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CASE REPORT

RHINOCLADIELLA SIMILIS A RARE CAUSE OF CHRONIC RECURRENT LYMPHOCYTIC MENINGITIS- A CASE REPORT

Prashant Mule., Niranjan Patil and Seema Gaikwad

Department of Microbiology and Molecular Microbiology, Metropolis Healthcare Ltd, Mumbai, India- 400 070

A R T I C L E I N F O

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A B S T R A C T

Phaeohyphomycosis is a rare but frequently fatal fungal infection caused by neurotropic black fungi belonging to the ascomycete order *Chaetothyriales*: *Cladophialophora* species, *Rhinocladiella* species and *Exophiala dermatitidis.* An 8 year boy old presented with recurrent headache and fever, lumbar puncture done thrice over the course of 3 months. CSF cytology was consistent with lymphocytic pleocytosis, raised protein and hypoglycorrhachia. CSF was subjected to panfungal DNA detection by PCR followed by fungal identification by DNA sequencing. The assay targets multicity genes, the ribosomal DNA (rDNA) genes (18S, 28S, and 5.8S) and the intervening internal transcribed spacer (ITS) regions (ITS1 and ITS2). Initial CSF sample submitted identified the etiologic agent as *Rhinocladiella similis* since it presented sequence identity at 99% and coverage at 100% with total score of 1000. As *Rhinocladiella* species are rare cause of chronic recurrent lymphocytic meningitis we had requested to submit repeat CSF specimens. Subsequent CSF sample submitted, identified the same etiologic agent on DNA sequencing. Here we present an unusual case of *Rhinocladiella similis,* a rare cause of chronic recurrent lymphocytic meningitis.

INTRODUCTION

Mycelial fungi (molds) are ubiquitous organisms found in soil, water, and decaying vegetation[1]. Respiratory tract is the most common route of entry, with subsequent haematogenous dissemination to the central nervous system (CNS). Direct inoculation of CNS or paraspinal tissue as a result of surgery, trauma, intravenous drug use, or contaminated medical supplies may also occur in immunocompetent persons. Phaeohyphomycosis is an uncommon but fatal fungal infection mainly due to neurotropic black fungi belonging to the ascomycete order *Chaetothyriales*: *Cladophialophora* species, *Rhinocladiella* species and *Exophiala dermatitidis*[2,3]. The infection may occur in immunosuppressed patients following inhalation of conidia. A high proportion of primary cerebral and intracranial infections is reported in apparently immunocompetent individuals without any obvious predisposing factors. Mortality may be as high as 100% within weeks, months, or years if left untreated[4]. For treatment of cerebral phaeohyphomycosis, in vivo and in vitro studies and single cases suggest that iatraconazole, voriconazole and posaconazole may provide better outcome[5, 6]. Rhinocladiella species are found to be resistant to Amphotericin B. Combination of a triazole plus an echinocandin and or flucytosine has shown better efficacy than monotherapy alone. For those who are treated, mortality is lower than without treatment but the prognosis continues to be poor, with a case fatality rate up to 70%. Here we present an unusual case of *Rhinocladiella similis* a rare cause of chronic recurrent lymphocytic meningitis in an 8 year old boy.

Corresponding author:* **Prashant Mule
Department of Microbiology and Molecular Microbiology, Metropolis Healthcare Ltd, Mumbai, India- 400 070

Case

An 8 year old boy with normal birth and development, third standard student with good scholastic performance was apparently normal till 4 months back when he presented with headache, fever, irritability and abdominal pain of 5-6 days duration to a local hospital. Evaluation at the time was consistent with dengue fever and patient was managed conservatively with intravenous fluids and electrolytes. Subsequently due to relapse of similar symptoms, within a week, patient was re-evaluated and managed on the lines of partially treated bacterial meningitis and then after a clinical worsening two weeks later in the form of an altered sensorium. He was initiated on anti-tubercular drugs with tapering steroids from his local hospital. Patient was referred to tertiary care centre for further evaluation after 4 months of disease onset while on continuation phase of anti-tubercular drugs. Examination revealed an alert intelligent child with normal fundus, no meningeal signs of irritation and no neurologic deficit. Laboratory parameters and imaging done previously were reviewed. Lumbar puncture and CSF done thrice over the

