CASE REPORTS

Fatal-Stroke Syndrome Revealing Fungal Cerebral Vasculitis Due to *Arthrographis kalrae* in an Immunocompetent Patient

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We report an uncommon clinical presentation of a unique case of fatal invasive fungal cerebral vasculitis due to *Arthrographis kalrae* in a nonimmunocompromised host. The identity of the fungus was determined by morphological characteristics and by analysis of internal transcribed spacer 1 sequences and was confirmed by postmortem examination of the brain tissues. Establishing rapidly the link between the clinical syndromes and the fungal infection of the central nervous system is essential to improve the outcome. As our case has shown, it is more challenging to make a diagnosis of fungal infection when there are no risk factors of immunodeficiency and when the clinical presentation seems uncommon.

CASE REPORT

A 39-year-old man, a cattle breeder, presented to the emergency department with a 1-month history of acute sinusitis, fever (temperature up to 39°C), dyspnea, cough with purulent sputums, and weakness. His past medical history was significant for malnutrition (body mass index, 16), chronic sinusitis, tobacco use, and alcohol abuse. A diagnosis of left pleuropneumonia caused by *Streptococcus pneumoniae* was supported by a positive urine *S. pneumoniae* antigen identification, a positive blood culture, and a positive culture from a protected-specimen brush. The patient was treated with amoxicillin for 2 weeks. The patient improved under treatment and mechanical ventilation for 10 days, and he was discharged from the intensive care unit on day 15. Serological tests for human immunodeficiency virus type 1 (HIV-1) and 2 (HIV-2) were negative. On day 16, the patient exhibited fever and a complete left hemiplegia. Magnetic resonance imaging (MRI) confirmed an extended right frontal stroke and showed a right frontal sinus-hemiplegia. Magnetic resonance imaging (MRI) confirmed an extended right frontal stroke and showed a right frontal sinus-hemiplegia. Magnetic resonance imaging (MRI) confirmed an extended right frontal stroke and showed a right frontal sinus-hemiplegia. Magnetic resonance imaging (MRI) confirmed an extended right frontal stroke and showed a right frontal sinus-hemiplegia. Magnetic resonance imaging (MRI) confirmed an extended right frontal stroke and showed a right frontal sinus-hemiplegia.

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Unfortunately, the outcome was marked within the week by an alteration of mental status requiring intubation and mechanical ventilation, the onset of a right hemiplegia, and finally by associated signs consistent with brain death confirmed by two flat electroencephalograms.

**Microbiology.** The initial CSF analysis suggested aseptic meningitis. A moderate growth of yeast-like colonies was observed after 9 days of culture of the CSF sample on chocolate agar plates supplemented with Polyvitex (BioMérieux, France) and incubation at 37°C with 5% CO₂. The isolate was subcultured onto various media (Chromagar BBL, Sabouraud agar, and potato dextrose agar), and a slide culture was done on 2% malt agar. Temperature studies performed on Sabouraud agar showed a slow growth of the isolate at 25°C, 30°C, 37°C, and 42°C. The colonies were initially mucoid, with a yeast-like appearance. They became hairy due to formation of hyphae after 3 days of incubation on Chromagar BBL (Fig. 2A) and Sabouraud medium at 30°C. After 5 days of incubation at 30°C, the colonies became pale yellow (Sabouraud agar and potato dextrose agar). The isolate was resistant to cycloheximide, and the urease activity was positive. The carbon assimilation patterns using ID32C (code 3511300417 E-) and 50CH were unknown in the manufacturer's databases (BioMérieux, Marcy-l’Etoile, France). Identification of the species *Arthrographis kalrae* was done based on phenotypic characteristics and microscopical morphology after 6 days at 30°C of slide culture in 2% malt agar using the description established by Sigler and Carmichael (11) and by de Hoog (6). The slide culture showed characteristic one-celled, hyaline, smooth-walled, and cylindrical arthroconidia formed by differentiation of undifferentiated hyphae (Fig. 2B). The mature arthroconidia were elongated. Furthermore, lateral spherical blastoconidia formed directly on hyphae or on short pedicels were observed.

The identification of *A. kalrae* was confirmed by sequencing the internal transcribed spacer 1 (ITS1) region of the ribosomal DNA gene using universal primers ITS1 and ITS2 (15).
The ITS1 region nucleotidic sequence (GenBank accession no. EU513380) was compared with those published so far in GenBank (for example, accession no. AB213455, AB213456, and AB213445) and had 99% similarity over 229 bp. The MICs of amphotericin B (0.125 μg/ml), flucytosine (64 μg/ml), fluconazole (16 μg/ml), itraconazole (0.5 μg/ml), voriconazole (0.25 μg/ml), and caspofungin (4 μg/ml) were determined using the EUCAST method (12).

