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CASE REPORT
Other

Autoimmune hypophysitis as a cause of adrenocorticotropic hormone deficiency in pulmonary arterial hypertension: a case report

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Background Severe pulmonary arterial hypertension (PAH) is generally treated with multiple PAH-specific vasodilators. If these agents are unsuccessful, additional treatment options are scarce, and the prognosis is poor due to right-sided heart failure. Some of these severe cases are also accompanied by endocrinological side effects. The most common side effect of prostacyclin is thyroid dysfunction, but in very few cases, adrenocorticotropic hormone (ACTH) deficiency may occur.

Case summary A 35-year-old woman was diagnosed with hereditary PAH 2 years ago. Since her mean pulmonary arterial pressure was high, combination therapy of vasodilators, including prostacyclin, was introduced. Several months later, she was hospitalized with a persistent fever. Laboratory tests showed no findings suggestive of infection. However, hypereosinophilia and decreased secretion of ACTH and cortisol were noted, which led to the diagnosis of ACTH deficiency. A multimodal diagnostic approach, including pituitary magnetic resonance imaging and axillary lymph node biopsy, indicated that the aetiology of the ACTH deficiency was likely autoimmune hypophysitis. She was treated with hydrocortisone supplementation, which significantly relieved her condition.

Discussion Endocrinological side effects in PAH patients using prostacyclin should be carefully addressed. If right-sided heart failure worsens during the administration of prostacyclin, it is essential to determine whether it is due to progression of pulmonary hypertension or endocrinological side effects. Careful diagnosis and treatment are important for managing the haemodynamics and symptoms of PAH patients given prostacyclin.

Keywords Bone morphogenetic protein receptor type II mutation • Pituitary lesion • Autoimmune hypophysitis • Aadrenocorticotropic hormone deficiency • Prostacyclin • Case report

Learning points

- Adrenocorticotropic hormone (ACTH) deficiency is a potential but rare side effect of prostacyclin therapy in pulmonary arterial hypertension patients.
- Diagnosis of ACTH deficiency is based on endocrinological findings, although fever and hypereosinophilia may be initial clues.
- In this case, the administration of hydrocortisone not only alleviated the symptoms of ACTH deficiency but also reduced the severity of right-sided heart overload.

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Introduction

Prostacyclin analogues, such as epoprostenol and treprostinil, are important treatment options for managing patients with pulmonary arterial hypertension (PAH).[1] However, this drug has many side effects, including headache, temporomandibular joint pain, facial flushing, diarrhoea, and thrombocytopenia. In addition, endocrine abnormalities, such as thyroid dysfunction, are known to occur.[2] A few cases of adrenocorticotropic hormone (ACTH) deficiency have also been reported.[3,4] However, its causal relationship or pathological mechanisms remain to be established.

Timeline

Age	Events
Thirty-three years old	She was diagnosed with heritable pulmonary arterial hypertension.
	Combination therapy including subcutaneous infusion of treprostinil was introduced.
Thirty-four years old	Mean pulmonary arterial pressure remained high and the World Health Organization functional class (WHO-FC) III symptoms persisted.
	Subcutaneous infusion of treprostinil was switched to intravenous epoprostenol.
Thirty-five years old before admission	She had several weeks of fever.
	Intravenous epoprostenol was switched to intravenous treprostinil, and her fever gradually disappeared.
	Several months later, she again developed a persistent fever with right-sided heart failure.
Thirty-five years old after admission	Based on various clinical investigations, she was diagnosed with adrenocorticotropic hormone deficiency.
	Hydrocortisone 15 mg/day was introduced.
	Her symptoms improved to WHO-FC II and right-sided heart overload was reduced.

Case presentation

The female patient was diagnosed with heritable PAH at 33 years old. She had a history of chronic thyroiditis, which had been treated with oral thyroid hormone replacement. Genetic testing using a method that we reported previously[5] revealed a rare genetic mutation, in which all exon regions in unilateral alleles of the bone morphogenetic protein receptor type II (*BMPR2*) gene are deleted (Supplementary material online, *Figure S1*). Whole exome analysis revealed no other mutations in genes associated with PAH. There was no notable family history of *BMPR2* gene mutation.

