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Disseminated *Verruconis gallopava* infection in a patient with systemic lupus erythematosus in Japan: A case report, literature review, and autopsy case

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ABSTRACT

Disseminated *Verruconis gallopava* infection is often reported in patients with severe immunodeficiency, such as those who have received an organ transplant or have hematological malignancies. The present report describes the first case of disseminated *V. gallopava* in a patient with systemic lupus erythematosus who used FK506 (Tacrolimus). In this case, β-D glucan was useful for diagnosis.

1. Introduction

Black fungi are ubiquitous in the environment, but are rarely pathogenic to humans, except in immunocompromised hosts. *Verruconis gallopava* (previously *Ochroconis gallopava*) was initially observed to cause central nervous system disease in poultry [1]. However *V. gallopava* infection has been increasing since the first human case was reported in 1986 [2]. There have been cases in immunocompromised patients, such as those who have received organ transplants [3,4], as well as those with hematological malignancies [5,6], HIV infection [7], or chronic granulomatous disease [8]. There have also been cases in high exposure workers, such as gardeners and wood pulp workers, even when they were immunocompetent, because *V. gallopava* is acquired by inhalation of environmental fungal spores [9] or direct invasion through skin wounds [2]. In the present report, we describe the first case of disseminated *V. gallopava* infection in a patient with systemic lupus erythematosus (SLE) treated using FK506. We saw significantly elevated serum levels of β-D glucan and suggest this is may be a clinically useful markers of disseminated *V. gallopava*.

2. Case

A 77 year-old Japanese man was admitted to our hospital due to edema in both lower legs and pain in the right inguinal region that had lasted 1 month. The patient was being followed up with diuretics. He was a retired sheet metal worker and was currently employed in weed control and garden maintenance. When he was admitted, his pain had worsened and it had become difficult for him to walk. He suffered from Sjögren syndrome that had started 11 years prior, SLE that had begun 3 years prior, interstitial pneumonia that had manifested 5 years prior, and latent tuberculosis that had arisen 4 months prior. He also had a history of nocardia pneumonia (3 years prior). He was taking tacrolimus (1 mg/day), prednisolone (20 mg/day), and sulfamethoxazole trimethoprim (sulfamethoxazole 400 mg and trimethoprim 80 mg/day) at the time of admission. Four months prior, surgical drainage had been performed on a right forearm abscess; the drainage solution was macroscopically milky white and no organisms were cultured using conventional bacterial culture agars.

The patient's blood pressure was 142/86 mmHg, with a respiratory rate of 18/min and an O_2 saturation of 99%, as measured using a 2L nasal cannula. A bulky hard mass with tenderness was palpable in the right inguinal region, and there was painful redness of the skin from the right popliteal fossa to the lower leg. The man's right hip joint had limited range of motion, but was neurologically normal. Blood tests at admission showed a white blood cell count of 10750/μL (lymphocyte percentage: 0%), hemoglobin of 12.4 g/dL, and platelets of 161,000/μL. C-reactive protein and β-D glucan were significantly elevated to 8.2 mg/dL and 7719 pg/mL, respectively. Chest X-ray only showed shadows that were likely due to interstitial pneumoniae. Computed tomography (CT) revealed a single nodule in his right lung (Fig. 1), as well as a huge low density area in the right iliopsoas muscle (Fig. 2).

Antibiotic treatment (tazobactam/piperacillin + teicoplanin) was

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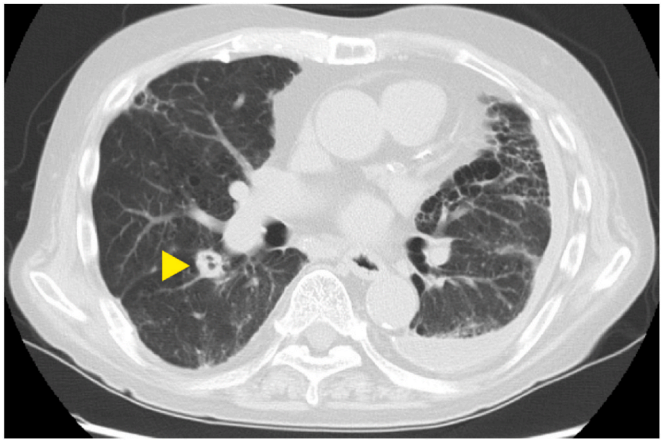


