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First case of *Rhinocladiella mackenziei* brain abscess in Turkey: Case report and review of the literature

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Abstract

Rhinocladiella mackenziei is a highly neurotropic fungus, mainly reported from the Middle East. However, in recent years, there have been some cases from outside this region. We described an additional fatal case of *R. mackenziei* cerebral infection for the first time from Turkey and made a literature review of all previously reported cases. During 34 years (1988–2022), there have been 42 *R. mackenziei* brain abscess cases. Most patients have been reported from Saudi Arabia ($n = 14$, 33.3%). It is noteworthy that 40.5% of patients, including our case, were immunocompetent at initial diagnosis and mostly presented with a single lesion ($n = 10$, 23.8%). The most frequent comorbidities were solid organ transplant ($n = 9$, 21.4%), diabetes mellitus ($n = 6$, 14.3%), malignancy ($n = 6$, 14.3%) and prior surgery ($n = 3$, 7.1%). The most commonly used initial antifungal regimen were amphotericin B together with itraconazole ($n = 9$, 21.4%), combinations of lipid preparations of amphotericin B, voriconazole and/or posaconazole ($n = 9$, 21.4%) and amphotericin B alone ($n = 8$, 19%). Although both surgical procedures and antifungal medication in the majority of patients were performed, mortality rates remained high (90.4%). The area at risk of *R. mackenziei* cerebral abscess cases extends to other countries. Clinicians should be aware of this emerging disease and take a detailed travel history in patients with atypical and undocumented brain abscesses. Our case confirms the hypothesis that this fungus might spread more widely than previously predicted regions.

KEYWORDS
cerebral abscess, neurotropic fungus, phaeohyphomycosis, *Rhinocladiella mackenziei*

1 | INTRODUCTION

Phaeohyphomycosis is a term used to describe infections caused by dematiaceous (darkly-pigmented) fungi that contain melanin in their cell walls and occur in tissue as dark, yeast-like cells, pseudohypha like elements, variously shaped hyphae or any combination of these forms.[1] Dematiaceous fungi are rare causes of invasive fungal disease, and all organisms do not have the same propensity to cause certain syndromes or can affect different hosts. Infections may be cutaneous or subcutaneous, sometimes skin lesions with no symptoms or warty nodules with lymphatic distribution, or they can incite life-threatening infections, such as brain abscesses and disseminated disease.[2–5]

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Primary cerebral phaeohyphomycosis is typically caused by *Cladophialophora bantiana*, *Fonsecaea pedrosoi*, *Exophiala dermatitidis*, *Ochroconis* spp. or *Rhinocladiella mackenziei*, all of which belong to the order *Chaetothyriales*.[6–8] *Rhinocladiella mackenziei* (formerly *Ramichloridium mackenziei*) is a highly neurotropic fungus and causes challenging infections with a poor prognosis despite the application of surgery and antifungal therapy.[5,9] It is one of the rare etiologic agents of cerebral phaeohyphomycosis and distinct from other agents of phaeohyphomycosis by two characteristics: special tropism to the brain and limited geographic distribution, which was mainly the Middle East.[10–12] In this report, we describe an additional fatal case of *R. mackenziei* cerebral infection in Turkey, where this infection has not been previously reported. We also aimed to make a literature review of previously reported cases.

2 | CASE PRESENTATION

A 63-year-old man from Turkey, a native of Corum, a province in the Black Sea region, with no previous disease history, living in Istanbul for 50 years, working as a hospital staff, with no travel to Middle Eastern countries, and no known contacts to people who travelled to Middle Eastern countries, was admitted to Istanbul University Faculty of Medicine, Department of Emergency Medicine (Istanbul, Turkey) for dysphasia. The physical examination of the patient revealed stable vital signs and unremarkable general evaluation. His neurological examination revealed right facial paresis, globally hyperactive deep tendon reflexes and dysphasia. The leukocyte count was 11,900 cells/mm^3, lymphocyte 3500 cells/mm^3, C-reactive protein was at 2 mg/dL, and urinary and blood cultures were negative.

Noncontrast cranial computed tomography (CT) showed a left frontal cystic lesion with peripheral vasogenic edema. Thorax CT showed a nodular structure in the apicoposterior segment of the left lung, and abdominal CT was normal. Magnetic resonance (MR) imaging showed a single ring-enhancing lesion in the left posterior frontal region, measuring 19 × 18 × 15 mm. The diffusion-weighted imaging (DWI) showed increased signal intensity with a low signal intensity in apparent diffusion coefficient (ADC) in the center, indicating diffusion restriction and abscess formation (Figure 1). MR spectroscopy revealed lipid and lactate increase indicating necrosis in the center of the lesion. A PET-CT scan showed increased metabolism in the apicoposterior segment of the left lung and multiple small lymph nodes with increased activity. The thorax CT findings were compatible with infectious processes, but none of the lesions was convenient for sampling. Intravenous amphotericin B, 375 mg once daily, was started.

