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**Pulmonary *Cladosporium* infection coexisting with subcutaneous *Corynespora cassiicola* infection in a patient: A case report**

WangWY *et al*. *Cladosporium* and *Corynespora cassiicola* infection

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**Abstract**

BACKGROUND

*Cladosporium* and *Corynespora cassiicola* (*C. cassiicola*) infections rarely occur in humans. Mutations in human caspase recruitment domain protein 9 (CARD9) are reported to be associated with fungal diseases. Pulmonary *Cladosporium* infection coexisting with subcutaneous *C. cassiicola* infection in a patient with a CARD9 mutation has not been reported in the literature.

CASE SUMMARY

A 68-year-old male patient was hospitalized for hypertrophic erythema and deep ulcers on the left upper extremity. He was diagnosed with pneumonia caused by *Cladosporium*, as identified through bronchoalveolar lavage fluid analysis, and deep dermatophytosis caused by *C. cassiicola*, as identified through morphological characteristics of the wound secretion culture. He underwent antifungal therapy (voriconazole) and recovered successfully. He carried two mutations in CARD9 (chr9:139266425 and chr9:139262240) and was therefore susceptible to fungal infections.

CONCLUSION

This case study is the first to report the coexistence of pulmonary *Cladosporium* infection and subcutaneous *C. cassiicola* infection in a patient with CARD9 mutation. Our findings will be helpful in enriching the phenotypic spectrum of fungal infections underlying CARD9 deficiency.

**Key Words:** *Cladosporium*; *Corynespora cassiicola*; Caspase recruitment domain protein 9; Lung lesion; Dermatosis; Case report

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**Core Tip:** The genus *Cladosporium* and *Corynespora cassiicola* (*C. cassiicola*) rarely cause human infections. Patient with caspase recruitment domain protein 9 (CARD9) mutation is reported to be more susceptible to fungal infections. Our case study is the first to report the coexistence of pulmonary *Cladosporium* infection and subcutaneous *C. cassiicola* infection in a patient with CARD9 mutation. Multiple fungal infections in patients with CARD9 mutation are worth clinicians’ attention.

**INTRODUCTION**

*Cladosporium* and *Corynespora cassiicola* (*C. cassiicola*), which are common plant pathogens existing in both indoor and outdoor environments, rarely cause illness in humans[1,2]. Pulmonary *Cladosporium* infection and subcutaneous *C. cassiicola* infection have been separately documented in the literature[3,4]. Thus far, however, there have been no reports on the coexistence of pulmonary *Cladosporium* infection and subcutaneous *C. cassiicola* infection in humans. Mutations in human caspase recruitment domain protein 9 (CARD9) lead to an autosomal recessive primary immunodeficiency disorder, resulting in the development of a wide spectrum of fungal infections[5].Herein, we present a case of pulmonary *Cladosporium* coexisting with subcutaneous *C. cassiicola* infection with CARD9 deficiency in a patient who was successfully treated with voriconazole.

**CASE PRESENTATION**

***Chief complaints***

A 68-year-old male farmer who was a non-smoker was admitted to the hospital for hypertrophic erythema and deep ulcers on the left upper extremity (Figure 1A) on 18 July 2019.

***History of present illness***

The patient had a six-month history of red, itchy rash on the left upper extremity.

***History of past illness***

The patient had a ten-year history of hypertension and a six-month history of sleep disorder.

***Personal and family history***

The patient had no remarkable personal or family history.

***Physical examination***

Initial medical examination showed a heart rate of 77 beats/min, respiratory rate of 18 breaths/min, body temperature of 36.8 °C, and blood pressure of 137/94 mmHg.

