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*Case Report*

# Invasive fungal infection caused by *geotrichum capitatum* in patients with acute lymphoblastic leukemia: a case study and literature review

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**Abstract:** *Geotrichum capitatum* infection has a very low incidence rate with atypical clinical symptoms, making diagnosis difficult, and it has a poor prognosis. The incidence is even more rare in China. This paper reports the first case of infection caused by *G. capitatum* during bone marrow suppression after chemotherapy in a Chinese patient with acute lymphoblastic leukemia. In addition, it reports a systematic literature review of diagnosis and treatment. The patient with acute lymphoblastic leukemia was confirmed to be infected with *G. capitatum*, involving lung, liver and skin, through a blood culture test. Caspofungin, amphotericin B loposome, and a combination therapy of amphotericin B liposome and voriconazole were used in succession for treatment. Despite normal body temperature and a slight improvement of clinical symptoms with the combination therapy treatment, the patient died 40 days after chemotherapy due to heart and lung failure.

**Keywords:** Invasive fungal infection, *G. capitatum*, immunodeficiency, acute lymphoblastic leukemia

## Introduction

Invasive fungal infections occur more often in immune-compromised patients, especially patients with hematologic malignancies, agranulocytosis and allogeneic hematopoietic stem cell transplantation. In recent years, the incidence rate of invasive fungal infection increased significantly, which has become one of the main causes of death for patients with hematologic malignancies. Pathogens of invasive fungal infection include *Candida*, *Aspergillus*, and *Mucor*. *G. capitatum* infection is a very rare type of fungal infection. According to foreign reports, it is common in immune-compromised patients with acute leukemia [1-9]. Currently, only one case of G. capitatum infection has been diagnosed in China through sputum culture in a patient with chronic obstructive pulmonary disease [10], yet no cases of *G. capitatum* infection have been diagnosed through blood culture. This paper introduces the first case of *G. capitatum* infection confirmed by blood culture test in a Chinese patient with acute lymphoblastic leukemia and review and analysis of the literature.

## Materials and methods

### *Anamnesis*

The patient, male, 25-year-old, was admitted to our hospital on June 5, 2014 due to intermittent fatigue and its aggravation for more than 10 days. The routine blood examination at admission gave the following results: white blood cell count 0.76 × $10^9$/L, hemoglobin 61 g/L, and platelet count 68 × $10^9$/L; No clear lesions were observed on the chest CT scan. Abdomen and heart were normal upon ultrasound examination. Bone marrow smears revealed the following: bone marrow hyperplasia was active, primitive and naive lymphocytes accounted for 0.776, NAP (-), POX: primitive or naive lymphocytes (-), PAS: part of the primitive and naive lymphocytes were granularly or columnarly positive, AS-DNCE: primitive or naive lymphocytes (-), a-NBE: primitive or naive lymphocytes (-), and AS-DAE: primitive and naive lymphocytes were weakly positive, not inhibited by NaF. The bone marrow biopsy showed diffuse proliferation of immature cells.

