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CASE REPORT

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Chronic *Candida albicans* meningitis misdiagnosed as polymyalgia rheumatica and successfully treated with voriconazole

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Abstract

The outcome of chronic meningitis depends to a large degree on the causative pathogen and the interval between onset of symptoms and diagnosis. We present a patient with a delayed diagnosis and several complications, for whom adequate therapy resulted in a favorable outcome. In a 76-year-old male patient, *Candida albicans* meningitis was diagnosed 4 months after the onset of symptoms. CSF findings (protein >1000 mg/L, predominance of intrathecal immunoglobulin A synthesis, lactate concentrations of approx. 10 mmol/L, leukocyte counts around 1000/µl, variable differential leukocyte counts) resembled tuberculous meningitis. In spite of the long interval without treatment, voriconazole 200 mg every 12 h for 7 weeks followed by fluconazole 300 mg/day maintenance therapy for 7 months led to a recovery with only mild deficits. The case illustrates that 1. *C. albicans* can cause chronic meningitis in patients without severe immune defects, 2. patients can survive *C. albicans* meningitis with mild long-term sequelae even when diagnosis and adequate treatment are delayed, and 3. voriconazole as a sole agent may be suitable for treatment of *C. albicans* meningitis.

KEYWORDS

Candida albicans, case report, cerebrospinal fluid, intrathecal immunoglobulin A synthesis, voriconazole

1 | BACKGROUND

Chronic meningitis presents a diagnostic and therapeutic challenge. In immunocompetent persons, common causative pathogens are *Mycobacterium tuberculosis*, *Treponema pallidum*, *Borrelia burgdorferi sensu lato*, *Listeria monocytogenes*, *Cryptococcus spp.*, *Taenia solium* (cysticercosis), and *Herpes simplex* type 2. Chronic meningitis can be maintained by infectious foci outside the central nervous system (CNS) such as endocarditis or sinusitis, mastoiditis, or otitis. In immunocompromised persons, the spectrum is very broad: in addition to those pathogens

already mentioned above, *Actinomyces spp*., *Nocardia spp*., *Candida spp*., and other fungi, *Toxoplasma gondii*, *Acanthamoeba spp*., *Human immunodeficiency virus* (HIV), *Cytomegalovirus* (CMV), and other human pathogenic herpesviruses can be involved.[1,2] The outcome depends to a large extent on the causative pathogen and the interval between onset of symptoms and diagnosis.[3]

2 | CASE PRESENTATION

The 76-year-old married former storeowner had a history of hypertension, coronary heart disease, and peripheral arterial disease. He presented with a 3-month history of fluctuating headache, fatigue, muscle weakness, elevated body temperature up to 38.3°C, joint pain (in the mandibular joint and others), muscle pain in the proximal upper extremities, temporal region pain with tenderness on palpation, and weight loss of 7 kg. The neurological examination was normal except for signs of sensitivity to pressure on the muscles of the proximal upper extremities, mild distal neuropathy, and essential tremor. Inspection of the eyes, reaction of the pupils, visual acuity, and confrontational visual field testing were normal. Nuchal rigidity was absent. The erythrocyte sedimentation rate was elevated (28 mm, normal ≤10 mm), and the C-reactive protein in plasma was normal (<5 mg/L). Rheumatic factor was <10 IU/ml (normal). Immune electrophoresis was performed and showed a monoclonal IgA gammopathy and a slight elevation of plasma IgA. In 8 blood workups, blood leukocyte count was marginally elevated once (10,600/µl), and blood leukocyte density was normal in the other 7 white blood cell counts carried out. Differential blood cell count showed 1% rod-nucleated granulocytes, 71% segmented granulocytes, 25% lymphocytes, 2% monocytes, 1% myelocytes, and no malignant cells. X-rays of the skull, spinal cord, pelvis, and the proximal limb bones were normal. Further diagnostic workups for suspected infection including repeated blood cultures, *Candida* antigen titer in plasma and transthoracic and transesophageal echocardiography as well as a dental examination were normal. Abdominal ultrasound, gastroduodenoscopy, colonoscopy, thoracic X-ray and computer tomography, and cranial computer tomography to rule out malignant diseases were also normal. The urologist noted benign prostate hyperplasia. The patient refused bone marrow biopsy and lumbar puncture. Because of the pain and sensitivity to pressure of the muscles of the proximal upper extremities, the weight loss and the elevated erythrocyte sedimentation rate, polymyalgia rheumatica was suspected. The patient was treated with prednisolone (initial dose 30 mg/day), experienced rapid relieve of his complaints and was discharged home.

