Lymphocytic panhypophysitis and anti-rabphilin-3A antibody with pulmonary sarcoidosis

Running head: Lymphocytic panhypophysitis with sarcoidosis

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Abstract

Purpose: To explore the clinical significance of anti-rabphillin-3A antibody for the differential diagnosis of lymphocytic panhypophysitis.

Methods and Results: A 58-year-old Japanese man developed uveitis of unknown cause in 2017. In 2019, he became aware of polyuria. In August 2020, he noticed transient diplopia and was diagnosed with right abducens nerve palsy. At the same time, he complained of fatigue and loss of appetite. Head magnetic resonance imaging demonstrated enlargement of the pituitary stalk and pituitary gland, corresponding to hypophysitis. Hormone stimulation tests showed blunted responses with respect to all anterior pituitary hormones. Central diabetes insipidus was diagnosed on the basis of a hypertonic saline loading test. Taking these findings together, a diagnosis of panhypopituitarism was made. Computed tomography showed enlargement of hilar lymph nodes. Biopsies of the hilar lymph nodes revealed non-caseating epithelioid cell granulomas that were consistent with sarcoidosis. Biopsy of the anterior pituitary revealed mild lymphocyte infiltration in the absence of IgG4-positive cells, non-caseating granulomas, or neoplasia. Western blotting revealed the presence of anti-rabphilin-3A antibody, supporting a diagnosis of lymphocytic panhypophysitis. Because the patient had no visual impairment or severe uveitis, we continued physiological hormone replacement therapy and topical steroid therapy for the uveitis.

Conclusion: To the best of our knowledge, this is the first case of anti-rabphilin 3A antibody positive lymphocytic panhypophysitis comorbid with sarcoidosis, diagnosed by both pituitary and hilar lymph node biopsy. The utility of anti-rabphilin-3A antibody for the differential diagnosis of hypophysitis like this case should be clarified with further

case studies.

Keywords: lymphocytic panhypophysitis, sarcoidosis, anti-rabphilin-3a antibody, panhypopituitarism

Introduction

Lymphocytic hypophysitis (LH) is a chronic inflammatory disease in which lymphocytes mainly infiltrate the anterior or posterior pituitary gland and/or the hypothalamic infundibulum, and this is associated with the presence of other autoimmune diseases. Because positivity for various autoantibodies occurs in some cases, an autoimmune mechanism has been considered for LH. LH is classified on the basis of pathological findings with respect to inflammation [1-5]. (1) Lymphocytic adenohypophysitis (LAH) is characterized by inflammatory lesions in the anterior pituitary gland and lower secretion of anterior pituitary hormones. (2) Lymphocytic infundibuloneurohypophysitis (LINH) presents with central diabetes insipidus, owing to localized inflammation in the stalk and posterior lobe. (3) Lymphocytic panhypophysitis (LPH) involves inflammation of the entire pituitary and is characterized by clinical features of both LAH and LINH. Although a definitive diagnosis requires the pathological assessment of a pituitary biopsy, biopsies are often difficult to collect. Furthermore, even if a pituitary biopsy is performed, it is difficult to distinguish LH from other diseases that cause inflammation in the suprasellar region, including craniopharyngioma, Rathke cleft cysts, sarcoidosis, infectious diseases, and germinoma. Here, we report a case of LPH with comorbid pulmonary sarcoidosis that was diagnosed on the basis of pathological findings in both the pituitary gland and hilar lymph node. In this patient, the autoantibody profile was investigated.

Case report

A 58-year-old Japanese man was diagnosed with uveitis of unknown cause at a local hospital in 2017. Then, in 2019, he became aware of polyuria. In August 2020, he

experienced transient diplopia and was diagnosed with right abducens nerve palsy. He also reported fatigue and a loss of appetite. At that time, he underwent head magnetic resonance imaging (MRI), which revealed enlargement of the pituitary stalk and gland. Hypophysitis was suspected to be the cause of the diplopia, fatigue, and loss of appetite. Physical examination was unremarkable and the patient had no family history of endocrinological disorder. No abnormal findings were made during 12-lead electrocardiography or echocardiography. In addition, there were no obvious hematological or biochemical abnormalities, but there were reductions in the serum concentrations of all the anterior pituitary hormones, which was suggestive of panhypopituitarism (Table 1). Pituitary biopsy was performed on admission with hydrocortisone drip 100 mg for the prevention of adrenal insufficiency, followed by a physiological dose of oral hydrocortisone. Because the patient's polyuria worsened after the administration of hydrocortisone, we prescribed oral desmopressin 60 μg/day. Levothyroxine was also started 7 days after the hydrocortisone administration.