An aspiration procedure via burr-hole drilling was performed under general anaesthesia, and 8 mL of creamy yellow pus was aspirated. Samples were sent to the Mycology Laboratory of Istanbul University, Faculty of Medicine, Medical Microbiology Department, and all laboratory procedures were performed in a level II biosafety cabinet. Clinical specimens were examined by fluorescence microscopy (Olympus BH2-RFCA, Japan) with 10% KOH calcofluor white mount, and septate hyphae were seen on direct microscopy. Specimens were inoculated onto Sabouraud dextrose agar (SDA) and brain heart infusion (BHI) agar with the addition of

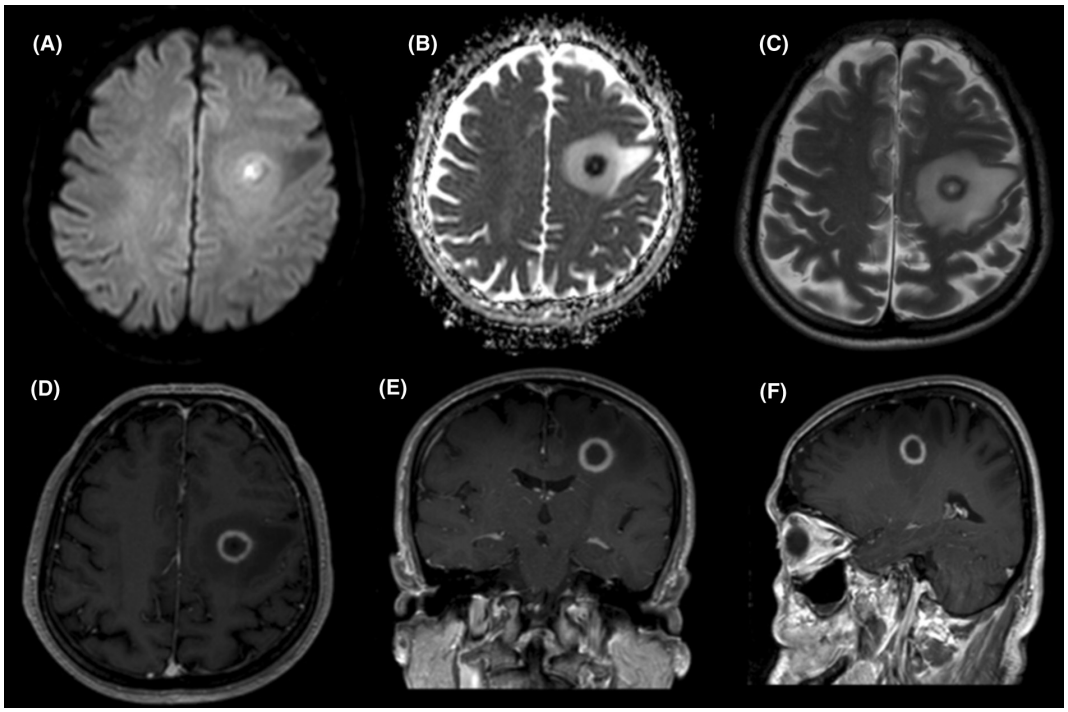


FIGURE 1 Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) show a diffusion-restricting lesion in the left frontal region (A, B). Axial T2 sequence MRI shows peripheral vasogenic edema (C). There is peripheral contrast enhancement, and the lesion is 19 × 18 × 15 mm (D, E, F).

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chloramphenicol (50 mg/L) and gentamicin (50 mg/L). All cultures were incubated at 37°C and 27°C under aerobic conditions and observed daily. After 7 days of incubation, velvety brown to black colonies with raised edges at the periphery appeared (Figure 2A). Lactophenol cotton blue was used to stain the dematiaceous fungus grown. The microscopic morphology examined by scotch tape and tease mount showed septate brown hyphae and *Rhinocladiella*-type sporulation ("Mickey Mouse" appearance) (Figure 2B).[13] There were no holoblastic chains of conidia which are usually seen with *Cladophialophora* strains. Conidia were brown ellipsoidal and thick-walled, with a prominent basal scar. Based on the morphological features described above, the fungus was identified as *Rhinocladiella* spp. Molecular identification was performed by the sequencing of internal transcribed spacer (ITS ribosomal DNA) regions. The Sanger sequencing method was used with the ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, USA).[7] D1-D2 domain of 28S ribosomal DNA was amplified with NL1 (5′ - GCA TAT CAA TAA GCG GAG GAA AAG - 3′) and NL4 (5′ - GGT CCG TGT TTC AAG ACG G - 3′) and sequenced directionally with BigDye 3.1 chemistry.[14] Sequences were compared with entries in GenBank by using the BLAST method. The fungus was identified as *Rhinocladiella mackenziei*. The sequence of the ITS rDNA region from the isolate has been deposited in GenBank under accession number OQ804484. Microbiological cultures were made from three aspirations, cerebrospinal fluid (CSF) samples, and brain biopsy. *R. mackenziei* was isolated from all aspiration samples and the biopsy material, while cultures of CSF samples remained sterile. The brain biopsy material was also examined histopathologically, and mixed inflammation granulation tissue and hyphal structures were observed. Antifungal susceptibility testing of this dematiaceous fungus was performed with the E-test method.[15] The minimal inhibitory concentration (MIC) values were as follows: fluconazole >256 μg/mL, voriconazole 0.032 μg/mL, itraconazole 0.25 μg/mL, posaconazole 0.064 μg/mL, amphotericin B > 32 μg/mL, caspofungin 0.002 μg/mL and anidulafungin <0.002 μg/mL.

The patient was tested for immunodeficiency. Viral serology, including anti-HIV antibodies, was negative, the peripheral smear was normal, serum immunoglobulin subgroups were in the normal intervals, complement levels C2 and C4 were only slightly decreased, protein electrophoresis revealed only a slight increase in A1 and A2 globulin levels, *Aspergillus* galactomannan in serum and *Toxoplasma* antibodies were negative. *Nocardia* culture remained negative. HbA1c was in the normal interval, with no signs of diabetes mellitus. Endoscopic, otoscopic evaluation, and CT scans showed no signs of sinusitis and otitis. No organomegaly was detected. Urinary and serum immunofixation were normal. The patient was also evaluated rheumatologically with ANA, anti-dsDNA, CH50 test, anti-A, and anti-B; all were normal.