Ten days after the start of prednisolone, that is, approximately 4 months after the onset of clinical symptoms, his clinical status deteriorated with rapid exhaustion while walking. He was admitted again (day 0). On Day 3, he developed fever up to 39°C. Clinical examination now revealed nuchal rigidity. Lumbar CSF (Table 1) contained 1621/µl leukocytes, 2650 mg/L protein, and 9.6 mmol/L lactate. Intrathecal synthesis of immunoglobulin (Ig) A and IgG (IgA >IgG) was noted. CSF microscopy and cultures and PCRs for *Herpes simplex* and *Varicella zoster* viruses, *Mycoplasma pneumoniae*, and the 16s rRNA pan-bacterial PCR were negative. The interferon-γ release assay (IGRA) for *Mycobacterium tuberculosis* was negative. Seven blood cultures performed during the second admission did not grow bacteria or fungi. Cerebral MRI performed 2 days after the second admission revealed a small left cerebellar infarction (and an older infarction on the right side). Spinal T1-weighted magnetic resonance imaging (MRI) on Day 15 showed strong meningeal contrast enhancement as a sign of meningeal inflammation (Figure 1). According to the Guidelines of the German Society for Neurology, treatment was started with ceftriaxone, ampicillin, and acyclovir on Day 3. After further deterioration with fatigue and fever, antibiotic therapy was switched to meropenem and linezolid on Day 15. Despite this therapy, peripheral left facial nerve palsy, dysarthria, and mild left upper limb weakness occurred on Day 17, so that the patient was transferred to the neurological intensive care unit. From Day 17 to Day 20, anti-tuberculosis drugs were added, and then discontinued. Immediately after the patient had been transferred to the intensive care unit, ventricular fibrillation developed, which could be treated successfully with immediate defibrillation. The 3rd and 4th lumbar puncture 15 and 18 days after admission grew *C. albicans* susceptible to amphotericin B, 5-flucytosine, caspofungin, fluconazole, and voriconazole as determined by E-test. On Day 18, voriconazole 200 mg every 12 h was started intravenously for a total of 7 weeks. Thereafter, voriconazole was shifted to oral fluconazole 300 mg/d maintenance therapy for 7 months. Both antifungals were well-tolerated. About 26 days after admission, the patient suffered a myocardial infarction requiring coronary angioplasty. However, after that he steadily recovered and was discharged into a rehabilitation unit on Day 58. He returned home on Day 185 fully oriented, without headache and with a positive attitude to life. Upon discharge from the rehabilitation clinic, the patient needed no help for most of his basic self-care tasks. He needed help to shower, to wash his feet and to put on his stockings and shoes. He was able to walk 100 m with a walking stick.

TABLE 1 CSF findings in *Candida albicans* meningitis

Day	Leukocytes /μl	Differential cell count	Protein [mg/L]	CSF/ serum albumin ratio	Intrathecal Immuno-globulin synthesis	Lactate [mmol/L]	Microscopy	Culture/PCR	Antigen
3	1621	>80% granulocytes	2650	33.2	IgG 61% IgA 79%	9.6	Ø	Ø	ND
8	880	84% granulocytes	2065	31.3	IgG 63% IgA 79%	9.0	Ø	Ø, 16S rRNA PCR Ø	ND
15	5160	85% granulocytes	3726	ND	ND	13.7	Ø	+	Ø
18	859	91% granulocytes	3159	71.3	IgG 50% IgA 71%	11.9	Ø	+	Ø
29	72	63% lymphocytes 16% granulocytes 12% monocytes 9% plasma cells	1066	31.3	IgG 85% IgA 92%	7.6	Ø	Ø	Ø
54	188	49% lymphocytes 40% granulocytes 7% monocytes 4% plasma cells	1370	15.0	IgG 77% IgA >85%[a] IgM 50%	4.6	+	ND	ND
61	77	89% lymphocytes 3% granulocytes 3% monocytes 5% plasma cells	1059	12.3	IgG 84% IgA >89%[a] IgM 62%	6.8	Ø	Ø, 18S rRNA PCR Ø	Ø
142	18	80% lymphocytes 4% granulocytes 14% monocytes 2% plasma cells	468	5.3	IgG 74% IgA 89% IgM 58%	4.0	Ø	ND	ND
192	33	ND	1372	14.5	IgG 72% IgA >84%[a] IgM 48%	2.6	ND	ND	ND
303	3	ND	256	ND	ND	1.7	Ø	Ø	Ø

Abbreviation: ND, not determined.

[a]Intrathecal IgA synthesis not quantified exactly due to analytical problems.