The patient's initial symptom was shortness of breath, and her World Health Organization functional class (WHO-FC) was IV at diagnosis. Her mean pulmonary arterial pressure at the start of treatment was markedly high (60 mmHg). Thus, combination therapy including phosphodiesterase-5 inhibitor, endothelin receptor antagonist, and subcutaneous infusion of treprostinil was introduced based on the current guidelines.[1] However, 1.5 years after the diagnosis, the mean pulmonary arterial pressure was still high (55 mmHg), and WHO-FC III symptoms persisted (*Figure 1*). Therefore, subcutaneous infusion of treprostinil was switched to intravenous epoprostenol. Two years after diagnosis, she reported several weeks of fever. Blood tests and computed tomography of the body showed no evidence of infection, although her eosinophil count was markedly elevated, suggesting a possible drug allergy with intravenous epoprostenol as the most likely cause. Therefore, it was switched to intravenous treprostinil, and her fever gradually disappeared. At 2.5 years after diagnosis, she again developed a persistent fever along with gradually worsening anorexia, depression, and general malaise. She was admitted to the hospital for further evaluation.

At admission, her blood pressure was 89/58 mmHg, heart rate 89 b.p.m., body temperature 37.9°C, respiratory rate 18/min, and percutaneous oxygen saturation 97% in room air. Physical examination showed no local signs suggesting focal infection. Jugular venous distension was obvious, suggesting exacerbation of right-sided heart failure. Levine grade II/VI pansystolic murmur and parasternal heave were identified at her left lower sternal border.

Contrast-enhanced computed tomography of the chest and abdomen showed no obvious sources of the fever. Multiple lymphadenopathy was present in her bilateral axillary, mediastinal, and inguinal lymph nodes (*Figure 2A*). Blood, urine, and sputum cultures were all negative. Blood tests showed only a mild increase in inflammatory responses, although hypereosinophilia and hyponatremia were present. Because these findings suggested adrenal insufficiency, we conducted an endocrinological evaluation.

Circadian variations in serum ACTH and cortisol concentrations showed low cortisol and low ACTH secretion throughout the day (Supplementary material online, *Table S1*). Rapid ACTH stimulation test revealed impaired adrenal gland function (Supplementary material online, *Table S2*). These results were suggestive of secondary adrenal insufficiency. Therefore, combined anterior pituitary function tests were performed (*Table 1*). The results showed secretory disturbance of the ACTH-cortisol system accompanied by mild growth hormone impairment, which was consistent with isolated or combined ACTH deficiency.

These disturbances suggested the presence of a pituitary lesion. Hence, gadolinium-enhanced magnetic resonance imaging (MRI) of the pituitary gland was performed, which showed a high-intensity cystic lesion in the anterior pituitary lobe (*Figure 2B* and *C*). Although invasive pituitary biopsy was not feasible because the patient had severe PAH, axillary lymph node biopsy was performed to evaluate for malignancy or lymphoproliferative disease. Axillary lymph node histopathology revealed a preserved but hyperplastic follicular structure pattern (*Figure 3*). Heavy infiltration of T and B lymphocytes was consistent with reactive lymphadenopathy. There was no evidence of malignancy.