Fig. 1. Computed tomography (CT) revealed a single nodule in his right lung (▶). Since it was a cavity lesion, we considered the possibility of fungal infection.

administered empirically on day 0 after admission. The culture from direct puncture was submitted for identification on day 2. CT-guided drainage was performed on day 4 because the abscess cavity was too large to treat without drainage. Voriconazole treatment was started on day 4 because the culture from direct puncture showed mold growth. (Fig. 3). The regimen for voriconazole was started with a loading dose of 360 mg once, and 200 mg was administered every 12 hours. We confirmed that the trough concentration of voriconazole on day 10 was sufficient (6.83 μg/mL), adjusted the amount, and switched to oral administration of 150 mg twice daily. Afterwards, the trough concentration was confirmed (day 66: 3.34 μg/mL, day 73: 2.57 μg/mL, respectively). Despite CT-guided drainage and voriconazole administration, CT showed a bigger size in the right iliopsoas abscess 14 days after the start of antifungal treatment. The culture was identified as *V. gallopava* on day 15. We performed additional molecular analysis of the ribosomal internal transcribed spacer (ITS) and ribosomal large-subunit D1/D2 regions by amplifying sequences of 503 bp and 519 bp, respectively. According to the MYCOBANK database (https://www.mycobank.org/page/Pairwise_alignment), the ITS sequence of the isolate was 99.21% identical to *V. gallopava* (accession number: LM644526), and the sequence of D1/D2 region was 99.62% identical to *V. gallopava* (accession number: AB125280) on day 21. Thus, we concluded that the isolate was *V. gallopava* and also found drug susceptibility test results (Table 1). After identifying the causative organism in this way, we performed contrast-enhanced MRI to search for brain abscesses on day 17, because *V. gallopava* is known to be neurotropic. Diffusion-weighted imaging high and apparent diffusion coefficient low areas were found in the left caudate nucleus. We interpreted this abnormal signal as either an acute stroke or a brain abscess. The patient continued to take antifungals and antibiotics, resulting in a gradual decline in β-D glucan. (day 10: 7092 pg/mL, day 18: 3180 pg/mL, day 51: 2405 pg/mL and day 71: 499 pg/mL, respectively). Paroxysmal atrial fibrillation was discovered during hospitalization, but anticoagulants were not used because there was bleeding from the drain site. On day 72, the man suffered a sudden decrease in consciousness level, and a simple CT scan of his head revealed extensive low absorption in the left middle cerebral artery region. He died on day 73 due to this event.

After death, a pathological autopsy was performed, with the consent of the bereaved family. Abscesses were found on both iliopsoas muscles, the left caudate nucleus, the lungs, and the kidneys. The same shaped fungi were detected at all sites.

3. Discussion

V. gallopava was once called *Ochroconis gallopava*, but it was renamed because of its heat resistance. It was once thought to cause fatal encephalitis in poultry only. However, since 1986, reports of human infection have increased [1]. We searched the literature and found 13 disseminated *V. gallopava* infection cases in humans. The age, background disease, and prognosis of these disseminated human cases are shown in Table 2.

In our patient, *V. gallopava* infection developed with pain in the groin. Although *V. gallopava* reportedly enters from the respiratory tract, previous cases of soft tissue lesions suggest that the skin is an entry site for pathogens [6]. In this case, the patent was a gardener with a high risk of exposure. The first symptoms appeared in the inguinal region; therefore, soft tissue infection was considered the reason for infection onset. Our patient showed disseminated infection and was immunodeficient because he used FK506 and steroids to treat SLE. The

