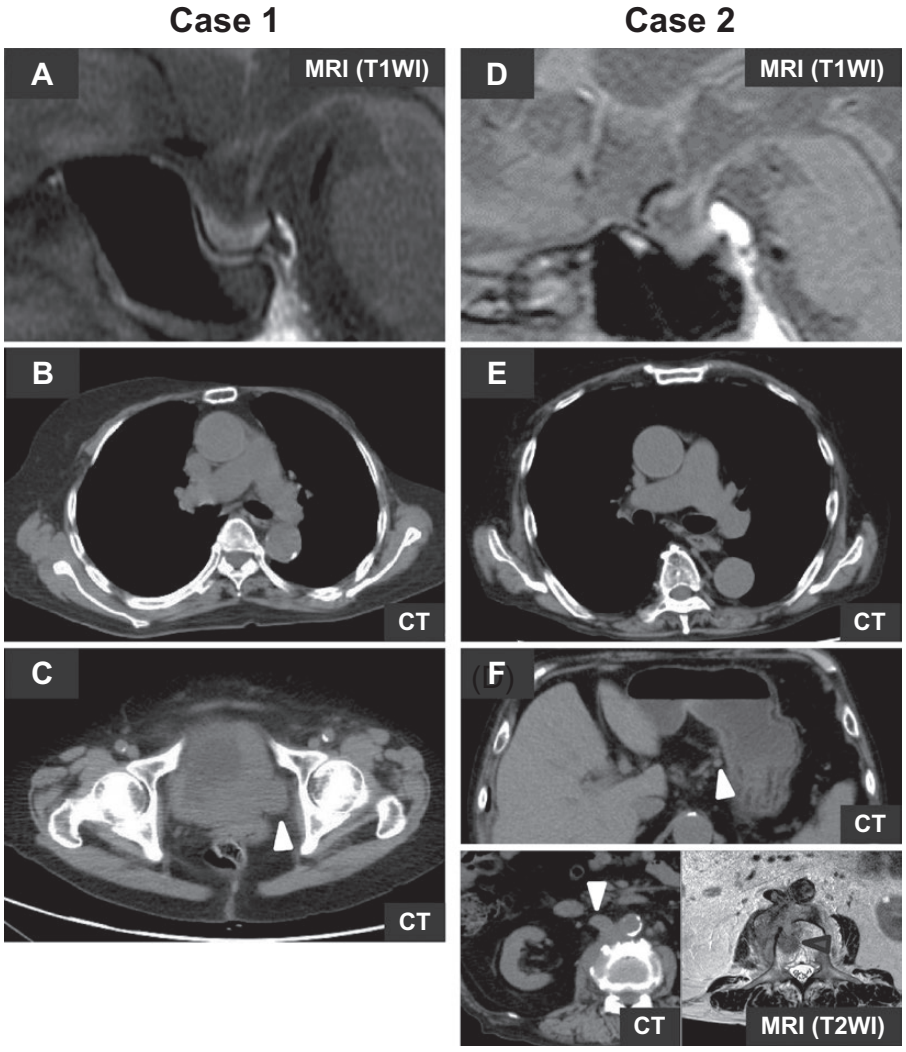

Figure 1. Magnetic resonance imaging (MRI) and computed tomography (CT) images of cases 1 and 2. A, B, and C, Case 1; D, E, and F, Case 2; A, A sagittal view of pituitary MRI showed that the pituitary was slightly atrophic. B No tumor was detected in the chest CT of the anterior mediastinum including thymoma. C, Lower abdominal CT demonstrated a bladder tumor (arrowhead) and thickening of the bladder wall. D, A sagittal view of the pituitary MRI showed that the pituitary was morphologically normal. E, Chest CT demonstrated no thymoma. F, Multiple lymphadenopathies (arrowhead) and vertebral body infiltrate (arrowhead) were detected.

immunoassay (CLIA; Abbott), and GH [15], insulin-like growth factor-1 [16], PRL [17], and ACTH [18] levels was assayed by electrochemiluminescence immunoassay (ECLIA; Roche), respectively.