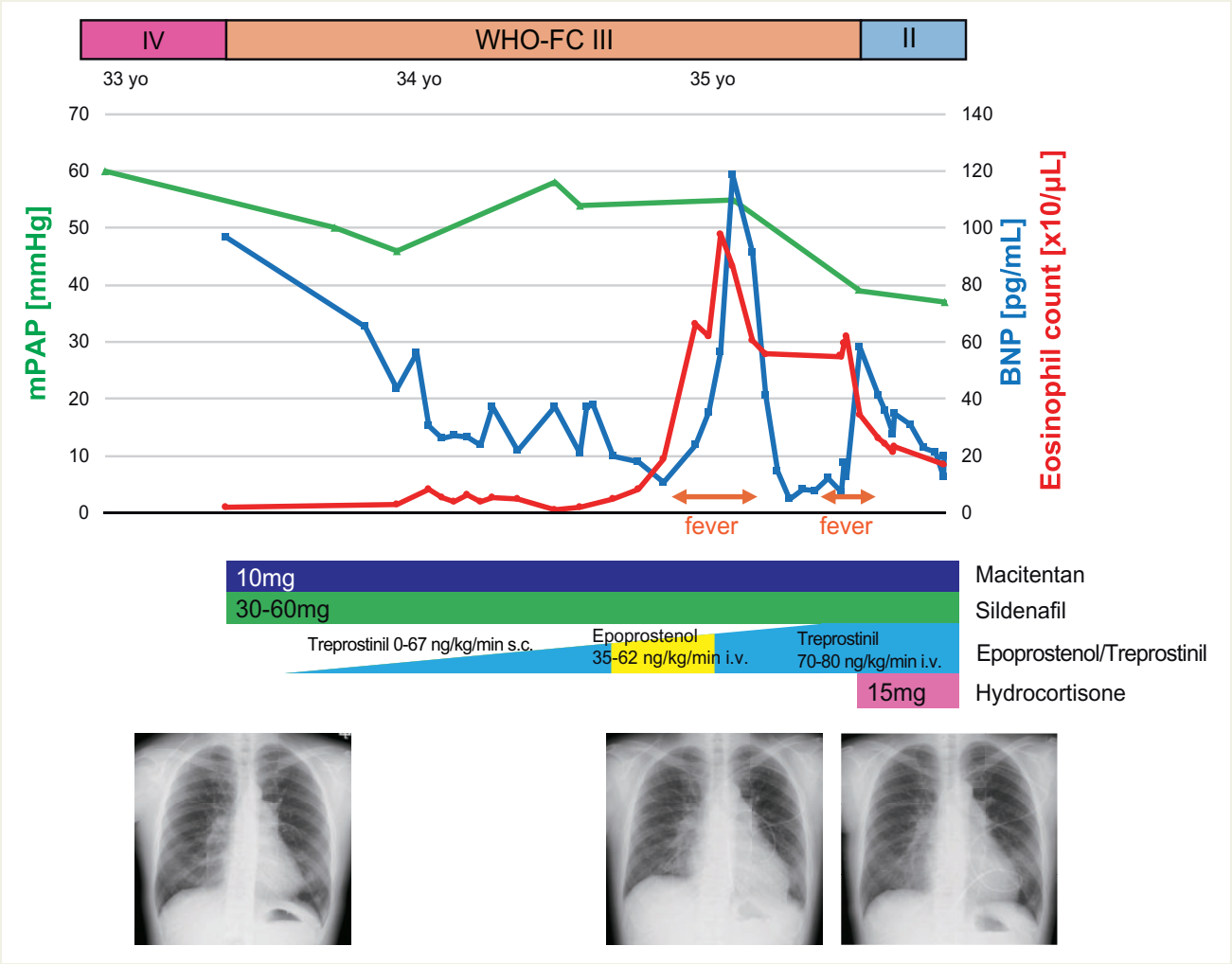

Figure 1 Clinical course. Mean pulmonary arterial pressure (mPAP), plasma brain-natriuretic peptide (BNP) concentrations, and blood eosinophil counts are shown over the time course, which includes the chest X-ray, World Health Organization functional class (WHO-FC) and drugs prescribed. i.v., intravenous injection; s.c., subcutaneous injection; WHO-FC, World Health Organization functional class; yo, years old.

We further used a diagnostic scoring system[6] to assess the type of pituitary lesion. Nine factors were assessed to classify the lesion as a pituitary adenoma or hypophysitis (Supplementary material online, *Table S3*). Her total score of -8 points indicated that her MRI findings suggested autoimmune hypophysitis instead of a non-functional pituitary adenoma with a 92% sensitivity, 99% specificity, and 97% positive predictive value. Based on these results, autoimmune hypophysitis was considered to be the most probable aetiology of ACTH deficiency.

Associations with other autoimmune diseases were evaluated. Her anti-thyroid peroxidase antibody was as high as 1482 IU/mL (normal range: 0–5 IU/mL) and anti-thyroglobulin antibody was 107 IU/mL (normal range: 0–21 IU/mL), which were consistent with autoimmune thyroiditis. No other autoimmune diseases were clinically suspected.

After an endocrinology consultation, the patient was started on hydrocortisone 15 mg/day. Her fever, anorexia, depression, and general malaise gradually disappeared. Two weeks later, right-heart catheterization showed a significant decrease in the mean pulmonary arterial pressure from 55 to 39 mmHg. Pulmonary vascular resistance also decreased from 12.8 to 4.7 Wood units, and cardiac output increased from 3.5 to 5.6 L/min. Her brain natriuretic peptide levels also decreased from 118.8 to 12.4 pg/mL, indicating alleviation of the right-sided heart failure. She was discharged since her symptoms improved to WHO-FC II (*Figure 1*). The administration of hydrocortisone was maintained while she was on prostacyclin.