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FIG. 1. Cerebral MRI showing a right frontal sinusitis (white arrowheads) and a recent right frontal lobe infarct (black arrowheads).

FIG. 2. (A) Colonies of *Arthrographis kalrae* on Chromagar BBL plates after 3 days of incubation at 25°C. Colonies were initially mucoid. (B) Lactophenol cotton blue stain showing the arthroconidia of *Arthrographis kalrae* (Nomarski interphase contrast; original magnification, ×1,000) after slide culture on 2% malt agar (6 days of incubation at 25°C).
Histopathological studies. The invasive fungal infection of the central nervous system (CNS) was confirmed by autopsy. Postmortem examination of the brain tissues revealed a necrotizing arteritis (Fig. 3A) and confluent fungal hyphae, sometimes dividing into arthroconidia, massively invading the meningeal space and infiltrating the brain arteries (Fig. 3B, C, and D). No other anatomic site was involved. The thrombosis, consecutive to necrosis of the arterial wall, was responsible for cerebral infarcts and for fatal-stroke syndrome. The brain was not submitted to microbiological culture.

Discussion. Arthrographis kalrae is an ascomycete. Arthrographis is a genus linked to Malbranchea; because of the presence of arthroconidia, it resembles Oidiodendron, but the conidiophores of Arthrographis lack the characteristic pigmentation. Furthermore, the arthroconidia of Arthrographis are smooth walled and lack the connectives between maturing conidia that are prominent in Oidiodendron (11). The characteristic of the species is the presence of one-celled, hyaline, smooth-walled, and cylindrical arthroconidia directly formed by fragmentation of undifferentiated hyphae or for the fresh cultures by disjunction and segmentation of hyaline fertile branches borne at the apex of the conidiophore (10, 13). Mature arthroconidia become bigger and elongated. In addition, single-celled, hyaline, smooth, spherical blastoconidia occurred directly on the sides of undifferentiated hyphae or on short pedicels. A. kalrae grows at 42°C and is urease positive. Of note, Pithoascus langeronii (synonym Eremomyces langeronii) was initially described as the teleomorph of A. kalrae, but in 1996, Gené et al. (8) showed that the molecular data did not support the connection between A. kalrae and E. langeronii and that two different species might be concerned.

Before appearance of the characteristic morphology, the presence of yeast-like colonies and arthroconidia in A. kalrae evoked more common species such as Trichosporon and Geotrichum species. Unlike Arthrographis and Trichosporon species, Geotrichum species are urease negative. Trichosporon species lack conidiophores, and Trichosporon assimilates a lot of carbon sources, which is not the case for Arthrographis. Finally,
This fungus, under the obsolete synonym of Oidiodendron kalrai, has been documented as a human pathogen in cutaneous and subcutaneous infections in France and India and New Zealand, keratitis mimicking corneal infection due to free-living amoebae in the United States, and panophthalmitis associated with invasive sinusitis in China. Few cases have been reported in HIV patients, including an onyxis in France and a pansinusitis associated with meningitis and vasculitis in the United States.

We report a stroke syndrome due to A. kalrae, in a patient without severe immunodeficiency (no neutropenia, HIV negative, normal blood picture, no detectable malignancy, no current or past chemotherapy, no immunosuppressive drugs, and no diabetes mellitus). The only factors which could have contributed to the infection by an opportunistic fungal pathogen were chronic alcoholism, malnutrition, and recent severe bacterial pneumonia.

Invasive fungal infections of the CNS are diagnosed in both immunocompromised and immunocompetent hosts. The most common causes of these infections are cryptococcosis, aspergillosis, zygomyces, histoplasmosis, coccidioidomycosis, phaeohyphomycosis, and scedosporiosis. Other fungi such as A. kalrae are involved only exceptionally. As shown here, however, it is more challenging to make a diagnosis of fungal infection when there are no risks factors of immunodeficiency and when the clinical presentation seems uncommon. In patients with persistent and worsening symptoms and who do not have a clear diagnosis, repeat lumbar puncture with CSF analysis may be indicated. In case of negative bacterial culture of the CSF, evaluation should include a CSF analysis with removal of a large volume of fluid for fungal and mycobacterial cultures onto various specific media and imaging of the CNS and sinuses with MRI.

**Nucleotide sequence accession number.** The isolate obtained in this study has been deposited in the Central Bureau voor Schimmelsculture (Utrecht, The Netherlands) (accession number CBS 123312).

**REFERENCES**