Cell culture, transfection experiment, and immunoblotting

COS-7 cells (RRID:CVCL_0224) were purchased from the American Type Culture Collection. The cells were maintained in Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin (Life Technologies). V5- and His-tagged human PIT-1 expression vector (pcDNA3.1D/V5-His-hPIT-1) and V5-tagged human PROP-1 expression vector (pcDNA3.1/V5-hPROP1) were constructed using pcDNA3.1 Directional TOPO expression kit (Invitrogen, catalog No. K490001) and pcDNA3.1/V5 TOPO TA Expression Kit (Invitrogen, catalog No. K480001), respectively. These plasmids were then transiently transfected into COS-7 cells using X-tremeGENE HP DNA Transfection Reagent (Roche, catalog No. 06 366 244 001). Circulating anti–PIT-1 antibody was detected using immunoblotting. A total of 30 μg of protein was loaded into each lane. The patients' serum (1:200) and anti-V5 antibody (1:5000, Invitrogen, catalog No. R960-25, RRID:AB_2556564) [19] were used as primary antibodies. Horseradish peroxidase (HRP)-conjugated goat antihuman immunoglobulin G (IgG) + A + M (1:50000, Invitrogen, catalog No. AP120P, RRID:AB_92453) [20] and HRP-conjugated antimouse IgG (1:15000, Invitrogen, catalog No. 62–6520, RRID:AB_2533947) [21] were used as

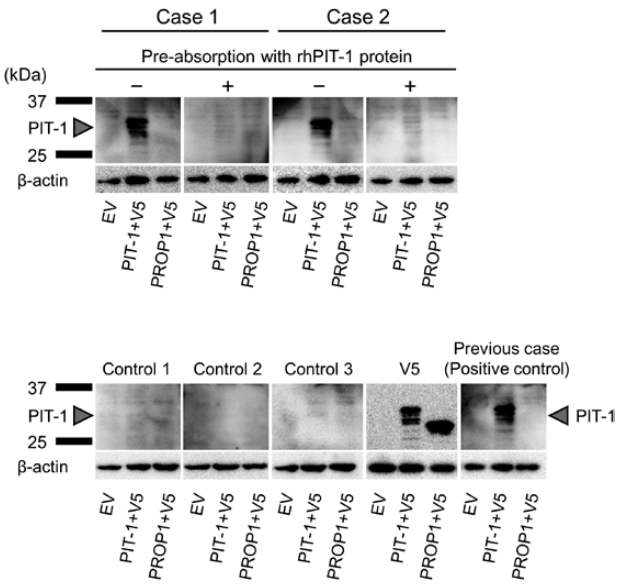

Figure 2. The detection of circulating anti–pituitary-specific transcription factor 1 (anti–PIT-1) antibody using immunoblotting. The upper panel shows the detection of the anti–PIT-1 antibody using patient serum as the primary antibody. Preabsorption of the serum with recombinant human PIT-1 protein diminished the specific signal, demonstrating the specificity of the autoantibodies for PIT-1. The lower panel shows the results of negative control using the serum of healthy individuals and positive control using the serum of the patient with anti–PIT-1 hypophysitis as previously reported (case 1, [1]).

secondary antibodies. Stripping antibodies from the membrane was applied by incubating the membrane with WB Stripping Solution Strong (Nacalai Tesque, catalog No. 05677-65) at room temperature for 15 minutes, then incubated with HRP-conjugated anti-β actin antibody (Abcam, catalog No. ab49900, RRID:AB_867494) [22]. Signals were detected using a Chemilumi-One chemiluminescence kit (Nacalai Tesque) and an image analyzer (Image Quant LAS 4000, GE Healthcare Life Sciences). Serum samples obtained from the previously described patients served as the positive control (case 1, [1]).

Immunohistochemistry

PIT-1 protein was detected as previously described [1]. For immunohistochemical staining of tumor specimens, fixed tissues were subjected to antigen retrieval and were permeabilized. Subsequently, the endogenous enzyme was removed using 0.3% hydrogen peroxide. The tissues were then blocked using Blocking One buffer (Nacalai Tesque). Further, the specimens were incubated with patient serum samples (1:200) or anti–PIT-1 antibody (1:150, catalog No. sc-442, RRID:AB_2166884) [23], and antihuman IgG rabbit polyclonal antibody (1:50000, DAKO, catalog No., RRID:AB_2335710) [24] was added to the serum samples