Discussion

This case describes a patient with heritable PAH who developed ACTH deficiency due to autoimmune hypophysitis while receiving prostacyclin. We found only two previously reported similar cases of PAH.[3] However, this case is the first in which detailed genetic testing and pathological evaluations were performed. Generally, it is difficult to perform biopsy of pituitary lesions. Therefore, most cases do not

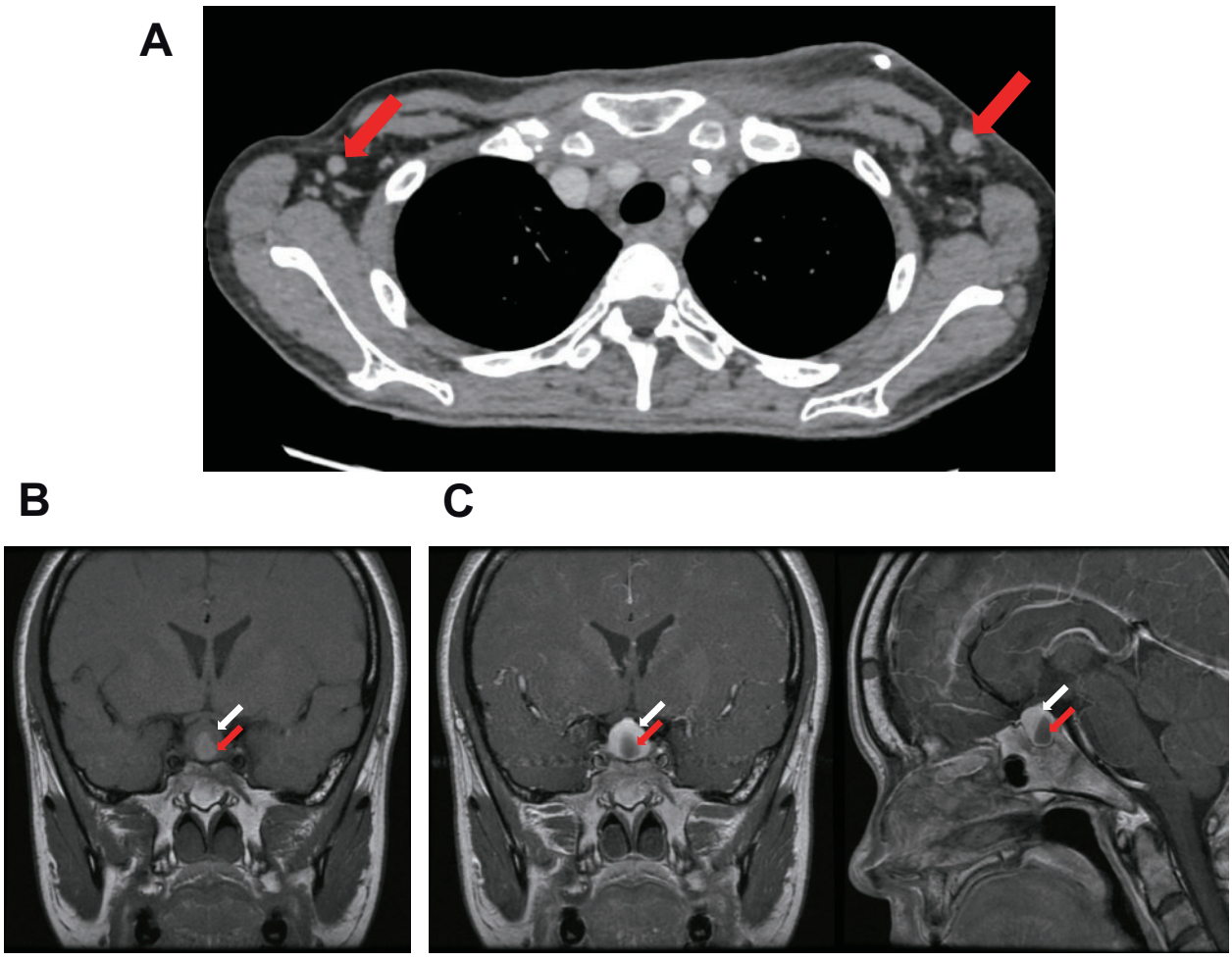

Figure 2 Imaging. (*A*) Computed tomography of bilateral axillary lymph nodes. Red arrows indicate lymphadenopathic lesions, one of which was harvested during biopsy. (*B*) Non-enhanced T1-weighted magnetic resonance imaging of the pituitary gland (coronal section). (*C*) Gadolinium-enhanced T1-weighted magnetic resonance imaging of the pituitary gland (left: coronal section; right: sagittal section). White arrows indicate the pituitary tumour, which shows a high-intensity signal on gadolinium-enhanced magnetic resonance imaging. Red arrows indicate haemorrhagic or cystic lesions inside the tumour, which are not enhanced by contrast medium. Normal pituitary tissue is compressed and almost unrecognizable.

reach a pathological diagnosis. This case was identified as autoimmune hypophysitis based on the comprehensive evaluation include axillary lymph node biopsy and pituitary MRI.

The causal relationship between the use of prostacyclin in PAH patients and the development of ACTH deficiency due to autoimmune hypophysitis is still unclear. However, in this case, fever and hypereosinophilia appeared shortly after switching from the subcutaneous treprostinil to intravenous epoprostenol and they appeared again even after switching intravenous eporpsotenol to intravenous treprostinil. Considering from the time course, we do not think that we can deny the possibility that treprostinil as well as eporpsotenol affected ACTH deficiency. In particular, prostacyclin has been experimentally reported to be involved in differentiation and proliferation of T lymphocytes,[7] suggesting that the prolonged use of high-dose prostacyclin may alter the balance of T lymphocytes *in vivo*, thereby causing systemic inflammation and increasing the risk of autoimmune hypophysitis. The pre-existing chronic thyroiditis might also be associated with the development of autoimmune hypophysitis, and their common immunological pathology may be a predisposing factor.