***Laboratory examinations***

Routine blood test results were normal (white blood cell count in serum of 5.1 × 109/L, absolute neutrophil count of 3.4 × 109/L, C-reactive protein of 1 mg/L). Serum cryptococcal antigen, antineutrophil cytoplasmic antibodies, antinuclear antibodies, human immunodeficiency virus antibody tests, HIV antibodies, and syphilis antibody tests were negative. The serum IgE level of *Aspergillus fumigatus* was low (0.1 KU/L). A skin biopsy was performed 4 d after hospital admission, which showed partial squamous hyperplasia with a dermal granulomatous lesion (Figure 1E). *C. cassiicola* was identified according to the morphological characteristics of the wound secretion culture (Figure 1C). The patient underwent bronchoscopy 6 d after admission, with a positive result for the bronchoalveolar lavage fluid (BALF) galactomannan test (with a value of 2.16), and BALF culture revealed the presence of *Cladosporium* (Figure 1D)*.* Two mutations in CARD9 were detected by ChIP-seq using high-throughput sequencing (detection region: exon region of approximately 20000 genes in the human genome; detection strategy: the explicit disease-causing genes included in OMIM database “2018.11” were analyzed) in the present case: (1) chromosomal location: chr9:139266425; nucleotide change: c.106C>T; and (2) chromosomal location: chr9:139262240; nucleotide change: c.1118G>C.

***Imaging examinations***

Chest computed tomography revealed the presence of multiple nodules with multiple patchy areas in both lungs (Figure 2).

**FINAL DIAGNOSIS**

We made a final diagnosis of pneumonia caused by *Cladosporium* as well as deep dermatophytosis caused by *C. cassiicola*.

**TREATMENT**

Piperacillin-tazobactam 3.375 g intravenous drip was administered every 8 h for 7 d, and then antifungal therapy (voriconazole: 200 mg twice daily for 3 mo) was initiated. The ulcer on the left upper extremity healed completely after one month of treatment (Figure 1B).

**OUTCOME AND FOLLOW-UP**

Follow-up imaging after 3 mo revealed very good resolution of the lesions in the lung (Figure 2). The lung lesions continued to shrink for 5 mo after antifungal therapy was discontinued (Figure 2).

**DISCUSSION**

Our case involved coexistence of pulmonary *Cladosporium* infection and subcutaneous *C. cassiicola* infection in a patient with CARD9 mutation.

The genus *Cladosporium* has been reported to cause several different types of opportunistic infections, including subcutaneous and deep infections, in humans and animals[1]. *Cladosporium* spores, which potentially lead to the development of respiratory allergy problems such as asthma, rarely cause pulmonary infection[6]. *Cladosporium* can affect the lungs, bronchi, and pulmonary artery branches, as revealed by our literature review[3,7-10]. *Cladosporium* spores can reach the lungs by inhalation[11]. The patient in the present case was a farmer; therefore, it is highly likely he was infected by *Cladosporium* via inhalation.

*C. cassiicola*, a member of *Pleosporales*, is a common plant pathogen[12]. Subcutaneous *C. cassiicola* infection in humans is extremely rare, and only six cases have been reported thus far[4,13-16]. In these cases, erythaematous change, ulcer, plaque, nodule, and erosion were clinical symptoms of all cases, and the face or extremities were the infection sites. Antifungal therapy has resulted in successful treatment outcomes in most cases, though two patients with CARD9 mutations did not respond well[4,13-16].

As a member of the CARD protein family, CARD9 plays an important role in the activation of antifungal mechanisms[17]. It is a key adaptor that can mediate Dectin-1-, Dectin-2-, and Mincle-induced activation of transcription factors through formation of the CARD9–B cell lymphoma/leukaemia-10–mucosa-associated lymphoid tissue lymphoma translocation protein 1 complex in response to fungal infection[5]. These activated transcription factors mediate translation of key cytokines such as nuclear factor κB, which promotes T-helper cell (Th)1/Th17 differentiation, stimulating antifungal mechanisms in innate cells[18]. CARD9 mutation is a rare inborn error of immunity and probably leads to impaired protection against fungal infections[19]. However, detailed and comprehensive reports on CARD9 deficiency susceptibility to fungal infection, clinical characteristics, diagnostic methods, and prognosis are still lacking. Human CARD9 deficiency is reported to be responsible for the spontaneous development of persistent and severe fungal infections (such as infections caused by *Candida albicans, Candida dubliniensis*, *Phialophora verrucosa*, *Trichophyton violaceum*, *Candida sp.*, *Trichophyton mentagrophytes*, *Exophiala sp.*, *Trichophyton rubrum*, and *Corynespora cassiicola*)[17, 20]. Conversely, *Cladosporium* infection has not been reported.

