



Title	Lymphocytic panhypophysitis and anti-rabphilin-3A antibody with pulmonary sarcoidosis
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1 **Lymphocytic panhypophysitis and anti-rabphilin-3A antibody with pulmonary**  
2 **sarcoidosis**

3

4 **Running head:** Lymphocytic panhypophysitis with sarcoidosis

5

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30

31 **Abstract**

32

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

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

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

55 case studies.

56

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

58 panhypopituitarism

59 **Introduction**

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

79

80 **Case report**

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

83 experienced transient diplopia and was diagnosed with right abducens nerve palsy. He  
84 also reported fatigue and a loss of appetite. At that time, he underwent head magnetic  
85 resonance imaging (MRI), which revealed enlargement of the pituitary stalk and gland.  
86 Hypophysitis was suspected to be the cause of the diplopia, fatigue, and loss of appetite.  
87 Physical examination was unremarkable and the patient had no family history of  
88 endocrinological disorder. No abnormal findings were made during 12-lead  
89 electrocardiography or echocardiography. In addition, there were no obvious  
90 hematological or biochemical abnormalities, but there were reductions in the serum  
91 concentrations of all the anterior pituitary hormones, which was suggestive of  
92 panhypopituitarism (Table 1). Pituitary biopsy was performed on admission with  
93 hydrocortisone drip 100 mg for the prevention of adrenal insufficiency, followed by a  
94 physiological dose of oral hydrocortisone. Because the patient's polyuria worsened after  
95 the administration of hydrocortisone, we prescribed oral desmopressin 60 µg/day.  
96 Levothyroxine was also started 7 days after the hydrocortisone administration.  
97 A growth hormone releasing peptide-2 (GHRP-2) loading test showed a poor response of  
98 growth hormone. therefore, severe adult growth hormone deficiency was diagnosed. A  
99 rapid ACTH stimulation test also revealed a poor cortisol secretory response, suggesting  
100 adrenal insufficiency. In a hypertonic saline loading test, antidiuretic hormone (ADH)  
101 was not secreted in response to an increase in serum Na, which led to a diagnosis of  
102 central diabetes insipidus. On the basis of these findings, the patient was diagnosed with  
103 panhypopituitarism.

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

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

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

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

126

## 127 **Discussion**

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



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

135 In general, a diagnosis of central nervous system sarcoidosis, including  
136 suprasellar lesions, is made on the basis of the clinical manifestations and biopsy findings,  
137 although biopsies are often obtained from tissues other than the pituitary gland, such as  
138 the hilar lymph nodes. The classical finding of sarcoidosis is noncaseating granulomas  
139 [10], which is not seen in the pathology of LH cases. In the present patient, we performed  
140 biopsies of both the pituitary gland and hilar lymph nodes, which facilitated a diagnosis  
141 of LPH.

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

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

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

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

182

### 183 **Conclusion**

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

188

### 189 **Declarations**

190 Funding: The authors did not receive support from any organization for the submitted  
191 work.

192 Conflicts of interest: The authors have no relevant financial or non-financial interests to  
193 disclose.

194 Availability of data and material: Not applicable.

195 Code availability: Not applicable.

196 Authors' contributions: Not applicable

197 Ethics approval: Not applicable

198 Consent to participate: Not applicable

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

201

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205

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263  
264

265 **Figure captions**

266

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

271

272 **Fig. 2** Histology and immunohistochemistry of biopsy specimens demonstrated mild  
273 lymphocytic infiltration of the anterior pituitary, with most of the lymphocytes being  
274 CD3-positive and few being CD20-positive. (A) Hematoxylin and eosin staining of the  
275 pituitary. Scale bar: 50  $\mu$ m. (B) CD3 immunostaining of the pituitary. Scale bar: 50  $\mu$ m.  
276 (C) CD20 immunostaining of the pituitary. Scale bar: 50  $\mu$ m. (D) IgG4 immunostaining  
277 of the pituitary. Scale bar: 50  $\mu$ m. There were no findings suggestive of IgG4-related  
278 disease. (E) Hematoxylin and eosin staining of the hilar lymph nodes. Scale bar: 100  
279  $\mu$ m.

280

281 **Fig. 3** Detection of anti-rabphilin-3A antibodies by Western blotting.

282 Recombinant full-length human rabphilin-3A expression was evaluated in HEK293FT  
283 cells transfected with the human rabphilin-3A gene (RPH3A + HEK293FT, left lanes) or  
284 with the empty vector (HEK293FT, right lanes) by probing with serum from the present  
285 patient (patient), from a patient who was diagnosed with LINH previously (positive  
286 control patient), or from a patient who was diagnosed with craniopharyngioma  
287 previously (negative control patient). The arrowhead indicates the presence of anti-  
288 rabphilin-3A antibodies. The dashed arrowhead indicates the absence of anti-rabphilin-  
289 3A antibodies. Recombinant full-length human rabphilin-3A expressed in HEK293FT  
290 cells was also probed with an anti-V5 antibody as positive control (Anti-V5 antibody) in

291 the first lane from the left.