In the present case, ACTH deficiency not only presented with symptoms of adrenal insufficiency but also exacerbated right-sided heart failure. Hydrocortisone supplementation might reverse this exacerbating factor, thereby improving the right-sided heart failure. Clinically, persistent fever and hypereosinophilia during intractable right-sided heart failure may be clues for diagnosing ACTH deficiency. Although the most important cause of worsening right-sided heart failure in PAH patients is the progressive severity of PAH itself, the use of prostacyclin may exacerbate heart failure due to endocrinological side effects. Careful diagnosis and treatment are important for managing the haemodynamics and symptoms in these patients.

Table I Combined anterior pituitary function tests

Parameters	Basal	30 min	60 min	90 min	Function	Impaired function criteria
ACTH (pg/ml)	3.3	13.5	9.3	6.8	Impaired	Peak value <30, or 2.0 × basal value
Cortisol (μg/dL)	0.8	4.1	4.8	3.6	Impaired	Peak value <15, or 1.5 × basal value
TSH (μU/mL)	8.04	24.36	35.8	37.2	Preserved	Peak value <6
PRL (ng/mL)	17.2	44.6	49.0	43.4	Preserved	Peak value <2 × basal value
LH (mIU/mL)	0.3	3.1	4.4	4.3	Preserved	Peak value <5 × basal value
FSH (mIU/mL)	2.5	5.2	7.6	8.6	Preserved	Peak value <1.5 × basal value
Parameters	**Basal**	**15 min**	**30 min**	**45 min**	**Function**	**Impaired function criteria**
GH (ng/mL)	2.8	7.2	7.3	5.8	Impaired	Peak value <9

Corticotropin-releasing hormone (100 μg), thyrotropin-releasing hormone (0.5 mg), and luteinizing hormone-releasing hormone (0.1 mg) were injected to assess ACTH, cortisol, thyroid-stimulating hormone, prolactin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone. Similarly, growth hormone-releasing hormone (100 μg) was injected to assess growth hormone.
ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin-releasing hormone; TSH, thyroid-stimulating hormone.