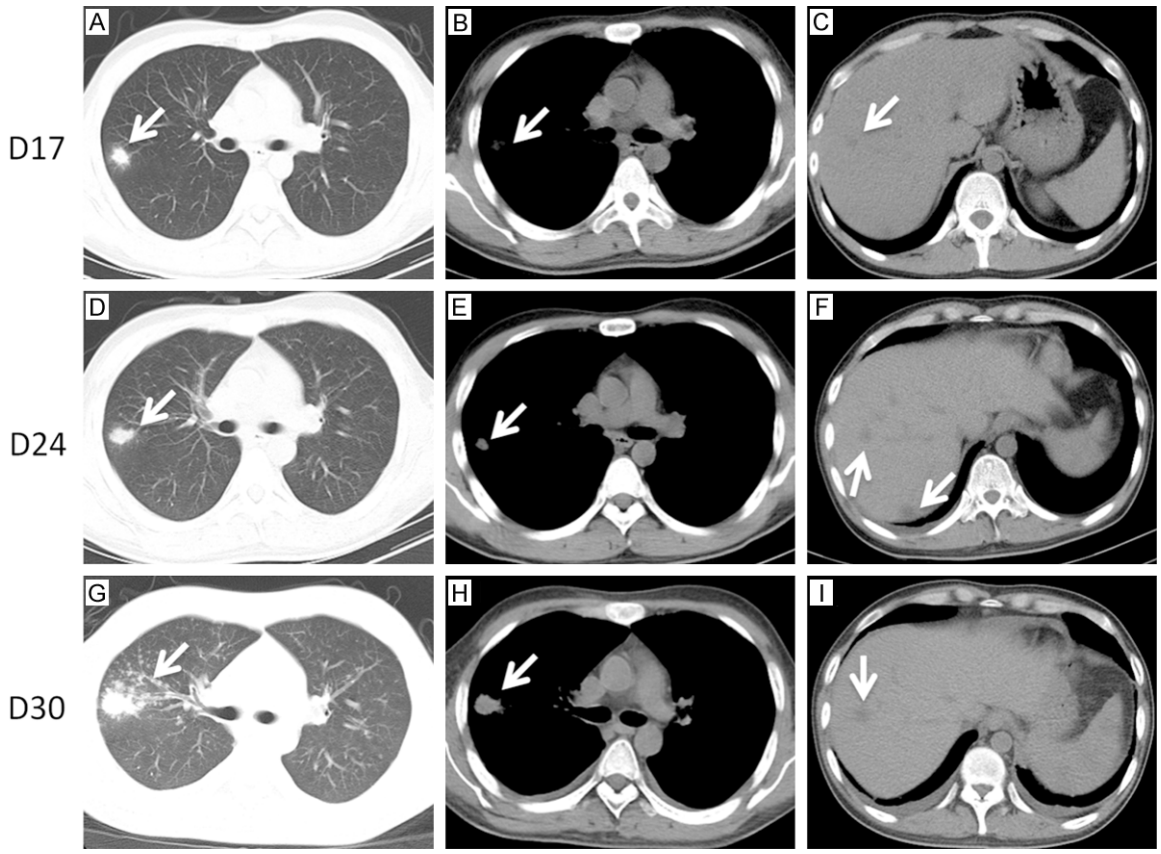


**Figure 1.** Infiltration and nodular lesions in lungs and liver detected by CT scans.

Bone marrow flow cytometry results demonstrated the following: abnormal cell subsets were detected, T lymphocyte antigens were predominantly expressed, among which MPO, CD19, CD10, CCD79a were negative, CD7: 62.5%, CD34: 73.7%, CD56: 90%, CD61: 12.6%, CD41: 11%, cCD3: 20.9%, TDT: 23 3%, CD71: 98.6%. Abnormalities in acute lymphoblastic leukemia-related genes were not detected (MLL/AF4, E2A/HLF, SIL/TAL1, CAML/AF10, HOX11, HOX11L2, TEL/AML1, EA2/PBX1, BCR/ABL, etc.); neither were chromosomal abnormalities. A final diagnosis was made as 'acute lymphoblastic leukemia (T-cell type)'. On June 11$^{th}$, 2014, VDCLP chemotherapy was started, and the patient body surface area was 1.8 m$^2$. The dosages were as follows: Vincristine 2 mg d1, 8, 15, 22; daunorubicin 72 mg, d1-3, 54 mg, d15-16; cyclophosphamide 1360 mg d1, 15; L-asparaginase 1 WU, d7, 9, 11, 13, 15; prednisone 65 mg, d1-14 and 35 mg, d15-28. Meanwhile, supportive and symptomatic treatments such as hydration, alkalinization, and anti-emetics were given.

*Diagnosis and treatments*

On chemotherapy day 9 (D9), the patient presented with a fever, and the body temperature rose up to 38.8°C, and no significant chills, chest tightness or shortness of breath were found. Routine blood examination results demonstrated the following: white blood cell count 0.20 × 10$^9$/L, hemoglobin 63 g/L, and platelet count 10 × 10$^9$/L. The blood culture test was negative. Quantitative procalcitonin test (PCT) was 0.3 ng/mL; quantitative endotoxin test (LPS), galactomannan test (GM test), and 1,3-β-D-glucan test (G test) were all negative. Chest CT scan showed no abnormalities. Considered as agranulocytosis with fever, the patient was given imipenem/cilastatin sodium (1 g, q6h), and the body temperature returned normal after this anti-infective therapy. On chemotherapy day 14 (D14), patient's body temperature rose up to 39°C again, and vancomycin (1 g, q12h) was added. On chemotherapy day 17 (D17), there was still intermittent fever, and the chest CT scan revealed high density