The appropriate antifungal therapy for CARD9 deficiency is mostly empirical. Antifungal agents itraconazole and voriconazole have been used for the treatment of pulmonary *Cladosporium* infection, whereas amphotericin B, voriconazole, posaconazole, liposomes, and itraconazole have been used to treat subcutaneous *Corynespora cassiicola* infection[13-16].Voriconazole had a very good therapeutic effect in our case. However, there is still no definitive conclusion on the antifungal treatment of these two diseases, including suitable medicine, reasonable dose, and course, which warrants further research.

**CONCLUSION**

A good prognosis for fungal infection is associated with prompt identification and proper treatment. Given the findings of our case and the results of our literature review, multiple fungal infections in patients with CARD9 mutations are worthy of clinicians’ attention. Further study into the clinical characteristics and pathogenesis of CARD9 deficiency will yield new insight into therapeutic measures for protecting humans from these devastating fungal diseases.

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**Footnotes**

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**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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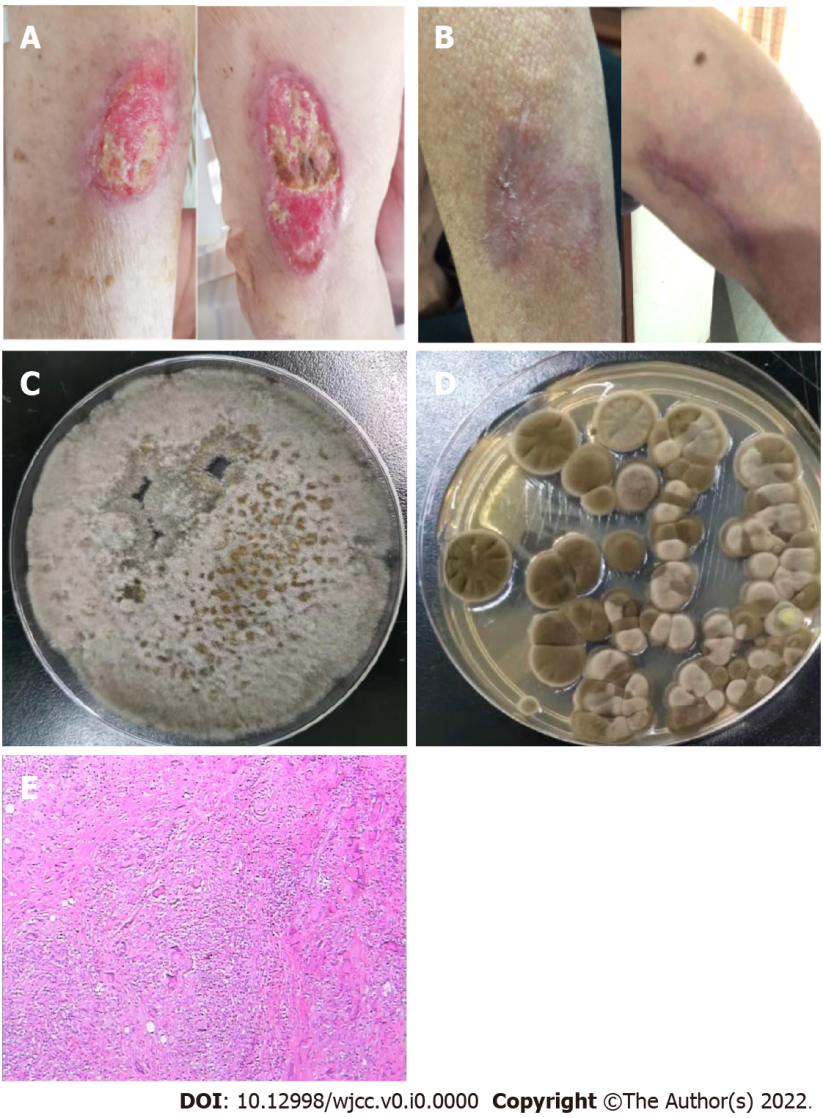
Grade C (Good): C