A growth hormone releasing peptide-2 (GHRP-2) loading test showed a poor response of growth hormone. therefore, severe adult growth hormone deficiency was diagnosed. A rapid ACTH stimulation test also revealed a poor cortisol secretory response, suggesting adrenal insufficiency. In a hypertonic saline loading test, antidiuretic hormone (ADH) was not secreted in response to an increase in serum Na, which led to a diagnosis of central diabetes insipidus. On the basis of these findings, the patient was diagnosed with panhypopituitarism.

Thoracoabdominal computed tomography showed swelling of the patient's longitudinal and hilar lymph nodes, but there were no findings suggestive of malignant tumors (Fig. 1A–E). A biopsy of the pituitary gland demonstrated mild lymphocytic

infiltration of the anterior pituitary, with most of the lymphocytes being CD3-positive and few being CD20-positive. In addition, no IgG4-positive cells were present (Fig. 2A–D). There were no findings suggestive of IgG4-related disease [6], sarcoidosis, or neoplasia, and none that were inconsistent with lymphocytic hypophysitis. No findings characteristic of malignancy were found on bronchoalveolar lavage (BAL), whereas the proportion of lymphocytes in the BAL fluid was elevated to 53.7%. Biopsies of the patient's hilar lymph nodes by an endobronchial ultrasound-guided transbronchial needle aspiration revealed non-caseating epithelioid cell granulomas, consistent with sarcoidosis (Fig. 2E). His uveitis was considered to reflect systemic sarcoidosis, but no other sarcoidosis lesions were identified, including in the liver and heart.

We investigated his autoantibody profile. ANA was borderlined, but the rest of routine autoantibodies were all negative (table 2). On the other hand, the presence of serum anti-rabphilin-3A antibody was detected by western blotting [7] (Fig. 3). Ultimately, we diagnosed lymphocytic panhypophysitis.

Because the patient had no visual field impairment and his uveitis was not severe, we continued physiological glucocorticoid replacement and local steroid treatment for the uveitis. The ongoing hormone replacement comprised hydrocortisone 15 mg/day, levothyroxine 75 μg/day, and oral desmopressin 60 μg/day, and the patient reported no symptoms at his most recent visit.

Discussion

In the case reported herein, examination of a pituitary biopsy supported a diagnosis of LH, but a diagnosis of pulmonary sarcoidosis, made on the basis of a lymph node biopsy, suggested the presence of central nervous system sarcoidosis, which complicated the

diagnosis. Ultimately, we diagnosed LPH, based on the presence of anti-rabphilin-3A antibody alongside the biopsy findings. A few cases of comorbid sarcoidosis and lymphocytic hypophysitis has been reported [8, 9], although no case was performed pituitary and hilar lymph node biopsy and testing for the anti-rabphilin-3A antibody.

In general, a diagnosis of central nervous system sarcoidosis, including suprasellar lesions, is made on the basis of the clinical manifestations and biopsy findings, although biopsies are often obtained from tissues other than the pituitary gland, such as the hilar lymph nodes. The classical finding of sarcoidosis is noncaseating granulomas [10], which is not seen in the pathology of LH cases. In the present patient, we performed biopsies of both the pituitary gland and hilar lymph nodes, which facilitated a diagnosis of LPH.

A diagnosis of LH is confirmed by the exclusion of other types of inflammatory disease in the suprasellar region. The histological findings of LH are the infiltration of the adenohypophysis with lymphocytes, plasma cells, and macrophages. The T and B lymphocytes that infiltrate the pituitary gland can also form lymphoid follicles with a germinal center [11]. IgG4-related disease, sarcoidosis, malignant lymphoma, malignant tumor metastasis, syphilis, and tuberculosis were considered as alternative causes of panhypopituitarism in the present case. Diseases other than sarcoidosis could be excluded on the basis of blood tests, imaging, and clinical findings. Although the pituitary biopsy showed features consistent with LH, the presence of pulmonary and ocular sarcoidosis might imply the presence of sarcoidosis-induced hypophysitis (Table 1), and indeed non-specific inflammation can be found in pituitary biopsy specimens, even if a germinoma exists in the suprasellar region, because of the choice of sampling site or if a small biopsy is obtained [12].