**Table 1.** *In vitro* susceptibility test of *G. capitatum*

| Drugs | Method | Value (mg/L) | Susceptibility |
|---|---|---|---|
| Fluconazole | MIC | 16.0 | I |
| 5-fluorocytosine | MIC | <4.0 | S |
| Amphotericin B | MIC | 1.0 | S |
| Itraconazole | MIC | 0.25 | I |
| Voriconazole | MIC | 0.50 | S |

S = susceptible, R = Resistance, I = intermediate.

area on the upper lobe of right lung, and small patch of low density on the right lobe of liver (**Figure 1A-C**). Therefore, the anti-bacterial treatment was combined with anti-fungal treatment, caspofungin acetate (70 mg, D1, 50 mg, q24h). In the meantime, the patient still had a fever, but it was not accompanied with chills, chest tightness, shortness of breath, cough or expectoration. On chemotherapy day 24 (D24), repeated blood culture tests suggested *G. capitatum* infection. Susceptibility testing showed sensitivity to amphotericin B, 5-fluorocytosine, and voriconazole and intermediate sensitivity to fluconazole and itraconazole (**Table 1**). Review of the chest CT scan revealed a slightly enlarged high density area on the upper lobe of right lung, and a small patch of low density on the right lobe of liver (**Figure 1D-F**). As a result, anti-fungal therapy was switched to *G. capitatum*-sensitive amphotericin B liposome. The patient's body temperature gradually returned to normal, and PCT and LTS levels decreased significantly. The antibiotic therapy was then adjusted to cefoperazone sodium/sulbactam sodium. On chemotherapy day 30 (D30), palpitation and shortness of breath had increased significantly, and a scattered wheeze and moist rale could be heard from both lungs. Review of the chest CT scan revealed a lesion on the upper lobe of right lung slightly larger than in the previous scan, multiple nodules were found in both lungs, opacities had formed on the medial segment of the lower lobe of left lung, pleural effusion was slightly raised, and minor cardiac effusion was observed; in addition, a small patch of low density on the right lobe of liver was identified (**Figure 1G-I**). Scattered papules and vesicular rashes could be observed on chest and back, partially accompanied with peripheral congestion (**Figure 2**); there was no significant itching or discomfort, and colorless liquid outflew from ruptured blisters without bleeding or ulcers. The following levels were reexamined and the results are as follows: PCT 7.79 ng/ml, LPS 20.3 pg/ml, galactomannan 8.53 μg/L, and 1,3-β-D-glucan 181.8 pg/ml. Considering the level of infection aggravation, cefoperazone sodium/sulbactam sodium combined with teicoplanin was started for anti-bacterial purposes, amphotericin B (80 mg/day) liposome combined with voriconazole (200 mg, 2/day) was started for anti-fungal purposes, and supportive treatment was given simultaneously for spasmolysis and asthma relief.

## Results

Through a combination of amphotericin B liposome and voriconazole, the patient's body temperature maintained normal a normal level and wheeze and moist rale from both lungs were reduced slightly, but the symptoms in the lungs and skin persisted. On chemotherapy day 36 (D36), a routine blood reexamination resulted in the following: white blood cell count 0.60 × $10^9$/L, hemoglobin 83 g/L, and platelet count 28 × $10^9$/L. Reexamined bone marrow smears showed: naive lymphocytes accounted for 9%, suggesting no remission of leukemia. Granting non-remission of leukemia and economic factors, on chemotherapy day 40 (D40), the patient gave up treatments here and returned to a local hospital, and died on chemotherapy day 42 (D42).

## Discussion

*G. capitatum* is an opportunistic pathogenic fungus; its teleomorph is *Dipodascus capitatus*, also known as *Trichosporon capitatum*, *Blastoschizomyces capitatus* or *Blastoschizomyces pseudo trichosporon*. Under a microscope, it can be seen that its hyphae divide into elongated arthrospores, making it easily confused for *Trichosporon*. But only arthrospores, no blastospores, could be found, and thus it can be differentiated from *Trichosporon*. *G. capitatum* can lead to systemic infections, including infections of blood, lung, liver, kidney, brain, and meninges, and the outbreak is concen-trated on immune-compromised patients such as patients with hematological malignancies [3, 5, 11].