After the first aspiration, 7 days later, the patient started to have motor weakness on the right side. In his neurological examination, 3/5 right-sided hemiparesis was detected. A control MR imaging showed an increase in the size of the lesion and the surrounding vasogenic edema (Figure 3). A second aspiration was performed, and 5 mL of creamy yellow pus was withdrawn. Intravenous voriconazole, 200 mg twice daily, was added to the therapy.

The patient had aphasia 12 days after the first surgery. Control cranial CT showed an increased size of the cystic lesion. A third aspiration procedure was applied on the 13th day of the first procedure. Four ml of creamy yellow pus was withdrawn. On the third postoperative day, the patient developed right hemiplegia. After the three aspirations, surgical excision was performed. The abscess was totally resected microscopically. Right-sided weakness improved, but on the 16th day, the patient started to have purulent discharge from his incision. Thus, control gadolinium-enhanced MR imaging was performed. The MR showed multiple bilateral ring-enhancing supratentorial and infratentorial lesions compatible with dissemination (Figure 4). To treat secondary bacterial infections, meropenem 2 gr three times daily, vancomycin 1 gr two times daily and metronidazole 500 mg 4 times daily were started. After 40 days of first admission, the patient deteriorated, and after two times of additional aspirations, he developed anisocoria and respiratory failure and was taken to the intensive care unit. After consecutive disseminated pulmonary infections, the patient died 3.5 months after his first admission to the Emergency Medicine Department.

3 | MATERIALS AND METHODS

3.1 | Data collection

In addition to our case, we searched other case reports and series of *R. mackenziei* caused brain abscesses, published in English and Turkish, from 1988 to the end of 2022, using the PubMed bibliographic database (U.S. National Library of Medicine, Bethesda, MD). The words '*Rhinocladiella*,' '*Rhinocladiella mackenziei*,' '*Rhinocladiella obovoideum*,' '*Ramichloridium obovoidea*,' '*Ramichloridium mackenziei*,' 'cerebral phaeohyphomycosis,' 'dematiaceous fungi,' 'melanized fungi,' 'cerebral fungal infection,' 'brain abscess,' were used as keywords in various combinations, with or without using the Boolean operators 'AND' or 'OR' to combine them. After this initial review of the reports, their references and similar articles in PubMed/MEDLINE were carefully scrutinised for additional case reports and series.

4 | RESULTS

During 34 years (1988–2022), there have been 23 publications, including 41 *R. mackenziei* brain abscess cases. Together with our case, the current case number is 42 (Table 1). The majority of cases have been reported from the Middle East. Among total cases, Saudi Arabia is the country where this fungus is most frequently encountered ($n = 14$, 33.3%). Among the publication providing information on gender, there were 24 male and 15 female patients. The age at the time of diagnosis ranged from 20 to 80 years (mean: 57.7). As a result of the information specified in the publications, the comorbidities

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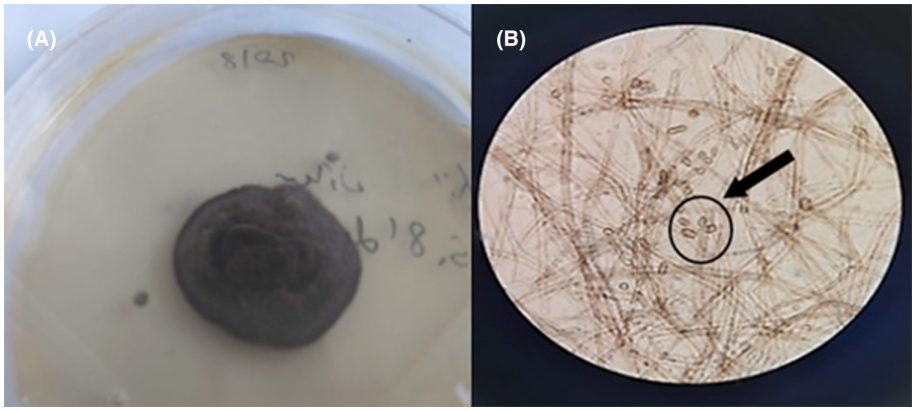


FIGURE 2 A mature colony of *R. mackenziei* on Sabouraud dextrose agar (A). Lactophenol cotton blue preparation showing dark pigmented septate hyphae and oval conidia (arrow: 'Mickey Mouse' appearance) (B).

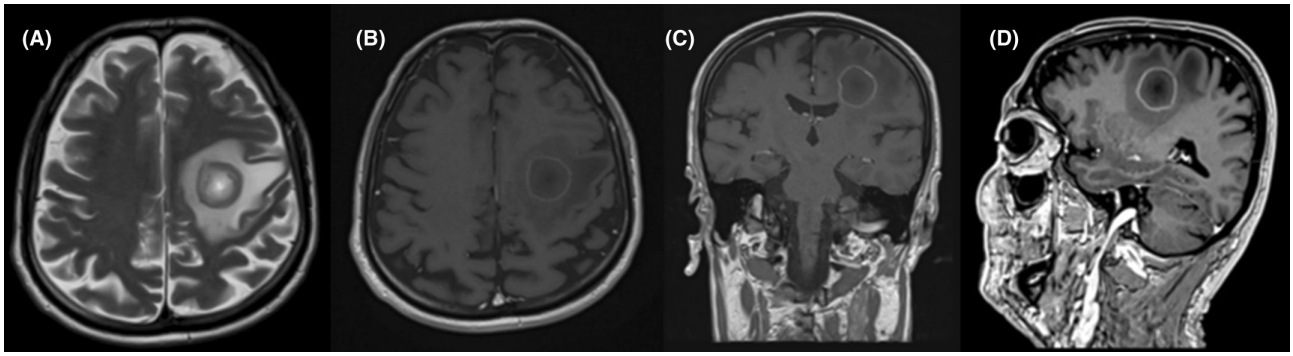


FIGURE 3 T2 axial MRI sequence (A) and axial, coronal, and sagittal contrast-enhanced MRI (B, C, D) on a postoperative day 7 shows an increase in the lesion size and peripheral vasogenic edema.