Sarcoidosis is a systemic granulomatous disease of unknown cause that often causes lesions in the lungs, eyes, and skin [13]. It has been reported that 5%–13% of patients present with neurological lesions [13-15], and of these, hypothalamic and pituitary lesions have been reported in ~3% [16]. Sarcoidosis often resolves spontaneously [17], but steroid treatment is often required to treat the neuropathies, including lesions of the hypothalamus and pituitary. However, such treatment is often unsuccessful: Anthony *et al*. studied 46 patients with neuropathy and poor thalamic/pituitary function [18], of which 43 required treatment with steroids, but only five patients improved with treatment. In the present case, bilateral enlargement of the hilar lymph nodes and the results of a biopsy of these lymph nodes were consistent with pulmonary sarcoidosis, but steroid treatment was not indicated because of the absence of respiratory symptoms. High-dose steroid therapy is usually required for the treatment of CNS sarcoidosis, but only physiological steroid replacement is recommended for the treatment of LH, except if symptoms of compression owing to enlargement of the pituitary are present.

Anti-rabphilin-3A antibody is an autoantibody that was first reported by Iwama *et al.* in 2015[7, 19]. It has a high sensitivity of 100% for the identification of pathologically diagnosed LINH and 76% for clinically diagnosed LINH, but there can be false positives in healthy individuals and patients with other autoimmune diseases. However, its specificity has been shown to be 100% for the differentiation of LINH from neoplastic diseases (pathological diagnoses), which implies that it is clinically useful for the differentiation of LINH from other diseases[7]. Even though the significance and the prevalence of anti-rabphilin-3A antibody in the diagnosis of LPH has yet to be fully established, the presence of the antibody in the present case definitely diagnosed as

lymphocytic hypophysitis with pituitary-biopsy suggests that the autoimmune process other than sarcoidosis existed in the pituitary injury, and that the utility of the antibody in the diagnosis of LPH.

Conclusion

We have reported a case of lymphocytic panhypophysitis and anti-rabphilin-3A antibody with pulmonary sarcoidosis. The utility of anti-rabphilin-3A antibody to distinguish LPH from other inflammatory disease in the suprasellar region should be clarified in the further case studies.

Declarations

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Code availability: Not applicable.

Authors' contributions:Not applicable

Ethics approval:Not applicable

Consent to participate: Not applicable

Consent for publication: Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

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Figure captions

Fig. 1 Imaging results. Sagittal gadolinium-enhanced T1-weighted brain magnetic resonance image on day 1: sagittal (A) and coronal (B). (C) Chest X-ray on day 1. (D, E) Axial iodine-enhanced computerized tomography images, showing bilateral enlargement of the hilar lymph nodes

Fig. 2 Histology and immunohistochemistry of biopsy specimens demonstrated mild lymphocytic infiltration of the anterior pituitary, with most of the lymphocytes being CD3-positive and few being CD20-positive. (A) Hematoxylin and eosin staining of the pituitary. Scale bar: 50 μm. (B) CD3 immunostaining of the pituitary. Scale bar: 50 μm. (C) CD20 immunostaining of the pituitary. Scale bar: 50 μm. (D) IgG4 immunostaining of the pituitary. Scale bar: 50 μm. There were no findings suggestive of IgG4-related disease. (E) Hematoxylin and eosin staining of the hilar lymph nodes. Scale bar: 100 μm.

Fig. 3 Detection of anti-rabphilin-3A antibodies by Western blotting.
Recombinant full-length human rabphilin-3A expression was evaluated in HEK293FT cells transfected with the human rabphilin-3A gene (RPH3A + HEK293FT, left lanes) or with the empty vector (HEK293FT, right lanes) by probing with serum from the present patient (patient), from a patient who was diagnosed with LINH previously (positive control patient), or from a patient who was diagnosed with craniopharyngioma previously (negative control patient). The arrowhead indicates the presence of anti-rabphilin-3A antibodies. The dashed arrowhead indicates the absence of anti-rabphilin-3A antibodies. Recombinant full-length human rabphilin-3A expressed in HEK293FT cells was also probed with an anti-V5 antibody as positive control (Anti-V5 antibody) in

the first lane from the left.