### *Epidemiology of G. capitatum*

*G. capitatum* mainly grows in food, soil, mucous membranes and on skin surfaces. It can usually be separated from the normal flora of human skin, respiratory tract and gastrointestinal tract, but generally does not cause

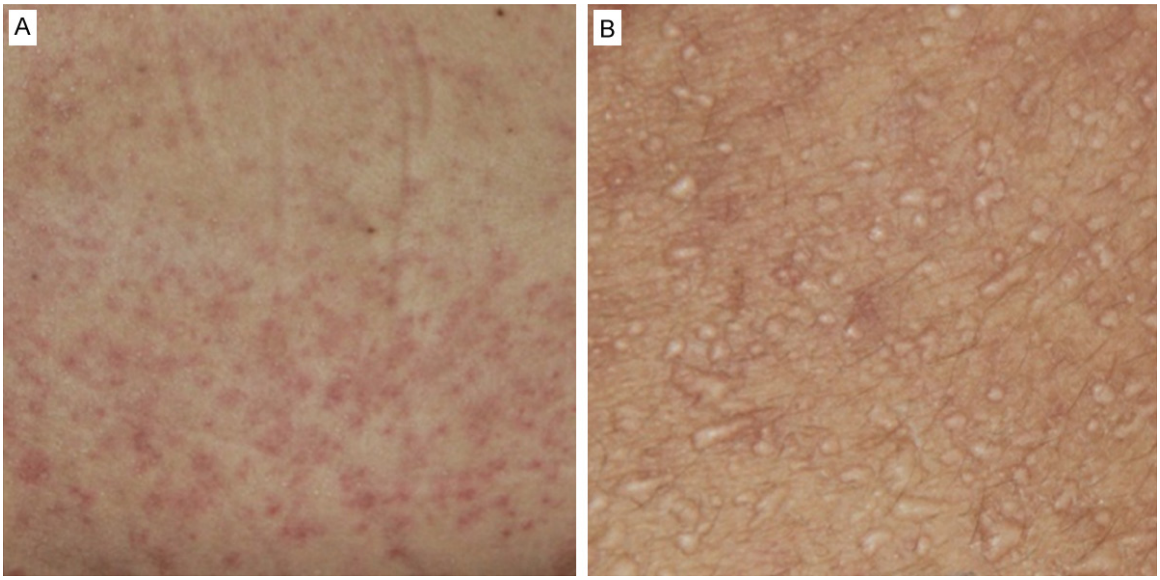


**Figure 2.** Dermal changes caused by *G. capitatum* infection.

infection and colonization [3, 5]. G. *capitatum* infection is very rare fungal infection, especially in Chinese patients with blood diseases, and no case had been reported until now. In general, *G. capitatum* has low virulence, and it is an opportunistic pathogen. In patients with normal immunity, it is generally not pathogenic. However, it can still be found in patients with non-neutropenia and local infection. According to the literature search in MEDLINE, between 1965 and 2011, there have been 202 reports about *Geotrichum*, *Blastoschizomyces* and *Trichosporon capitatum*, among which there were 186 cases of invasive infection, with a mortality rate of up to 50%, and the youngest patient was only 7 years old [5].

*G. capitatum* infection occurs mainly in patients with hematologic malignancies, and long-time neutropenia, glucocorticoid treatment, deep venous catheterization, chemotherapy and the use of broad-spectrum antibiotics are all risk factors of fungal infection, including *G. capitatum* infection [1-9]. Systemic *G. capitatum* infection has been reported in Europe, Japan and the Mediterranean area, but this is the first case in China [12].

Chronic neutropenia is one of the major risk factors for invasive *G. capitatum* infection. There are beliefs that preventive and earlier empirical anti-fungal therapy may induce *G. capitatum* infection [5]. The infection routes of *G. capitatum* are mainly considered to be respiratory tract and digestive tract, it parasitizes in the intestinal tract, respiratory tract and skin. When in an immune-compromised state, it causes opportunistic infection, thereby giving rise to infection of the liver, spleen and blood. Overall, various infection routes are likely to happen in immune-compromised patients [3, 5].