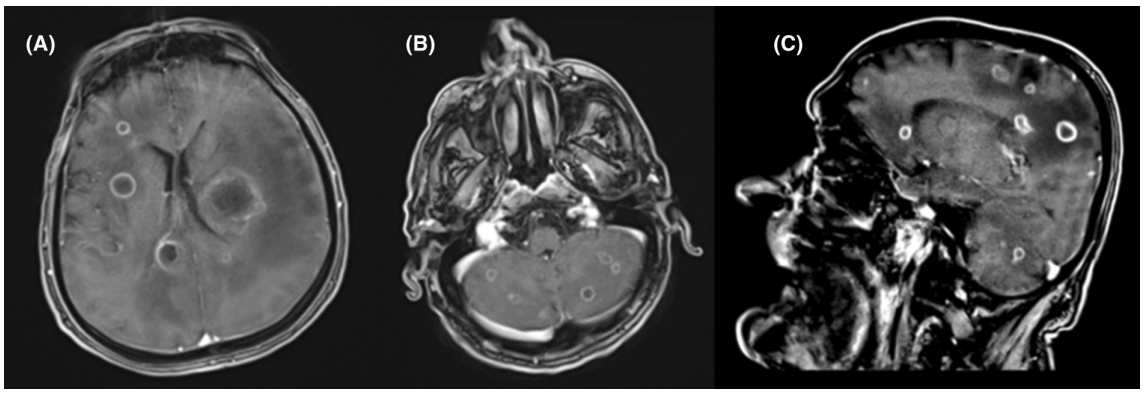


FIGURE 4 Postcontrast axial, coronal and sagittal T1-weighted MR images showing multiple bilateral ring-enhancing supratentorial and infratentorial lesions.

associated with the *R. mackenziei* brain abscess included: solid organ transplant ($n=9$, 21.4%), diabetes mellitus ($n=6$, 14.3%), malignancy ($n=6$, 14.3%), prior surgery ($n=3$, 7.1%), rheumatological disease ($n=3$, 7.1%), trauma ($n=2$, 4.7%), tuberculosis ($n=2$, 4.7%) and post-COVID-19 ($n=2$, 4.7%). Among the cases in which the number of abscesses was mentioned, single and multiple brain abscesses were noted in 24 and 15 (57.1%, 35.7%) patients, respectively. It is noteworthy that 40.5% of patients, including the current case, were immunocompetent at initial diagnosis ($n=17$). Immunocompetent individuals mostly present with a single lesion ($n=10$, 23.8%), while multiple lesions can occur in immunocompromised hosts.

There were five cases that reported antifungal susceptibility results tested by using a broth microdilution method according to the CLSI standard M38-A2 documented.[13] Although categorical breakpoints do not exist for the moulds, there were high amphotericin B minimum inhibitory concentration (MIC) values that could indicate

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resistance and low values for azoles that suggested susceptibility (Table 2). The most commonly used initial antifungal regimen were amphotericin B together with itraconazole ($n=9$, 21.4%), combinations of lipid preparations of amphotericin B, voriconazole, and/or posaconazole ($n=9$, 21.4%) and amphotericin B alone ($n=8$, 19%). A fatal outcome was observed in 90.4% of the cases with known outcomes, despite surgical procedures and antifungal medication in most patients. The mean survival from the start of treatment to death was approximately 2 months. Only two patients were cured,[15,16], and two more patients reported at the end of December 2022 were alive at the time of the report.[17,18]

5 | DISCUSSION

To our knowledge, this is the first case of cerebral abscess due to *Rhinocladiella mackenziei* reported from Turkey. Brain abscess cases caused by dematiaceous fungi are also very rare in our country. Only in four cases *Cladophialophora bantiana* and in one case, *Fonsecaea pedrosoi* been isolated.[19] The environmental niche of *R. mackenziei* is unknown, and until now, the fungus has been only isolated from brain biopsy specimens.[20,21]

This fungus is mostly reported in patients from Middle Eastern countries, Afghanistan, the Indian subcontinent or among immigrants from those regions (Table 1). It could be related to the hot and arid climate in these countries and is thought to possibly be geographically restricted to this area.[4,9,10] However, cerebral phaeohyphomycosis cases with this fungus are increasingly reported from regions outside the Middle East.[22] There were some cases from the United States,[23,24] France[25] and Denmark,[26] which were unusual places for this fungus. However, it was stated that the patients in these publications were also Saudis, Kuwaitis and Afghans who currently lived in that countries. Recently cases of cerebral abscess due to *R. mackenziei* have been reported from India, Afghanistan and Morocco, which are also nonendemic regions.[20–22] These patients claimed that they had never travelled outside the country. In our case, the patient, a Turkish man, had no travel story abroad. Thus, these cases showed that the fungus might not be restricted to the Middle Eastern region as previously thought. Also, Rapronil et al. reported in 2021 that this fungus might spread more widely than previously predicted regions, and Turkey, Kenya, Egypt and Somalia may be at risk.[27]