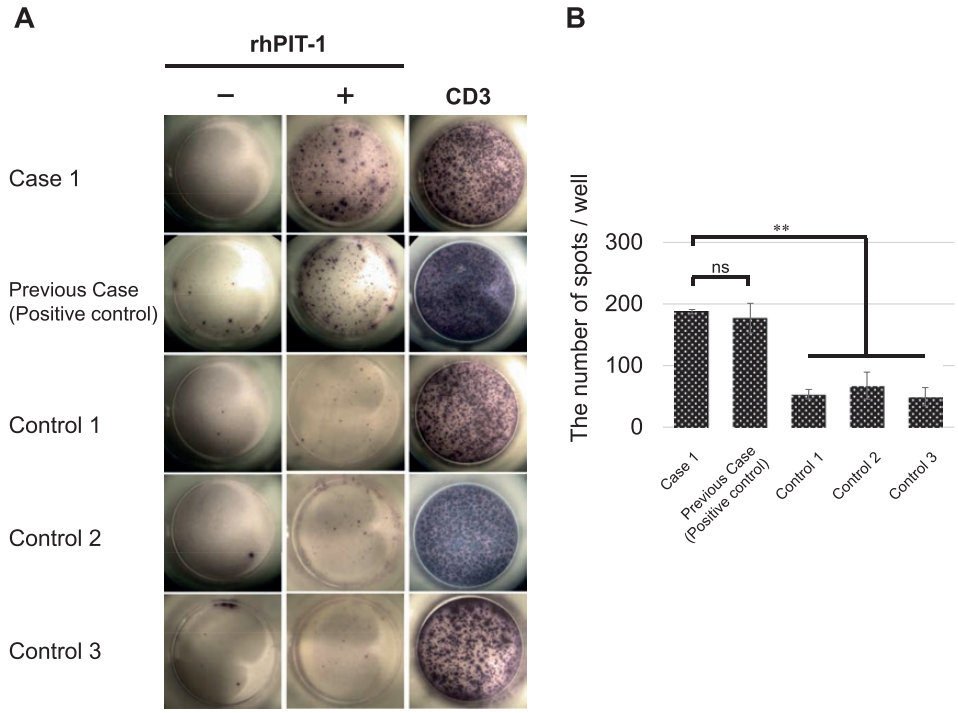

Figure 3. Detection of pituitary-specific transcription factor 1 (PIT-1)-reactive cytotoxicT cells (CTLs) by enzyme-linked immunospot (ELISPOT) assay using peripheral blood mononuclear cells (PBMCs). A, Images of the results of ELISPOT assay. Responses of interferon-γ (IFN-γ) secretion fromT cells under the stimulation of PIT-1 protein was detected as the spots. As a positive control, PBMCs of the previously reported patient with anti–PIT-1 hypophysitis [1] was used. PBMCs from case 2 were not available because of best supportive care. B, Quantitative analysis of the spots showed a significant increase in the number of spots as compared with controls. Data are plotted as mean ± SEM. Unpaired *t* test or one-way analysis of variance with Bonferroni multiple comparison post hoc test was used to assess significance levels. Significance levels were set at **P* less than .05 and ***P* less than .01.

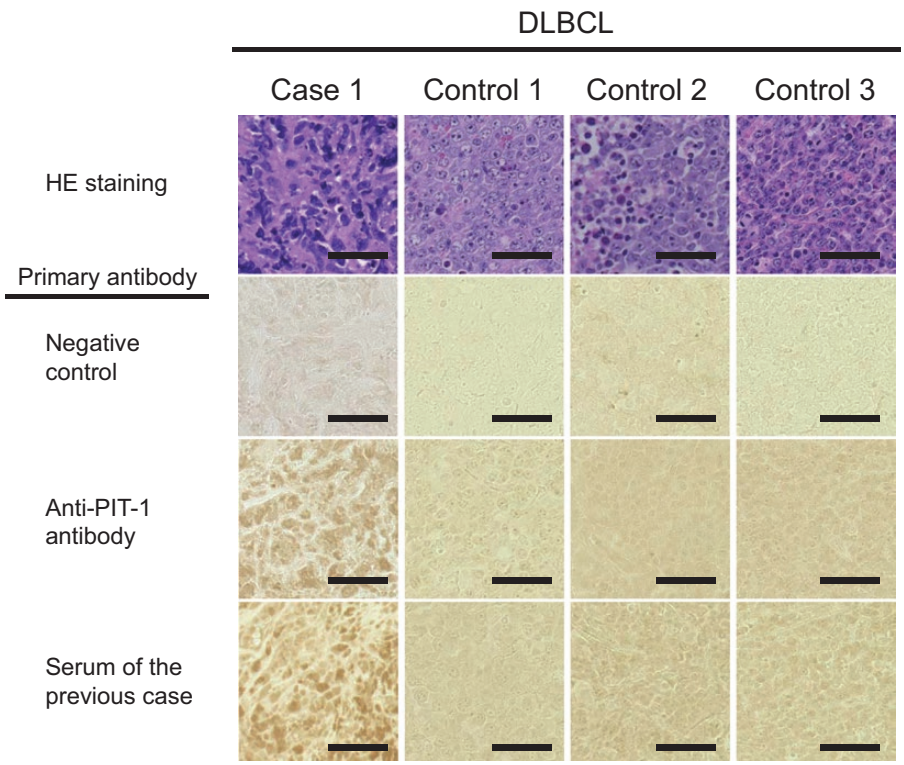

Figure 4. Ectopic pituitary-specific transcription factor 1 (PIT-1) expression in the diffuse large B-cell lymphoma (DLBCL) cells in case 1. Immunohistochemistry for PIT-1 using DLBCL tissues of case 1 and control cases without anti–PIT-1 hypophysitis. DLBCL cells in case 1 specifically expressed PIT-1 expression, whereas control DLBCL cells were negative for PIT-1. The serum of the patient [1] and a commercially available anti–PIT-1 antibody specifically showed the signal. Scale bars: 50 μm.