292



**Table 1.** Laboratory findings at the admission

<CBC>				Cl	101	mEq/L	101-108 *	<Endocrinology>				<Urine testing>		
WBC	8.5×10 <sup>3</sup>	/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 <sup>6</sup>	/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 <sup>4</sup>	/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 <sup>2</sup>		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: immunoglobulin A, IgM : immunoglobulin M, IgG: immunoglobulin G, IgG 4: immunoglobulin G4, RPR: rapid plasma reaction, TPLA: toreponea pallidum antigen method, ACTH: adrenocorticotrophic 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 $\beta$ 2GP1 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

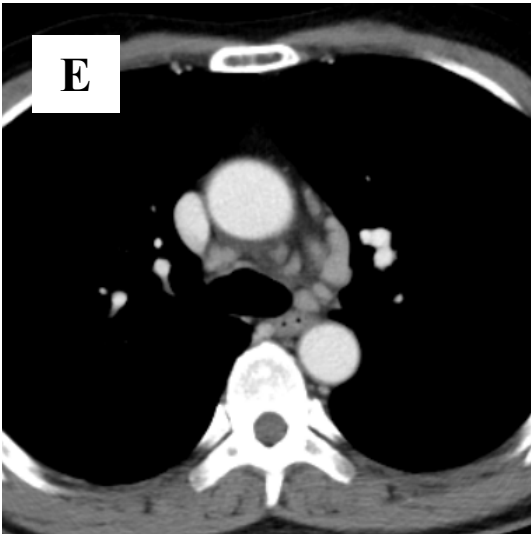
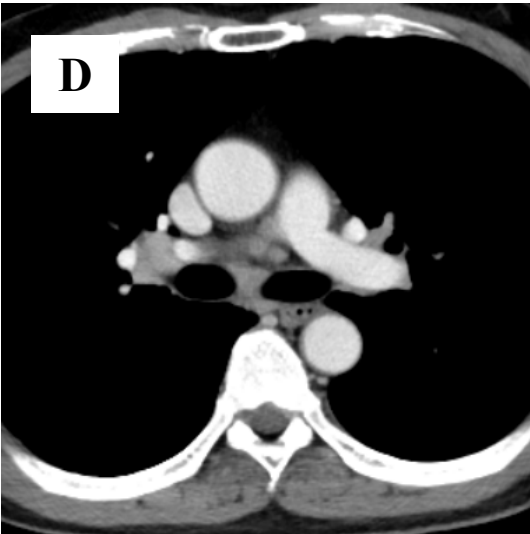
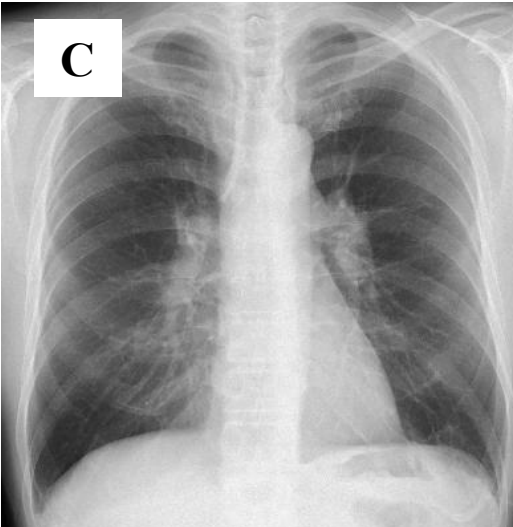
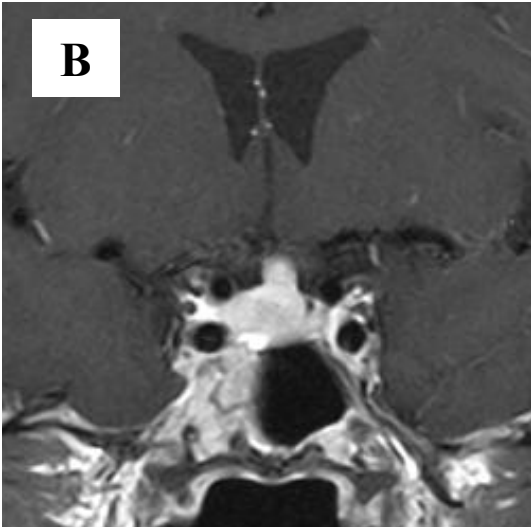
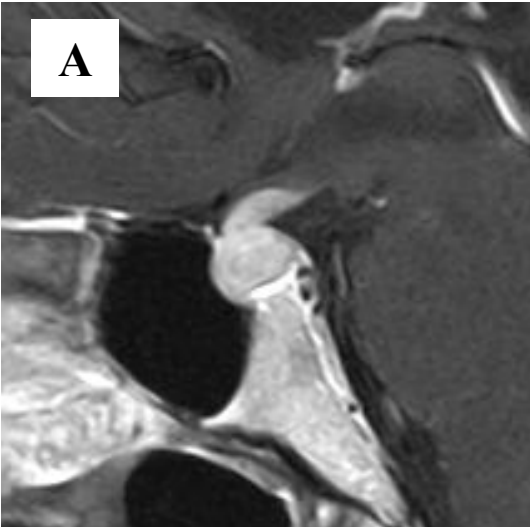