Fungal brain infections have long been implicated in individuals with predisposes of immunodeficient states, like solid organ transplant recipients, connective tissue disorders, chronic liver disease or prolonged steroid use.[9] Also, inherited CARD9 deficiency which is a primary immunodeficiency disease and leads to defects in antifungal defence mechanisms, can be an underlying cause of these infections.[28,29] Other potential risk factors mentioned in the literature included head trauma, concurrent sinusitis and smoking marijuana.[30–32] The common species responsible for CNS infections caused by brown-black fungi are *Cladophialophora bantiana*, *Rhinocladiella mackenziei*, *Lomentospora prolificans*, *Verruconis gallopavum*, *Chaetomium strumarium*, *Exophiala dermatitidis*, *Fonsecaea monophora*, *Bipolaris spicifera and Curvularia lunata*.[33] In the literature, the incidence of *R. mackenziei* brain abscess cases is growing in immunocompetent individuals (25% of cases) (Table 1). Our patient also had no known immunodeficient state. In immunodeficient patients, solid organ transplantation was the most frequent underlying condition (20%) (Table 1). Nonetheless, some reports have also been reported this infection in patients with diabetes, Hodgkin lymphoma and systemic lupus erythematosus.[22,23,34–37]

Cerebral infections with *R. mackenziei* have been associated with very low survival rates. The mortality rate exceeds 92.5%, with an average survival of about 2 months following diagnosis (Table 1). However, there are only two patients in the literature who developed infection with this fungus secondary to trauma (Table 1). Among the publications in which patient survival was stated, there were two cured patients; one was treated by surgical debridement and intravenous voriconazole; also, surgical debridement with posaconazole therapy was applied to the other one.[15,16] Two more patients reported at the end of 2022 December were alive at the time of the report.[17,18]

The sporadic and nonrandom distribution of these infections often leads them to be thought of as isolated events. Thus far, the infection has only been diagnosed after the pathogenic agent has been cultured from biopsy specimens, which delays treatment and results in high mortality.[5,15,34,38–47]

Cerebral *R. mackenziei* infections may result from either hematogenous or direct spread from the accidental introduction of spores at contagious sites.[48] The ability of *R. mackenziei* to stay dormant inside a human host has also been postulated in a case report of an Afghan patient in whom the infection appeared 20 years after her last visit to an endemic area.[25] Symptoms of the infections presenting in almost all patients have been restricted to the central nervous system (CNS). Space-occupying lesion effects with weakness, seizures, headache, focal and hemiparesis or hemisensory loss, and/or confusion were the main presenting symptoms (Table 1). Also, skin rashes were observed in one disseminated case.[49] So it is impossible to establish a diagnosis solely based on clinical presentations with these symptoms as they may indicate differential diagnoses, including brain tumour, stroke, tuberculosis, and parasitic and other infections can be made.[50–53] So, there is no specific difference other than a brain abscess. The universally accepted surgical method, which is a burr-hole aspiration, is the treatment of choice, also providing a specimen for culture. Radiological images are characterised by peripheral contrast-enhanced centrally hypointense round shape lesions in T1 MRI sequences. In addition, central necrosis can be seen in spectroscopy and perfusion sequences. Despite characteristic radiographical images, pigmented hyphae and other fungal elements must be present in tissue specimens to confirm the fungal infection.

Regarding laboratory diagnosis, taking direct samples from the infected site, such as pus aspirate, is important to detect the etiologic agent. There are no specific serologic antigens or polymerase chain reaction tests readily available to detect dematiaceous fungi in tissue or blood. CSF culture could be negative[49] and may delay

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TABLE 1 Summary of cases of cerebral phaeohyphomycosis caused by *Rhinocladiella mackenziei*.

		Year of publication	Patient gender/age	Country or nationality	Risk factors or underlying diseases	Clinical presentation
1	[63]	1988	Female/55	Saudi Arabia	-	Headache, generalised tonic–clonic seizures
2	[63]	1988	Male/80	Saudi Arabia		Fever, headache and increasing drowsiness o
3	[63]	1988	Male/60	Saudi Arabia		Left hemiparesis, headache
4	[11]	1993	Male/70	Saudi Arabia	Unknown	Unknown
5	[11]	1993	Male/70	Saudi Arabia	Extensive bowel surgery	Unknown
6	[11]	1993	Female/55	Saudi Arabia	Unknown	Unknown
7	[11]	1993	Female/32	Oman	Renal transplantation	Unknown
8	[11]	1993	Female/75	Saudi Arabia	Renal transplantation	Unknown
9	[11]	1993	Unknown / Unknown	United Arab Emirates	Unknown	Unknown
10	[11]	1993	Female/ about 60	Israel	Unknown	Unknown
11	[11]	1993	Male/55	Qatar	Renal transplantation, fungal eye infection	Unknown
12	[23]	1998	Male/36	Saudi living in United States	Hodgkin's lymphoma and chronic hepatitis B	a 2-week history of right-hand weakness which worsened to involve the entire right upper extremity. a focal motor seizure with rotation of the head and eyes to the right, followed by secondary generalisation
14	[24]	1999	Female/58	Kuwaiti living in United States	Haemodialysis, steroid usage	Decreased memory, right-hand weakness
15	[35]	2000	Female/67	Saudi Arabia	Diabetes mellitus	Headache
16	[35]	2000	Female/65	Saudi Arabia	Hodgkin's lymphoma	Fatigability, palpitations and fever
17	[51]	2001	Male/71	Saudi Arabia	Chronic myelogenous leukaemia	Dizziness and an episode of loss of consciousness
18	[51]	2001	Male/42	Saudi Arabia	Asthmatic bronchitis	Progressive left thumb and index finger weakness that suddenly became worse 2 days before admission
19	[12]	2002	Male/56	Egyptian living in Kuwait	Chronic Hepatitis B	Headache, progressive loss of vision
20	[15]	2005	Male/62	Saudi Arabia	Renal transplantation	Left-sided hemiparesis and hemisensory loss
21	[34]	2007	Female/66	Saudi Arabia	Diabetes mellitus, steroid usage, systemic lupus erythematosus	Decrease level of consciousness and dysarthria
22	[64]	2010	Female/59	Qatar	Breast cancer surgery, chemotherapy	Left-sided hemiparesis of 10 days duration
23	[65]	2010	Male/50	India	Diabetes mellitus	Unknown
24	[25]	2010	Female/80	Afghan living in France	Colon cancer surgery	A transient episode of aphasia
25	[36]	2010	Male/45	Pakistan	Diabetes mellitus, hypertension, paraplegia with bed sores	Fever for one month, slurred speech, dysphagia, right hemiparesis
26	[36]	2010	Male/30	Pakistan	Head injury with tree bark 2 years prior to presentation	Progressive right arm weakness, fever, and vomiting
27	[36]	2010	Male/45	Pakistan	Unknown	Fever, vomiting, and focal deficits
28	[36]	2010	Male/20	Pakistan	20 days postpartum	Fever, headache, vomiting, and right-sided weakness
29	[36]	2010	Male/53	Pakistan	Liver transplantation	Fever, headache, vomiting, and left-sided weakness
30	[36]	2010	Male/75	Pakistan	History of pulmonary tuberculosis	Fever, left-sided hemiplegia since 2 months