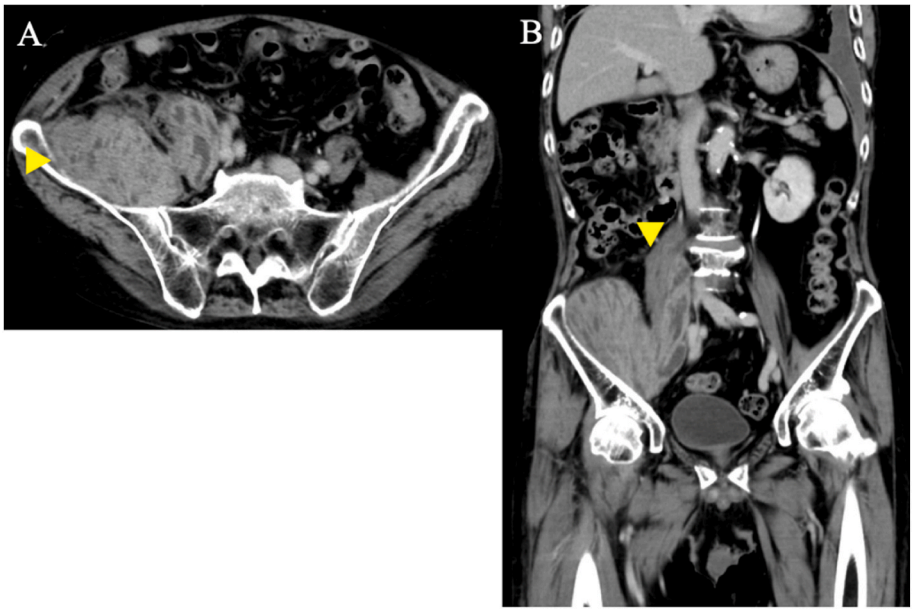
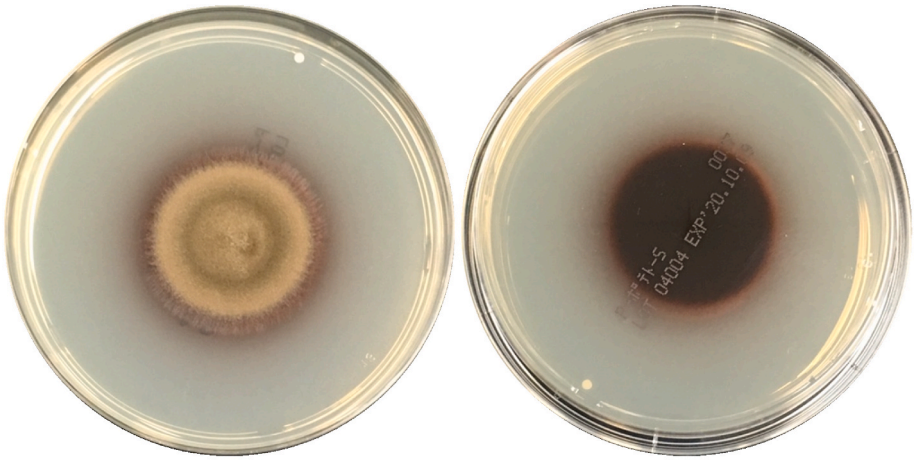
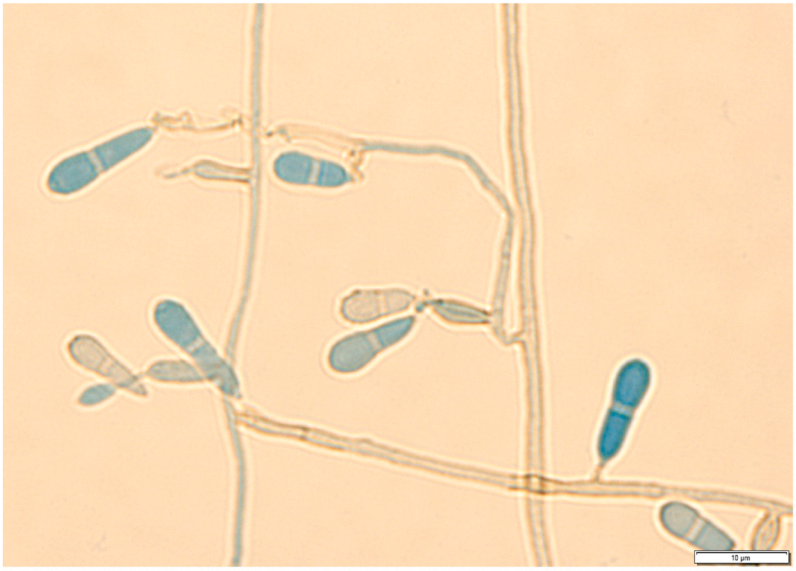


Fig. 2. This figure is CT images of the inguinal lesion. A: Axial section of CT. B: Coronal section of CT. A huge low density area with contrast effect was observed on the wall in the right iliopsoas muscle(▶).



a.



b.