Table 1. Laboratory findings at the admission

<CBC>				Cl	101	mEq/L	101-108 *	<Endocrinology>				<Urine testing>		
WBC	8.5×10^3	/ μL	3.3-8.6 *	Ca	9.1	mg/dL	8.8-10.1 *	ACTH	6.53	pg/mL	7.2-63.3 *	pH	5.0	4.5-8.5 *
RBC	4.5×10^6	/μL	4.3-5.5 *	P	3.7	mg/dL	2.7-4.6 *	Cortisol	1.2	μg/dL	2.9-19.4 *	Protein	-	- *
Hb	13.2	g/dL	13.7-16.8 *	CRP	0.11	mg/dL	0-0.14 *	GH	0.33	ng/mL	0.0-0.17 *	Glucose	-	- *
Ht	39	%	40.7-50.1 *	TG	160	mg/dL	40-234 *	IGF-1	63	ng/mL	81-235 *	Ketone	-	- *
Plt	28.7×10^4	/μL	15.8-34.8 *	HDL-C	41	mg/dL	38-90 *	LH	<1.0	mIU/mL	2.2-8.4 *	Blood	-	- *
< Biochemistry>				LDL-C	181	mg/dL	65-163 *	FSH	<1.0	mIU/mL	1.8-12.0 *			
TP	7.4	g/dL	6.6-8.1 *	Glucose	120	mg/dL	73-109 *	Testo	<12.0	ng/dL	131-871 *			
Alb	4.1	g/dL	4.1-5.1 *	HbA1c	6.3	%	4.9-6.0 *	ADH	0.6	pg/mL				
T-bil	0.6	mg/dL	0.4-1.5 *	ACE	16.9	U/L	8.3-21.4 *	TSH	0.64	μU/mL	0.34-4.22 *			
AST	33	U/L	13-30 *	sIL-2 R	578	U/mL	0-613 *	FT3	1.93	pg/mL	2.24-3.94 *			
ALT	24	U/L	10-42 *	IgA	273	mg/dL	93-393 *	FT4	0.57	ng/dL	0.77-1.59 *			
γ-GTP	16	U/L	13-64 *	IgM	48	mg/dL	33-183 *	Renin	<0.2	ng/mL/h	0.2-3.9 *			
BUN	11	mg/dL	8-20 *	IgG	1662	mg/dL	861-1747 *	Ald	76	pg/mL	36-240 *			
Cre	1.16	mg/dL	0.65-1.07 *	IgG4	77.9	mg/dL	11.0-121.0 *							
eGFR	51.4	ml/min/1.73m^2		RPR	-		- *							
Na	136	mEq/L	138-145 *	TPLA	-		- *							
K	4.0	mEq/L	3.6-4.8 *	TSPOT.TB	-		- *							

pH: power of hydrogen, CBC: complete blood count, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma glutamyl transpeptidase, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, CRP: c-reactive protein, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, ACE: angiotensin-converting enzyme, sIL-2 R: soluble interleukin-2 receptor, IgA: immunoglobin A, IgM : immunoglobin M, IgG: immunoglobin G, IgG 4: immunoglobin G4, RPR: rapid plasma reaction, TPLA: toreponema pallidum antigen method, ACTH: adrenocorticotropic hormone, GH: growth hormone, IGF-1: insulin-like growth factor-1, LH: luteinizing hormone, FSH: follicle stimulating hormone, Testo: Testosterone, ADH: antidiuretic hormone, TSH: thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, Ald: Aldosterone

* nomal range

Table 2. Autoantibody profile

Antinuclear antibody	80	times	<40 *
Anti SS-A antibody	3.8	INDEX	<10 *
Anti SS-B antibody	0.7	INDEX	<10 *
Anti β2GP1 antibody	<0.7	U/mL	<3.5 *
Anti TPO antibody	<3.0	IU/mL	0-5.6 *
Anti TG antibody	<3.0	IU/mL	0-4.11 *

SS-A:Sjogren syndrome-A, SS-B:Sjogren syndrome-B, GPI:glycoprotein 1, TPO: thyroperoxidase, TG: thyroglobulin.