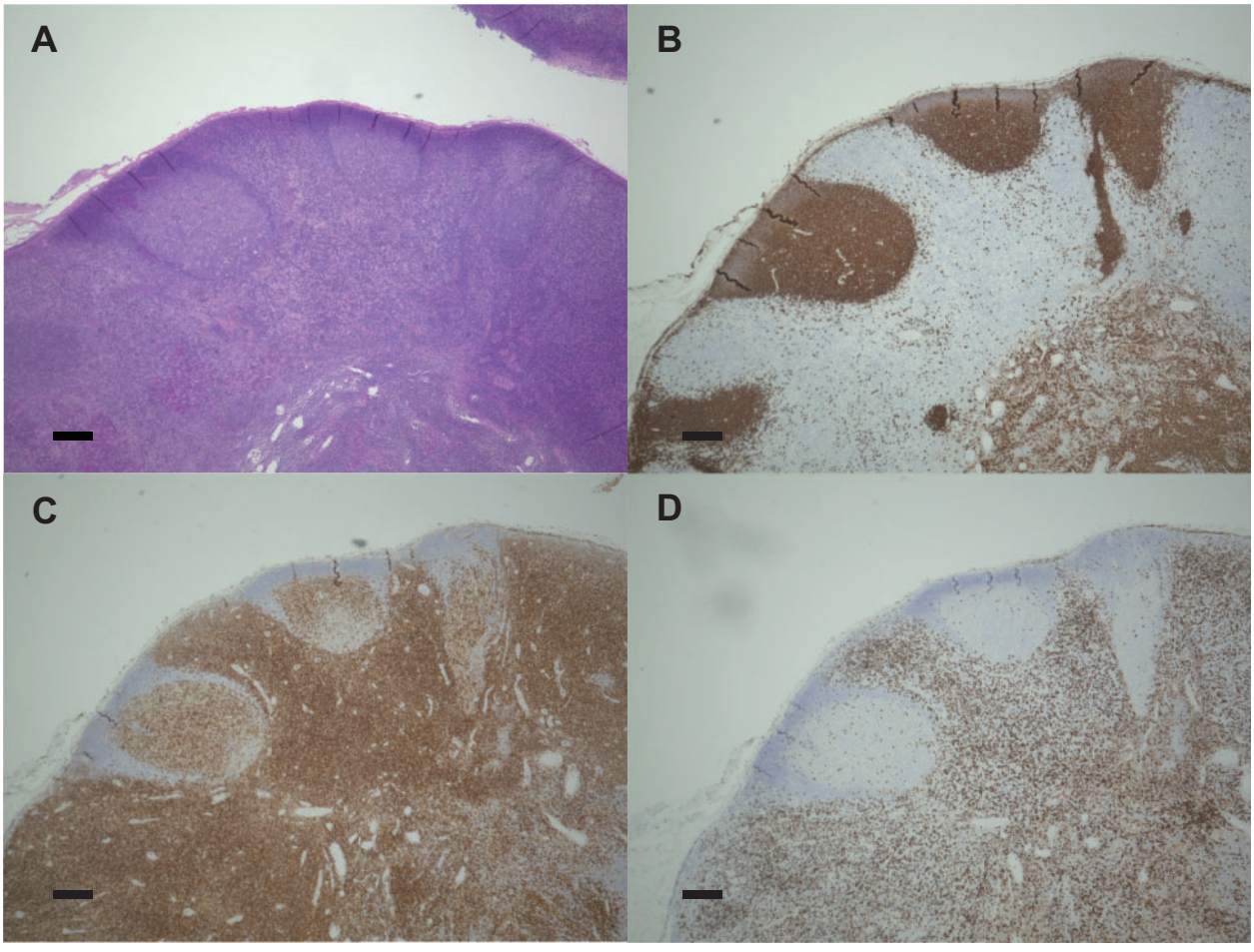

Figure 3 Histopathology of axillary lymph nodes. (*A*) Haematoxylin and eosin stain. (*B*, *C*, *D*) Immunohistochemistry staining for the B-cell marker CD20 (*B*), T-cell marker CD4 (*C*), and T-cell marker CD8 (*D*). Scale bars: 100 μm.

Lead author biography

Genki Ichihara is a cardiologist at Keio University School of Medicine. After graduating from the University of Yamanashi, Faculty of Medicine, he trained at Saiseikai Utsunomiya Hospital and is currently conducting basic research on myocardial metabolism and imaging at Keio University.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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