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Site of infection/number of abscesses	Surgical intervention	Diagnostic methods	Antifungal therapy[a]	Outcome after diagnosis
Occipital lobe/>	Craniectomy and debridement	Direct microscopy, histopathology, culture[b]	AMB, 5FC	Died after 6 months
Frontal lobe/>1	Aspiration	Direct microscopy, culture[b]	AMB, 5FC, KTC	Died after 2 month
Right parietal region/1	Aspiration	Direct microscopy, culture[b]	AMB, 5FC, KTC	Died after 8 weeks
Unknown/1	Aspiration	Direct microscopy, culture[b]	AMB	Died after 2 weeks
Unknown/>1	Aspiration	Direct microscopy, culture[b]	AMB, 5FC	Died
Unknown/1	Aspiration	Direct microscopy, culture[b]	AMB, 5FC, KTC	Died
Unknown /1	Aspiration	Direct microscopy, culture[b]	Unknown	Unknown
Unknown />1	Aspiration	Direct microscopy, culture[b]	Unknown	Died
Unknown /1	Unknown	Direct microscopy, culture[b]	Unknown	Died
Unknown /1	Aspiration	Aspirated pus was sent to the reference laboratory	Unknown	Unknown
Thalamus/1	Aspiration	Direct microscopy, culture[b]	AMB	Died
Left parietal subcortical region /1	Craniectomy and debridement	Direct microscopy, histopathology, culture[b]	ITC	Died after 8 months
Left parietal subcortical region/>1	Aspiration	Direct microscopy, culture	AMB, ITC	Died after 1 months
Left parietal region/1	Aspiration	Direct microscopy, Culture[b]	AMB	Died after 2 days
Right parietal region /1	Aspiration	Direct microscopy, Culture	AMB	Died after 3 weeks
Right parietal lobe/>1	Craniectomy and debridement	Direct microscopy, culture, histopathology[b]	AMB, ITC	Died after 10 days
Right frontal lobe/1	Craniectomy and debridement	Direct microscopy, culture, histopathology[b]	AMB, FLC, ITC	Died after 2 weeks
Left occipital lobe/1	Aspiration	Direct microscopy, culture, molecular method	AMB	Died after 18 days
Right parieto-frontal region/1	Aspiration, Craniectomy and debridement	Direct microscopy, culture[b]	AMB, ITC, 5FC, POS	Cured
Both side of cerebellum, left frontal lobe, left temporal lobe/>1	Aspiration	Direct microscopy, culture[b]	AMB, VRC	Died after 5 weeks
Right posterior parietal and occipital region />1	Craniectomy and debridement	Histopathology, direct microscopy, culture[b]	AMB, VRC, POS	Died after 58 days
Unknown/1	Craniectomy and debridement	Direct microscopy, culture, molecular method	AMB	Died after 2 weeks
Frontal and left temporal region/>1	Aspiration	Direct microscopy, culture, molecular method[b]	VRC, POS	Died after 7 months
Left middle peduncle, and right periventricular region/>1	Craniectomy and debridemen	Histopathology, direct microscopy, culture, molecular method	AMB, ITC	Died after 1 months
Fronto-parietal lesion/1	Craniectomy and debridement	Histopathology, direct microscopy, culture, molecular method	AMB, ITC	Unknown
Unknown		Histopathology, direct microscopy, culture, molecular method	AMB, ITC	Died after 1 months
Left posterior frontal cortex lesion/>1	Craniectomy and debridement	Histopathology, direct microscopy, culture, molecular method	AMB, ITC	Unknown
Anterior fossa space occupying lesion/1	Craniectomy and debridement	Histopathology, direct microscopy, culture, molecular method	AMB	Died after 2 months
Left frontal lobe ring enhancing lesion/1	Craniotomy	Histopathology, direct microscopy, culture, molecular method	ITC	Died after 4 months

(Continues)

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TABLE 1 (Continued)