Grade D (Fair): 0

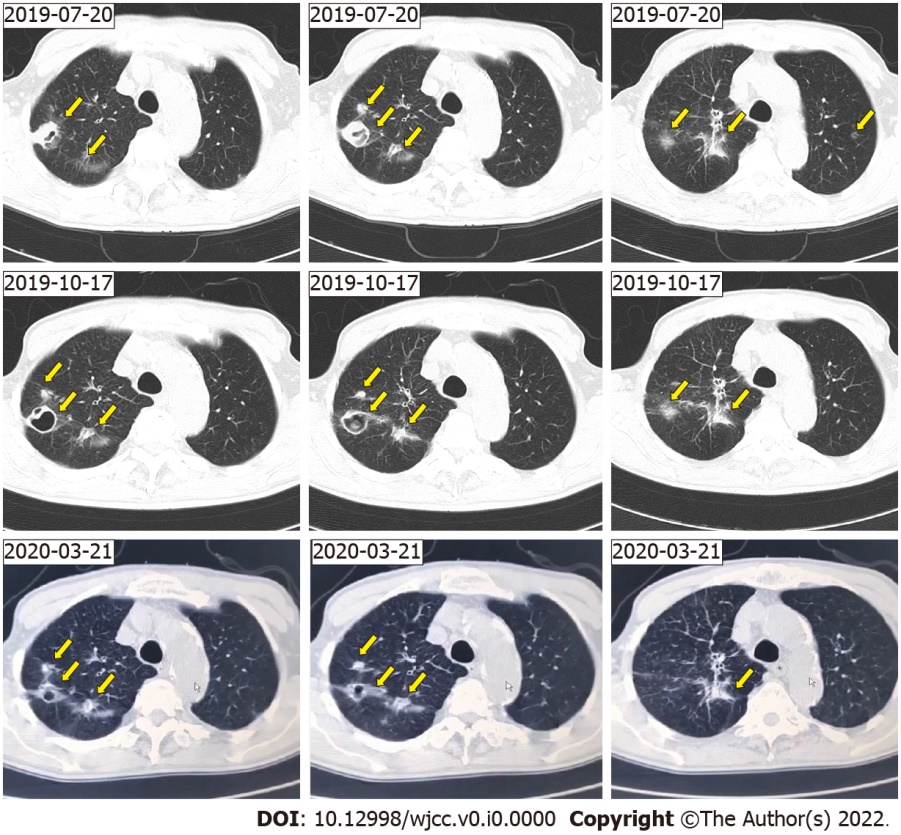
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**Figure Legends**

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**Figure 1 Symptoms, culture and pathology.** A:Hypertrophic erythema and deep ulcers on the left upper extremity; B: The ulcer on the left upper extremity had completely healed after treatment; C: Wound secretion culture revealed *Corynespora cassiicola*; D: Bronchoalveolar lavage fluid culture analysis revealed the presence of *Cladosporium*; E: Skin biopsy showed a partial squamous hyperplasia with a dermal granulomatous lesion.

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**Figure 2** **Imaging.** A chest computed tomography scan showing multiple nodules with multiple patchy areas in both lungs (arrow).