A retrospective multi-center clinical study of *Trichosporon* infection in Italy showed that 52 cases of *Trichosporon* infection were identified within 20 years, and 65.4% of the patients were diagnosed with acute myeloid leukemia, where 35 cases were identified as having *G. capitatum* infection. The rate of *G. capitatum* infection is around 0.5% among patients with acute leukemia. Among the 35 patients with *G. capitatum* infection, 76.9% were identified by blood culture test, 26.9% involved the lungs, and the mortality rate was as high as 57.1%. Another retrospective study showed that *G. capitatum* infection primarily occurs in Europe, especially in the Mediterranean area. Among the patients with *G. capitatum* infection, 91.7% were diagnosed with hematological diseases, 84% with acute leukemia, and the mortality rate was 55.7%. *In vitro* studies confirmed that voriconazole and amphotericin B were effective medications while *in vivo* therapeutic effects need further study. The effective treatment of *G. capitatum* infection has yet to be further explored in clinical courses [3].

*Clinical features of G. capitatum infection*

The clinical manifestations of *G. capitatum* infection are similar to other fungal infections. Most patients develop agranulocytosis and fever, and are not sensitive to the broadspectrum antibiotic treatments. *G. capitatum* infection is mostly a disseminated systemic infection, and in non-agranulocytosis patients, it is commonly a focal infection, such as endocarditis, meningitis, osteomyelitis, or intervertebral disc infection [1-10, 13, 14]. Clinically, it is hard to differentiate *G. capitatum* infection from *Candida* and *Aspergillus* infections.

Typically, *G. capitatum* infection is diagnosed using blood culture test, and some cases can be confirmed by sputum culture test. According to the literature, the positive rate of blood culture test is up to 70% of in patients infected by *G. capitatum*, while that of *Candida* is less than 50%, *Aspergillus* is less than 10%, and *Fusarium* is roughly 56%. Deep organ involvement can take place in 60-80% of patients infected by *G. capitatum* [5]. The *G. capitatum* infection here was confirmed by blood culture test, which invaded the lungs (**Figure 1**), liver (**Figure 2**) and skin.

In patients with *G. capitatum* septicemia, lungs are often involved, as with other invasive pulmonary fungal infections, there regularly are halo signs, crescent signs and other typical radiographic features [15]. In this study, the radiographic manifestations presented a high-density patch on the upper lobe of right lung, small low-density patches on the right lobe of liver, and the emergence of halo sign (**Figure 1**). Mucocutaneous damage often occurs in patients with *G. capitatum* septicemia that vesicular and purpura papules can be found, wherein some can further develop into central necrosis. The most common ones are mucosal lesions in the mouth and throat and the pathogen can be detected by skin biopsy and throat swab culture [14]. Here, the patient had typical vesicular and purpura papules (**Figure 2**).

*Diagnosis and treatment of G. capitatum infection*

*G. capitatum* infection is usually diagnosed through blood culture test, as was the case described herein. This systemic *G. capitatum* infection involved the liver and lungs, but no fungal pathology or GI tract evidence was obtained; thus the infection route was not clear. During chemotherapy-induced neutropenia, *G. capitatum* might colonize in the lung, then diffuse into the blood, and finally cause systemic infection. It is also possible that *G. capitatum* firstly leads to systemic blood infection, which further diffuses to the lungs and liver, as shown in the CT scan; scattered nodules could be found in the lung and liver. As the patient had a rather low level of platelets, other organs did not undergo further examination and it is unclear if any other parts had been involved [3, 5, 16].

The serological G test (1,3-β-D-glucan) chiefly detects 1,3-β-D-glucan as a component of the fungal wall. It is applicable in early diagnosis of all fungal infections, especially *Candida* and *Aspergillus* infections and except for *Cryptococcus* and *Zygomycetes* infections, but it cannot determine the specific infectious species [16]. The patient's (1,3)-β-D-glucan levels increased significantly, suggesting that *G. capitatum* infection can result in significant increase of (1,3)-β-D-glucan, however, it cannot be differentiated from other fungal infections. Galactomannan antigen enzyme-linked immunosorbent assay (GM-ELISA) is now widely used in serological diagnosis of invasive A*spergillosis*. GM release is positively proportional to the bacteria amount, which can reflect the degree of infection. Continuous detection of GM can monitor treatment efficacy. Nonetheless, with a high rate of false positives and cross-reactions with other opportunistic pathogens, dynamic changes in values tend to be more important in terms of clinical significance [17-19]. The index increased significantly in this case, and along with infection aggravation, the quantity of galactomannan antigen displayed an increasing trend. Therefore, GM-ELISA is an essential diagnostic method for invasive A*spergillosis*, and can also be used for diagnosis of other fungal infection such as *G. capitatum* infection. So for hematological cancer patients with persistent fever and poor response to broad-spectrum antibacterial therapy, fungal infections should be considered and blood culture test, CT scan and serological tests can contribute to the diagnosis of *G. capitatum* infection.