		Year of publication	Patient gender/age	Country or nationality	Risk factors or underlying diseases	Clinical presentation
31	[37]	2011	Female/64	Saudi Arabia	Diabetes mellitus	A long-term care facility with chronic respiratory failure
32	[26]	2011	Male/50	Somalian, living in Denmark	B cell lymphoma	ataxia appeared and gradually progressed to right hemiplegia with subsequent rapid clinical deterioration.
33	[66]	2014	Male/54	Iran	History of falling down 2 years ago from a height of 12 meters and he was in coma for 1 month with several bone fractures	fever, frontal headache, dizziness, and facio-brachial tonic–clonic seizures and left-sided hemiparesis
34	[20]	2017	Female/67	Iran	Diabetes mellitus and Behçet's Disease	weakness, lethargy, left sided paresis and radicular pain w
35	[16]	2017	Male/76	Indian, spent 25 years in Nairobi, Kenya, living in the United Kingdom for the past 43 years, recent travel history included Egypt a year previously and Turkey 2 years previously	History of spinal tuberculosis, rheumatoid arthritis and recent dental extractions	7-day history of progressive confusion, disorientation and unsteadiness on his feet
36	[54]	2019	Male/67	Iraq	Renal transplantation	Right-sided facial weakness and expressive dysphasia.
37	[49]	2021	Female/50	Kuwait	Renal transplantation	Febrile neutropenia
38	[17]	2022	Male/57	Unknown	Liver transplantation	Acute onset of nonremitting painless blurred vision
39	[18]	2022	Female/53	Arabic ethnicity	Post–COVID-19	Facial palsy and left hemiparesis
40	[67]	2022	Unknown	India	Post–COVID-19	Neurological deficit
41	[67]	2022	Unknown	India	Renal transplantation	Neurological deficit
42	(Present case)	2023	Male/63	Turkey	-	Right facial hemiparesis, globally increased deep tendon reflexes and dysphasia

[a]Abbreviation: AMB, Amphotericin B; ANIDO, anidulafungin; CASPO, caspofungin; 5FC, 5-flucytosine; FLC, fluconazoleKTC; ITC, itraconazole; ketoconazole; MICA, micafungin; POS, posaconazole; VRC, voriconazole.

[b]*Note*: Strain was sent to the reference laboratory for identification.

TABLE 2 Antifungal susceptibility testing minimal inhibitory concentration (MIC μg/mL) for *Rhinocladiella mackenziei*.

REF.	AmB	FLC	VRC	POS	ITC	5FC	KTC	ANIDO	CASPO
12	>32	32	0.5	-	0.125	16	0.25	-	-
15	1	-	-	≤0.015	≤0.015	16	-	-	-
19	16	-	0.25	0.063	0.125	-	-	-	-
23	1	16	-	-	≤0.015	8	-	-	-
34	0.3	-	≤0.015	≤0.015	≤0.015	4	-	-	-
63	16	-	≤0.03	≤0.03	≤0.03	-	-	4	1
64	16	32	0.5	0.031	0.063	-	-	4	8
Present case	>32	>256	0.032	0.064	0.25	-	-	<0.002	0.002

Abbreviations: AMB, amphotericin B; ANIDO, anidulafungin; CASPO, caspofungin; FLC, fluconazole; 5FC, 5-flucytosine; ITC, itraconazole; KTC, ketoconazole; POS, posaconazole; VRC, Voriconazole.

the diagnosis. Direct microscopy using potassium hydroxide (KOH) is very useful since it allows clear visualisation of the brown pigmented hyphae, and hence the diagnosis of phaeohyphomycosis can be made. The fungus can grow on Sabouraud dextrose medium but has a slow growth rate and could be missed unless cultures are incubated for sufficient time. On culture, the colonies appear in brown to black colour microscopically. Conidiophore arises from brown septate hyphae. Conidia are produced in a sympodial manner, oval in shape, and have a dark basal scar. Serum biomarkers, such as[1–3] beta D-glucan test, are not specific but can be used as a prognostic marker, as shown in the case report.[54] In the cerebral phaeohyphomycosis cases related to *R. mackenziei* reported in the literature,

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Site of infection/number of abscesses	Surgical intervention	Diagnostic methods	Antifungal therapy[a]	Outcome after diagnosis
Deep right posterior frontal and parieto-occipital lobes />1	Aspiration	Direct microscopy, culture[b]	AMB, VRC, CASPO	Died after 34 days
Cerebrum and cerebellum/1	Aspiration	Postmortem PCR analyse	AMB, VRC	Died
Right fronto-parietal region/1	Aspiration	Direct microscopy, culture, molecular method	AMB, ITC	Died after 2 weeks after
2 adjacent frontal irregular ring-enhancing mass lesions/>1	Aspiration	Direct microscopy, culture, molecular method[b]	AMB, VRC, POS	Died after 55 days
Right temporal-occipital region/>1	Craniectomy and debridement	Direct microscopy, culture, molecular method	VRC	Cured
Left posterior frontal lobe/1	Craniectomy and debridement	Direct microscopy, culture, molecular method	AMB, VRC, POS, 5-FC	Unknown
Frontal, parietal and occipital/>1	Aspiration	Direct microscopy, culture, molecular method	AMB	Died
Parieto-occipital/1	Aspiration	Direct microscopy, culture	VRC	Alive
Frontal/1	Craniectomy and debridement	Direct microscopy, culture	AMB, CASPO	Alive
Unknown	Unknown	Culture, molecular method	AMB, VRC and 5FC	Unknown
Unknown	Unknown	Culture, molecular method	AMB, VRC and 5FC	Unknown
Frontal/1	Aspiration, surgical drainage	Direct microscopy, culture, histopathology, molecular method	AMB, VRC	Died after 3.5 months

except for two, the diseases were diagnosed by direct microscopy and culture methods. In one case, postmortem PCR analysis was performed (Table 1).