and stored overnight at 4 °C. This was followed by incubation with the secondary antibodies, namely, rabbit IgG antibody labeled with peroxidase (1:50000, Nichirei, catalog No. 424144, RRID:AB_2868561) [25]. Color development was performed using 3,3′-diaminobenzidine (DAB) as a chromogen. All images were captured using a BZ-X710 fluorescence microscope (Keyence) and reconstructed using BZ-H3A advanced analysis software (Keyence).

Enzyme-linked immunospot assay

ELISPOT assays were performed using ELISpotPRO for Human IFN-γ (Mabtech, RRID:AB_2877719) [26], following the manufacturer's instructions as previously described [2, 6]. Briefly, a total of 2.5×10^5 isolated PBMCs were seeded into each well and incubated with recombinant PIT-1 protein (10 μg/mL, Santa Cruz Biotechnology) in 96-well microtiter plates precoated with 10 μg/mL of antihuman IFN-γ antibody [26] for 40 hours. After washing, 1 μg/mL of an antihuman-IFN-γ detection antibody (clone: 7-B6-1, RRID:AB_907273) [27] was added and incubated for 2 hours. The plates were then incubated with streptavidin-alkaline phosphatase for 1 hour, followed by development with 0.45-μm filtered 5-bromo-4-chloro-3-indolyl-phosphate/nitro blue tetrazolium substrate solution for 10 to 20 minutes. Stimulation with anti-CD3 antibody (clone: OKT3, RRID:AB_2744380) [28] was used as a positive control. PBMCs obtained from the previously described patient served as the positive control (case 1, [1]).

Discussion

In this study, we describe 2 cases of anti–PIT-1 hypophysitis. Acquired GH, TSH, and PRL deficiency and the presence of circulating anti–PIT-1 antibody met the criteria for this disease in both cases [5]. Although cases of anti–PIT-1 hypophysitis associated with thymoma have been reported previously, chest CT confirmed no thymomas in these cases. However, case 1 was diagnosed with DLBCL, and case 2 was clinically diagnosed with malignancy with multiple metastases of unknown origin. These data clearly demonstrate that anti–PIT-1 hypophysitis is associated not only with thymoma but also with other malignancies, suggesting that anti–PIT-1 hypophysitis is a form of paraneoplastic syndrome.

Paraneoplastic syndromes involve organ damage mediated by autoimmune mechanisms including autoantibodies and/or antigen-specific CTLs [29]. Generally, ectopic antigen presentation in tumors evokes disruption of immune tolerance, causing autoimmunity [3]. In previous cases of anti–PIT-1

hypophysitis, ectopic expression of PIT-1 in thymoma tissue has eventually led to the production of autoreactive PIT-1–specific CTLs as well as circulating autoantibodies [6]. It is well known that thymoma is closely associated with several autoimmune diseases such as myasthenia gravis and red cell aplasia. The thymus plays an essential role in the education and maturation of T cells [30]. Initially, thymoma was considered to play a crucial role in the development of the disease. However, these 2 cases clearly indicate that it is not necessarily associated with thymoma but can also be associated with other malignancies.

DLBCL cells ectopically express PIT-1, and the presence of PIT-1–reactive CTLs indicates the underlying mechanisms similar to those in patients with thymoma. These data also suggest that anti–PIT-1 hypophysitis is a form of paraneoplastic syndrome that may be associated with several malignancies, including breast cancer [31, 32] and gastric cancer [33], because ectopic expression of PIT-1 has been reported in these tumors. In these cases, it has been reported that the expression of PIT-1 plays a role in tumor characteristics such as invasiveness and drug resistance. Recently, a case was reported [4] of acquired isolated ACTH deficiency, a form of paraneoplastic syndrome in which a complicated tumor ectopically expressed ACTH and evoked a production of POMC-reactive CTLs. Additionally, several cases of isolated ACTH deficiency with malignant tumors have also been reported [34, 35]. These data suggest that autoimmune pituitary disease with an unknown cause may at least in part be associated with occult malignancy as a form of paraneoplastic syndrome.

In conclusion, we demonstrated 2 cases of anti–PIT-1 hypophysitis associated with malignancy, clearly indicating that anti–PIT-1 hypophysitis is defined as a form of paraneoplastic syndrome. Although further studies are required, our findings provide insight into a novel mechanism underlying autoimmune pituitary diseases.

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Additional Information

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in "References."

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