Figure. 2

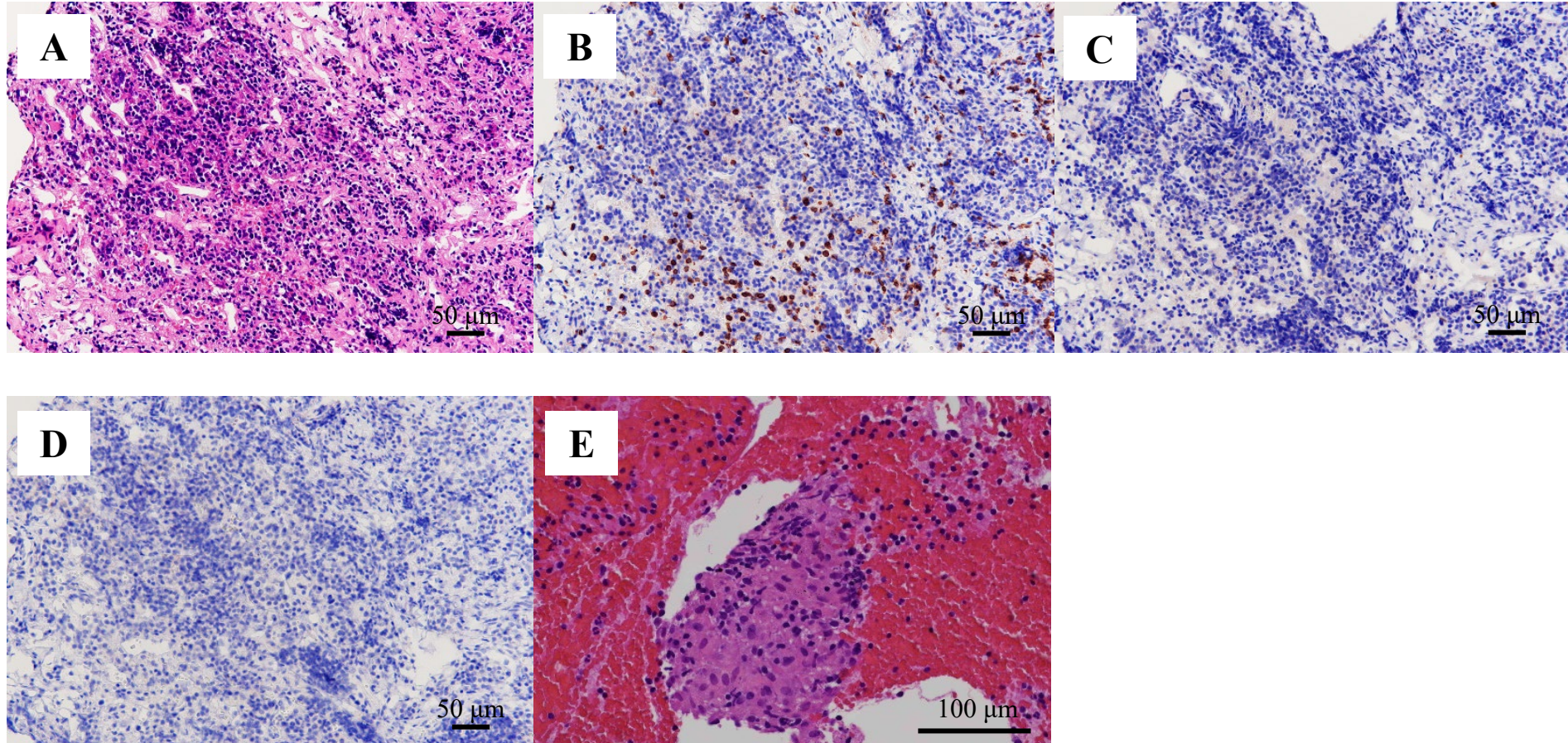


Figure. 3