The identification of this fungus at the specimen level must be confirmed with molecular methods. However, the diagnostic workup can be limited at some hospitals due to the lack of resources available for molecular and susceptibility testing of these rare fungi. For this reason, these hospitals may have to send the strains they cannot identify to reference laboratories (Table 1).

Concerning antifungal therapy, choosing the right agent is challenging, as there are only a few reported cases in the literature, mostly with unfavourable outcomes. Treatments include surgery (abscess puncture), combined antifungal therapy, and immune enhancement, although an isolated lesion can be removed without chemotherapy.[15,55–57] According to the European Society of Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology, joint clinical guidelines for phaeohyphomycosis, a combination treatment of complete excision of the brain abscess and antifungal therapy is recommended.[58] Single cases show that voriconazole and posaconazole can provide clinical improvement in cases where surgical excision is not possible. Triazole, echinocandin, and flucytosine combination therapy can also be applied.[58] It is difficult to make a treatment decision based on in vitro susceptibility when the initial identification cannot be made. Even if in vitro sensitivity was detected to some of the antifungal drugs, they may not be able to cross the blood–brain barrier, or the patient might not tolerate these drugs.[59,60]

Although the broth microdilution method is recommended by The National Committee for Clinical Laboratory Standards for antifungal susceptibility testing, this method is labour-intensive. In addition, some studies have reported that the gradient test (E-test) also represented simple and efficacious results for antifungal susceptibility testing of dematiaceous fungi.[9,20,61] There are eight studies reporting antifungal susceptibility results of *R. mackenziei* strains (Table 2). For these isolates, amphotericin B (AMB) susceptibility appears to be strain-dependent, and fluconazole (FLC) and 5-flucytosine (5-FC) MICs were generally high. However, MIC values against itraconazole (ITC), voriconazole (VRC) and posaconazole (POS) were consistently low. Since we were not able to apply the broth microdilution method, antifungal susceptibility testing of this dematiaceous fungus was performed with the E-test method. Our findings are similar to the drugs mentioned above.

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Badali et al.[22] evaluated ten *R. mackenziei* clinical strains using the reference method and showed that posaconazole had the lowest MICs (0.016–0.063 mg/L), followed by itraconazole (0.063–0.25 mg/L). Voriconazole MIC values were relatively higher (0.25–2 mg/L). Other antifungals, such as amphotericin B and fluconazole, have been shown to have low in vitro activity ranging from 2 to 64 mg/L.[22] Voriconazole, which has good CNS penetration properties, seems inefficient in treating this pathogen, as multiple patients, including ours, who received this drug had a poor outcome,[34,37] except for one patient who was successfully treated by using this agent.[16] On the contrary, posaconazole appears to be promising. Besides its potent in vitro activity,[22] it was also effective in an animal model.[15] However, the CNS concentration of this antifungal is low. According to a recent study by Barde et al.,[62] who examined posaconazole concentration in various CNS tissues in an infected patient, low levels of posaconazole have been found compared to plasma level, which was suggestive of low penetration of posaconazole into the brain and CSF. Despite the low CNS concentration, their patient showed steady clinical improvement. The authors concluded that extensive surgical intervention is required to overcome the drug limitation.[62]

In conclusion, although cerebral phaeohyphomycosis has been recognised for decades, the infection is still poorly understood and can be easily overlooked. *R. mackenziei* infection of the central nervous system is a challenging disease with a high mortality rate. Successful therapy for this serious infection does not seem to be related to surgical intervention, and the available therapy also the optimal antifungal agent have not been identified yet. Our case confirms the hypothesis that this fungus might spread more widely than previously predicted regions. Even if the patient does not have an underlying immunological deficiency or is not in a country that is endemic for this fungus, it should be kept in mind that this fungus may be the causative agent of infection. As the area at risk of *R. mackenziei* cerebral abscess is extending to new countries, clinicians should be aware of this emerging disease and take a detailed travel history in patients with atypical and undocumented brain abscesses. To make the correct diagnosis and start the treatment, managing this rare fungal infection requires a multidisciplinary team effort and support from a specialised mycology laboratory for definitive species identification. Although the colony morphology and microscopic features of these fungi can be helpful for identification, molecular methods are essential for the accurate identification result. Even if laboratories cannot provide molecular methods, they should conserve the strains and try to send them to another equipped laboratory for identification. This data is important to clarify the epidemiologic distribution and transmission of these dematiaceous fungi. Here, we reported the first case of cerebral phaeohyphomycosis caused by *R. mackenziei* in our country. Highlighting documented cases in the literature can increase awareness with gradual progress toward earlier detection. This rare infection has a poor diagnosis and high mortality rate and needs further studies to understand its pathogenesis better.

6 | LIMITATIONS

The limitation of this study is that the antifungal susceptibility test of the strain was not performed with the broth microdilution reference method. However, our results are similar to other cases in the literature.

AUTHOR CONTRIBUTIONS

Ilvana Caklovica Kucukkaya: Methodology; visualization; writing – original draft. **Cafer Ikbal Gulsever:** Data curation; visualization; writing – original draft. **Ilyas Dolas:** Data curation; visualization. **Gonca Erkose Genc:** Writing – review and editing; methodology. **Mert Ahmet Kuskucu:** Methodology. **Pulat Akin Sabanci:** Supervision; writing – review and editing; methodology. **Zayre Erturan:** Supervision; writing – review and editing; methodology.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Informed consent was obtained from the next of kin due to the patient's death.

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