Girmenia, et al. reported that *G. capitatum* is sensitive to amphotericin B, flucytosine, flucon-

azole, itraconazole and voriconazole on basis of *in vitro* susceptibility test results [3]. It has also been reported that *G. capitatum* is dose-dependently sensitive to fluconazole, but insensitive to itraconazole, terbinafine or amphotericin B. More studies have suggested that anti-fungal activity and *in vivo* efficacy of amphotericin B and voriconazole are the highest while that of fluconazole, itraconazole and flucytosine are the lowest [1-10, 18-22]. In this case, susceptibility test results suggested *G. capitatum* was sensitive to amphotericin B, 5-fluorocytosine and voriconazole, but intermediate to fluconazole and itraconazole. Amphotericin B combined with flucytosine treatment was used in patients infected by *G. capitatum* in some studies, but the combination therapy was not proven superior to the single use of amphotericin B. In some cases, monotherapy of voriconazole or caspofungin could effectively inhibit *G. capitatum* infection, but most reports suggest that monotherapy efficacy of either voriconazole or caspofungin is lower than amphotericin B or its combination therapy with voriconazole. It has been reported that a 7-year-old patient with leukemia and *G. capitatum* infection was successfully treated with a combination therapy of voriconazole and amphotericin B, and a patient with agranulocytosis and systemic *G. capitatum* infection successfully treated with a combination therapy of amphotericin B liposome and itraconazole [3, 5, 18-22].

*G. capitatum* infection is associated with poor prognosis. If diagnosed and given an effective anti-fungal therapy early enough, the patient might come out of agranulocytosis earlier and receive better efficacy. Therefore, early anti-fungal treatment is a key factor in reducing mortality. The mortality rate of disseminated infections caused by *G. capitatum* is high. For patients with neutropenia or immunodeficiency disorders, prognosis is even worse, even when treated with intense amphotericin B liposome, itraconazole and flucytosine, the mortality rate is still as high as 50-90%. When voriconazole or caspofungin in monotherapy or in combinational therapy with amphotericin B or amphotericin B liposome were used, although most patients died, some still achieved a certain effect. This suggests that the combinational therapy may be effective [3, 5, 18-22]. New anti-fungal agents such as posaconazole and isavuconazole may be effective against *G. capitatum* infection and remain to be confirmed in future clinical practices [23, 24]. Though given a potent anti-fungal treatment, which showed certain clinical efficacy, the patient had experienced long-time agranulocytosis with no remission of the primary disease, and eventually resulted in treatment failure.

In Asia, *G. capitatum* infections have been reported in Japan [25]. In China, the incidence of *G. capitatum* is low and the cause is unclear. Only one case has been reported [10], which was confirmed by sputum culture test. It is the first time that a patient was confirmed to be infected by *G. capitatum* through a blood culture test. For patients with positive serological biomarkers, rare fungal infections like *G. capitatum* infection should be considered as a possibility. Based on our and other scholars' experiences, prophylactic and empirical anti-fungal therapy with fluconazole or echinocandin cannot effectively prevent rare fungal infections.

In summary, incidence rate of *G. capitatum* infection is low, relative clinical symptoms are atypical, diagnosis is difficult, and prognosis is poor. Combining patient's clinical manifestations and various tests including blood culture test, GM-ELISA, G test and CT scans can help with the diagnosis. No effective treatments have been established for *G. capitatum* infection to date. Using amphotericin B liposome or amphotericin B combined with voriconazole or other new antifungal agents may achieve a certain effect, and early diagnosis, early combination therapy and early recovery from agranulocytosis are the crucial factors to successful treatment.

## Disclosure of conflict of interest

None.

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