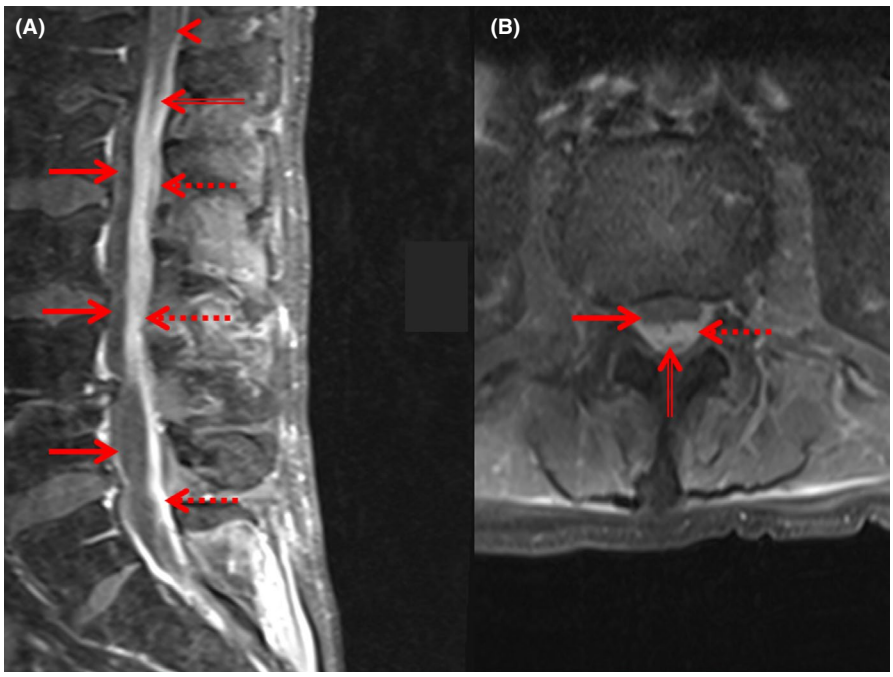

FIGURE 1 Spinal magnetic resonance imaging (MRI) in a 76-year-old man with chronic *Candida albicans* meningitis. T1-weighted MRI (A: sagittal section; B: transversal section) revealed strong meningeal contrast enhancement as a sign of meningeal inflammation. ⟶ Cerebrospinal fluid. ⟹ Fibers of the equine cauda. ⋯→ Strong meningeal contrast enhancement indicating pus in the spinal subarachnoid space. > Conus medullaris

3 | DISCUSSION

In adults, *Candida spp*. usually cause brain abscesses or (sub)acute meningitis. In preterm infants and neonates, meningitis is the most common form of *Candida spp*. infection of the CNS.[4] Patients predisposed to *Candida spp*. infections of the CNS are preterm infants and neonates with an immature immune system, patients immunosuppressed by HIV, hepatitis C and heroin addiction, neutropenic patients, patients receiving immunosuppression after organ transplantation and chemotherapy for malignancies,[4-11] and patients after neurosurgery.[12] The most frequent species isolated is *C. albicans*, but other species including *C. tropicalis*, *C lusitaniae*, and *C. dubliniensis* can also cause meningitis.[4,9,10]

Chronic meningitis is an uncommon manifestation of *Candida spp*. infection. On rare occasions, it can affect persons without known immunosuppression: in 18 patients with a history of *Candida spp*. meningitis up to 8 months, an apparent underlying risk factor for *Candida* meningitis was present in 13 (10 adults: hematologic malignancies, AIDS, intravenous drug abuse, diabetes mellitus, bacteremic *Haemophilus influenzae* pneumonia requiring artificial ventilation, colon carcinoma; 3 infants) and absent in five cases.[13] The five adults without apparent risk factor were 23- to 49-year-old (median 30 years), and in four of these cases, diagnosis was made at autopsy.[13] Headache, fever, malaise, and nuchal rigidity were the predominant clinical findings. Analysis of CSF showed mononuclear or neutrophilic pleocytosis, an elevated protein level, and a decreased level of glucose.[13] In the present case, neutrophils predominated initially, whereas in the course of the disease a shift toward lymphocyte preponderance was noted (Table 1). In only 3 of 18 cases (17%) were *Candida spp*. detected in CSF by microscopy, and only 44% of the initial CSF cultures grew *Candida spp*..[13] In four cases, *Candida spp*. were only cultured with special culture techniques, and in three cases, CSF cultures repeatedly were negative.[13] When the diagnosis was missed, the outcome was eventually fatal[8,13]: of 12 patients who were treated, 4 died (33%).[13] As in the present case, CSF findings in chronic meningitis caused by *Candida spp*. resembled cerebral tuberculosis or cryptococcosis (high CSF protein and lactate concentrations, variable differential leukocyte counts).[13] Predominant intrathecal IgA synthesis (IgA > IgG > IgM), as observed in the present case, is considered typical for tuberculous meningitis.[14] The spectrum of causative pathogens of community-acquired meningitis in older adults is broader than in adolescents and young adults.[15] We hypothesize that this is a consequence of immunosenescence.[16] *Candida spp*., however, are no typical pathogens causing meningitis in immunocompetent old persons.[15] Previous reports of other patients aged ≥75 years with the diagnosis of *Candida spp*. meningitis had some form of immunosuppression, for example, diabetes mellitus,[17] or debilitating hemorrhagic stroke.[18] Immunosuppression caused by treatment with prednisolone in the present case probably contributed to the rapid deterioration of the pre-existing Candida CNS infection after the first discharge.