* nomal range

Figure. 1

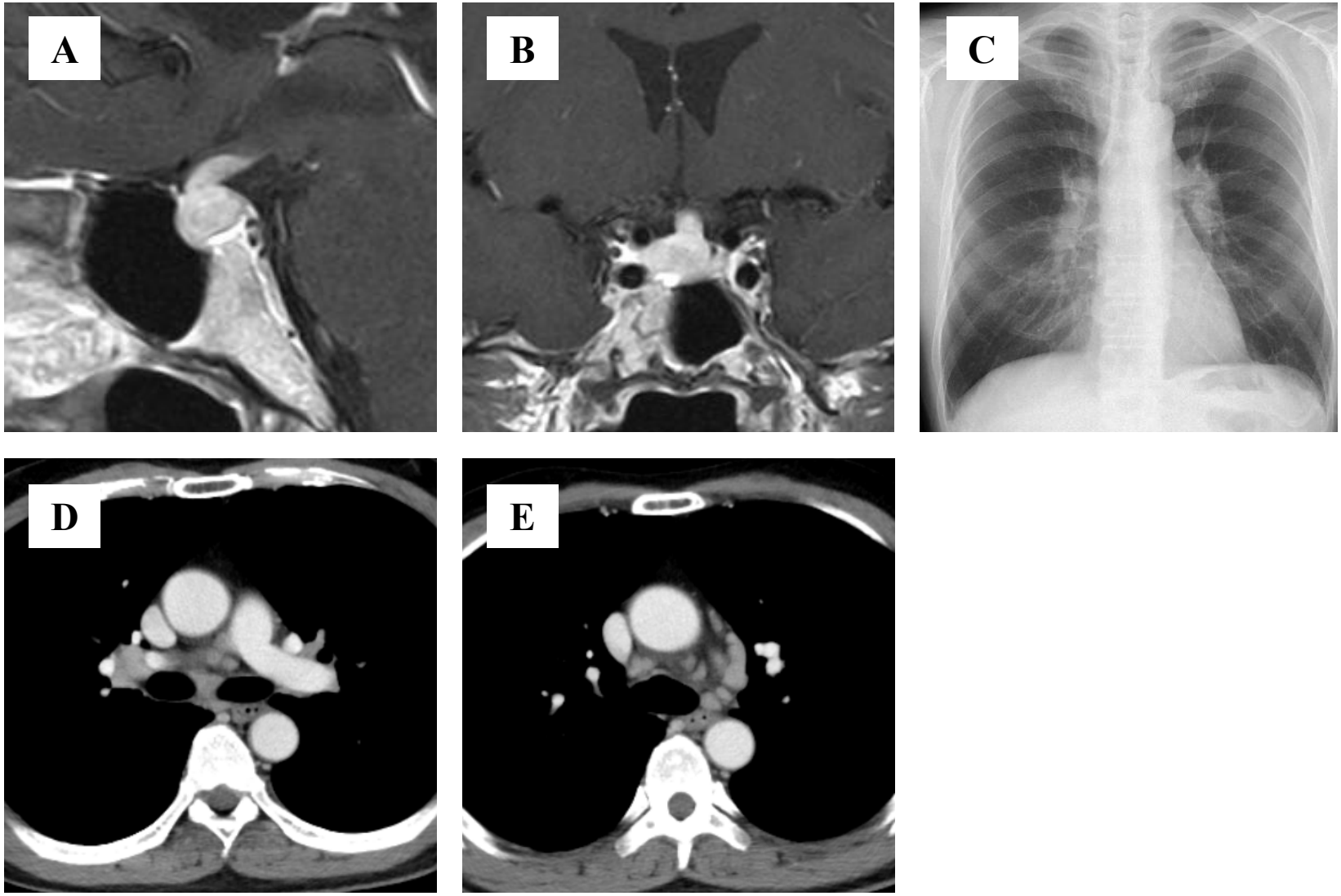


Figure. 2

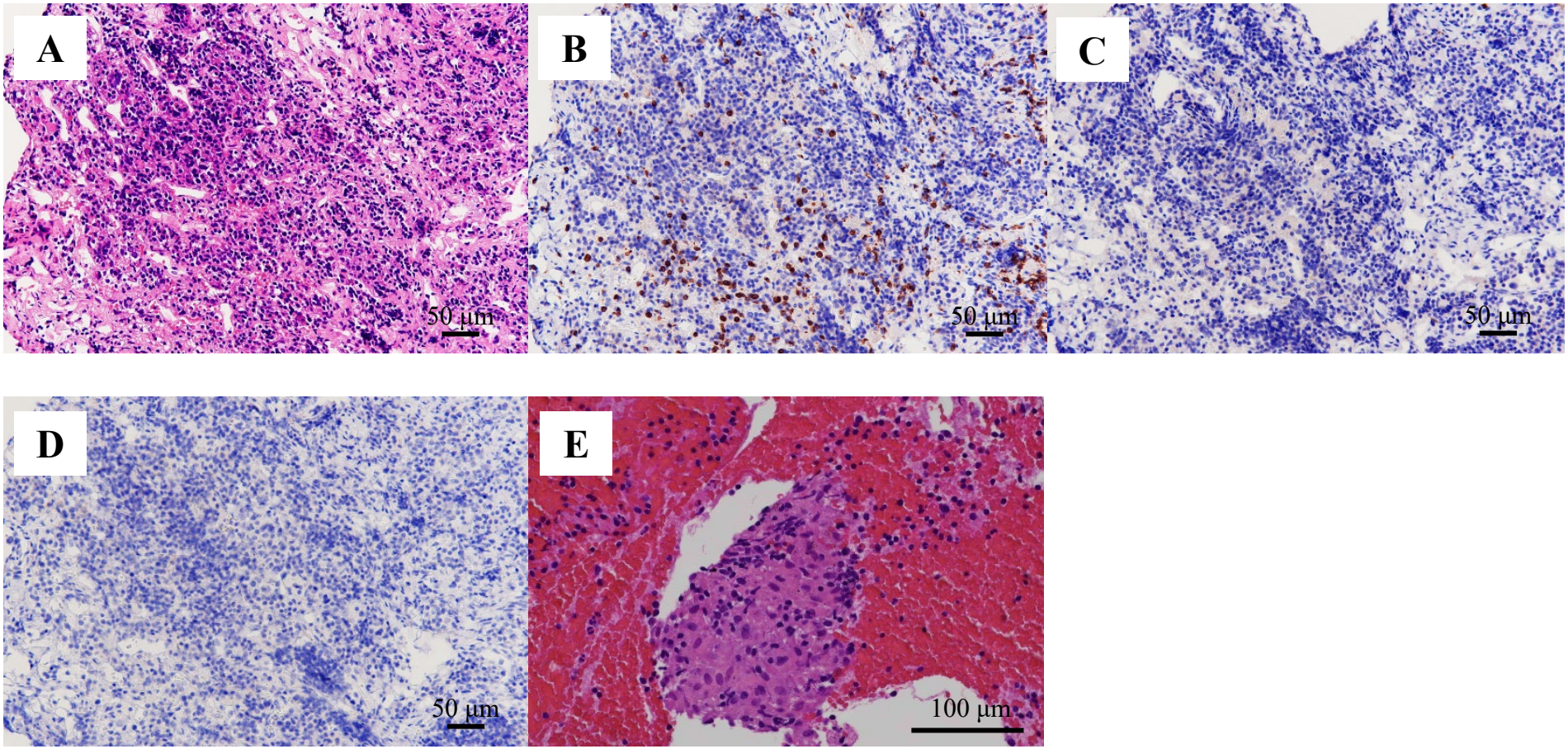
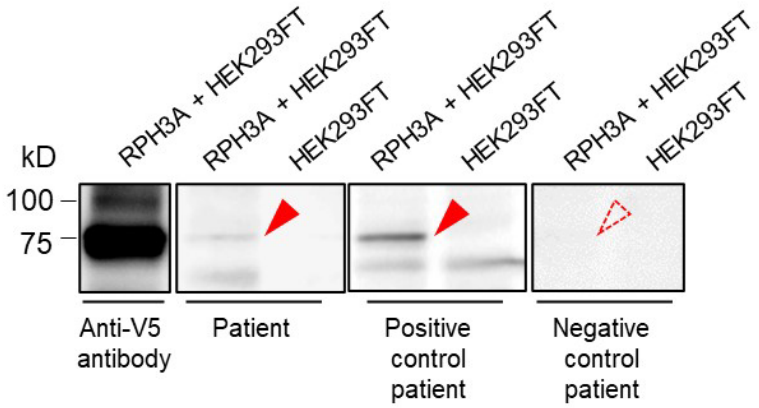


Figure. 3


RPH3A + HEK293FT
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RPH3A + HEK293FT
HEK293FT
RPH3A + HEK293FT
HEK293FT
kD
100
75
Anti-V5 antibody
Patient
Positive control patient
Negative control patient