Fig. 3. a. (left) Large colony (light olive green) grown on PDA (potato dextrose agar) at 28 °C on day 10 from a specimen obtained by a direct puncture. (right) The colony underside shows a reddish pigment. It has a two-celled cylindrical conidium at the tip. The shape of conidia is constricted at the septum. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Results of drug susceptibility tests for *V. gallopava*.

Drug	MIC(μg/mL)
MCFG	0.03
CPFG	0.5
5-FC	64
FLCZ	>64
MCZ	4
ITCZ	0.25
VRCZ	1
AMPH-B	0.25

dissemination had spread to the brain, kidneys, lungs, and both iliopsoas muscles at autopsy. Qureshi et al. [3] reported that *V. gallopava* infection can take hold in cases of severe immunodeficiency, such as after bone marrow or organ transplantation. However, in the present case, FK506 was used to treat SLE in a non-transplant patient; we suggest that this treatment may be a risk factor for *V. gallopava* infection. In a mini review featuring five cases of hematological malignancy combined with *V. gallopava* infection, all patients had abnormalities in the T cell lineage, and many patients with chronic lymphocytic leukemia were treated with purine analogs, which can lead to persistent T cell lymphocytopenia and result in immunodeficiency similar to that after organ transplantation [6]. Moreover, T cell immunosuppressive drugs are often used to prevent graft-versus-host disease after transplant. Infection with *V. gallopava* is more common in patients with HIV, pemphigus treated using 300 mg/day cyclosporine A [10], or T cell immunodeficiency. It follows that abnormalities in the T cell system mainly lead to immunodeficiency.

The present case involved *V. gallopava* infection in a patient with SLE who was being treated using FK506. His first symptom was right groin pain. A definitive diagnosis of right iliopsoas abscess was reached. The culprit organism was then identified from a culture of the puncture fluid. A blood test at the time of admission showed a marked decrease in cell-mediated immunity, with a lymphocyte percentage of 0%, suggesting that the patient's immunodeficiency contributed to the infection.

The usefulness of β-D glucan in *V. gallopava* has not been clarified. A retrospective check of case reports revealed that few studies have considered β-D glucan [6,19]. The present case was a disseminated infection, and the structural characteristics of the fungal cell wall suggested that increased β-D glucan is a useful marker of disseminated *V. gallopava* mycosis.

Table 2
Summary of previously reported *V. gallopava* infections in humans.

Reference	Year	Age	Sex	Risk	Sites of involvement	Treatment	Outcome
[5]	1990	62	M	ATL	Lung, Liver, Kidney, Brain, Spleen	No data	Died
[6]	2005	66	F	CLL	Brain, Lungs, Femoral Mass	AMPH-B + 5-FC, ITCZ	Died (4 months)
[11]	1995	63	M	Liver Transplantation	Brain, Lungs	No data	Died
[12]	2001	32	F	Lung Transplantation	Shoulder joint abscess, Brain	Surgery + AMPH-B, 5-FC, ITCZ	Survived
[13]	2003	13	M	Renal Transplantation	Brain, Lung, Spleen	ITCZ + AMPH-B → VRCZ	Died
[7]	2006	28	M	HIV	Lungs, Brain, Joint	VRCZ + Caspofungin	Died (17 days)
[4]	2010	58	M	Heart Transplantation	CAPD fluid, Peritoneum	VRCZ	Survived
[3]	2012	53	M	Renal Transplantation	Lungs, Transverse process, Subdural empyema	ITCZ + AMPH-B	Survived
[14]	2013	55	M	Heart Transplantation, DM	Lungs, Subcutaneous, Brain, Peritoneum	L-AMB + VRCZ	Died (2 months)
[15]	2015	55	M	Immunocompetent	Cutaneous	Terbinafine + AMPH-B	Follow interuption
[16]	2016	67	F	Renal Transplantation	Brain, Vegetation of the Heart valve, Lungs	L-AMB + VRCZ	Died (55 days)
[17]	2018	65	F	Lung Transplantation	Endophthalmitis, Respiratory tract infection	No data	Survived
[18]	2019	84	F	Myelofibrosis	Brain, Lungs, Subcutaneous	No data	No data

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Declaration of competing interest

There are no conflicts of interests.

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