Most fungi and bacteria that can infect the CNS, without adequate treatment rapidly cause severe injury

to the brain and spinal cord leading to severe sequelae and rapid death. Unlike *Aspergillus spp*. and *Mucor spp*. which frequently infiltrate and occlude vessels, causing cerebral infarctions, *Candida spp*. infections either lead to meningitis, meningoencephalitis, or brain abscess,[4] but rarely are responsible for vasculitis. In the present case, in spite of the long interval from the onset of symptoms to the start of effective treatment, only a small cerebellar infarction which did not cause long-term deficits was noted in cerebral MRI. The low predilection to infiltrate vessels or destroy nervous tissue is probably the reason why chronic meningitis by *Candida spp*. can be overcome without severe sequelae, even when—as in the present case—diagnosis and treatment is delayed. However, to the best of our knowledge, no spontaneous cure without appropriate antifungal treatment is possible.[8,13]

New molecular methods may facilitate the diagnostic evaluation of chronic meningitis.[2] In the present case, we did not use next-generation sequencing. Therefore, it remains unclear whether this method would have speeded up the identification of the pathogen.

Our patient was treated with voriconazole as a sole antifungal agent. The standard treatment for *C. albicans* meningitis in adults is intravenous liposomal amphotericin B often combined with intravenous or oral flucytosine and followed by fluconazole when the patient has improved and when the isolate is susceptible to fluconazole.[19-21] In a recent study on *Candida spp*. CNS infections after neurosurgical interventions, all patients were treated with azole antifungals alone (fluconazole and/or voriconazole) in addition to the removal of foreign intracranial materials, and 8 out of 9 patients survived.[22] An infant with *C. glabrata* meningitis was rescued by voriconazole after other antifungals had failed.[23] However, treatment failure due to the loss of voriconazole susceptibility of *C. tropicalis* during treatment has also been reported in an immunocompetent adult with a ventriculo-peritoneal CSF shunt infection.[24] The *C. albicans* strain isolated in the present patient was susceptible to voriconazole. Voriconazole was chosen, because tuberculous meningitis was suspected, and the patient received quadruple antituberculous therapy when antifungal therapy was started. By choosing voriconazole, in the present case, the treating physicians wanted to limit the side effects of a combined antituberculous and antifungal therapy. When the diagnosis *C. albicans* meningoencephalitis was firmly established, the patient had improved and there was no need to switch antifungal therapy from the well-tolerated voriconazole to an antifungal combination with more potential adverse effects. Taken together with other reported cases,[22,23] the disease course in our patient illustrates that *C. albicans* meningoencephalitis indeed may be successfully treated by voriconazole alone.

The weakness of this case report is the uncertainty whether the symptoms leading to the first admission truly were symptoms of chronic *C. albicans* meningitis. The patient suffered from fluctuating headache, fatigue, and elevated body temperature. These symptoms were almost identical to those reported in a 72-year-old woman with a history of *C. albicans* meningitis of 8 months.[13] Nuchal rigidity was absent in our patient. However, in geriatric patients, even in bacterial meningitis nuchal rigidity is not as sensitive nor as specific a sign as in younger patients.[25] Since after successful treatment headache, fatigue, and elevated body temperature had disappeared, we are confident that the initial symptoms indeed were caused by *C. albicans* meningitis. The misdiagnosis of polymyalgia rheumatica was a consequence of the symptoms muscle pain in the proximal upper extremities, temporal region pain with tenderness on palpation, fatigue, elevated body temperature up to 38.3°C, and weight loss considered typical for this disease.[26]

4 | CONCLUSION

Several lessons can be learned from this case. First, *C. albicans* can cause chronic meningitis in patients without severe immune defects. Second, patients can survive *C. albicans* meningitis with mild long-term sequelae, even when diagnosis and adequate treatment is delayed. Third, CSF findings in *Candida* meningitis can resemble those encountered in tuberculous meningitis, including predominance of intrathecal IgA synthesis. Finally, voriconazole as a sole agent may be well suitable to treat *C. albicans* meningitis.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

I.G. and R.N. wrote the first draft of the manuscript. U.G. contributed the microbiological data, P.L. the CSF analytical data, H.H.R. the neuroradiological data, and E.B. the rehabilitative expertise. All authors discussed and revised the manuscript and phrased the final form.

CONSENT

Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. Confidential patient data cannot be shared.

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