course of 3 months was consistent with tubercular aetiology in the form of lymphocytic pleocytosis, raised protein and hypoglycorrhachia. Serial CSF examination did not show any improvement in the laboratory parameters. On clinical examination, heart rate- 90/min, respiratory rate- 18/min, weight- 39.4 Kg. Systemic examination, S1 and S2 +, no murmer, chest was clear. On neurological examination, GCS score 15/15, conscious, interactive and playful, speech normal, cranial nerve examination was normal. Fundus examination showed no pappilledema, no ptosis and nystagmus, pupils were bilaterally equal and reacting to light, no facial asymmetry found. Motor system examination showed power 5/5 in all four limbs. No cerebellar signs. Serological markers like HBsAg, HCV and HIV were non-reactive. Haemoglobin 13.9 Gms/dl, Total count 9100 cells/mm^3 with lymphocytes 62%, eosinophils 2%, and neutrophils 36%. Prothrombin time 14.9 seconds with INR 0.90. Random glucose 75 mg%, serum urea nitrogen 9 mg%, serum potassium 3.3 mEq/L, serum sodium 135 mEq/L, Serum creatinine 0.44 mg/dL, SGOT 14 IU/L. SGPT 30 IU/L, total bilirubin 0.3 mg%, total proteins 6.9 gm%, serum LDH 195 IU/L, creatinine phosphokinase 34 IU/L, calcium 9.3 mg/dL. TSH 3.64 mIU/ml, FT3 5.81 pmol/L, FT4 15.33 pmol/L. CSF VDRL was Non-reactive, India ink preparation did not show any capsulated yeast. Serum Lyme Borrelia burgdorferi IgM and IgG antibody were negative. ANA profile negative, Anti ds DNA, APLA, ANCA negative, serum Angiotensin converting enzyme (ACE) level 13.9 U/L, tumour markers CA 19.9, Serum AFP and serum CEA were negative. Serum LDH levels were 198 IU/L. MRI of Brain was essentially normal except for small evidence of old blood in the form of blooming in the cerebellar folia. MRI spine screening was normal. Digital subtraction angiography study showed no significant abnormality in intracranial vessels. No evidence of steno occlusive lesion or aneurysm seen. On neuropsychology evaluation on the Wechsler Intelligence Scale for Children (*WISC) he* obtained Full Scale IQ (FSIQ) of 112. CSF cytological evaluation showed total count of 2 cells/mm^3, no polymorphs, no RBCs with 100% lymphocytes (lymphocytic pleocytosis). CSF glucose- 41 mg%, protein- 39 mg%, chloride- 720 mg%. Routine aerobic and tuberculosis liquid culture were sterile on 42 days of incubation. CSF adenosine deaminase (ADA) levels were 0.1 U/L. Nucleic acid amplification tests like Gene x pert and TB PCR, CMV, HIV, enterovirus and herpesvirus PCR were negative. CSF was subjected to panfungal DNA detection by PCR (Table.1) followed by fungal identification by DNA sequencing.

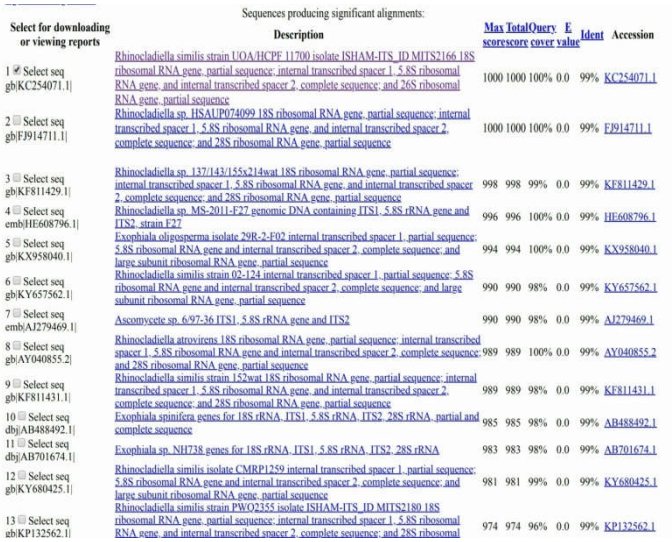
Table 1 Steps of PCR with temperatures and corresponding holding time

Steps	Temperature	Time
Initial Denaturation	95ºC	5 Minutes
30 cycles	95 ºC, 58 ºC, 72 ºC	30 Sec, 45 Sec, 1 Minute
Final Extension	72 ºC	10 Minutes
Hold	4 ºC	-

The assay targets multicity genes, the ribosomal DNA (rDNA) genes (18S, 28S, and 5.8S) and the intervening internal transcribed spacer (ITS) regions (ITS1 and ITS2). Initial CSF sample submitted identified the etiologic agent as *Rhinocladiella similis* since it presented sequence identity at 99% and coverage at 100% with total score of 1000. As *Rhinocladiella* species are rare cause of chronic reccurrent meningitis we had requested to submit repeat CSF specimens. Subsequent CSF samples submitted identified the same etiologic agent on pan fungal DNA sequencing following DNA extraction.

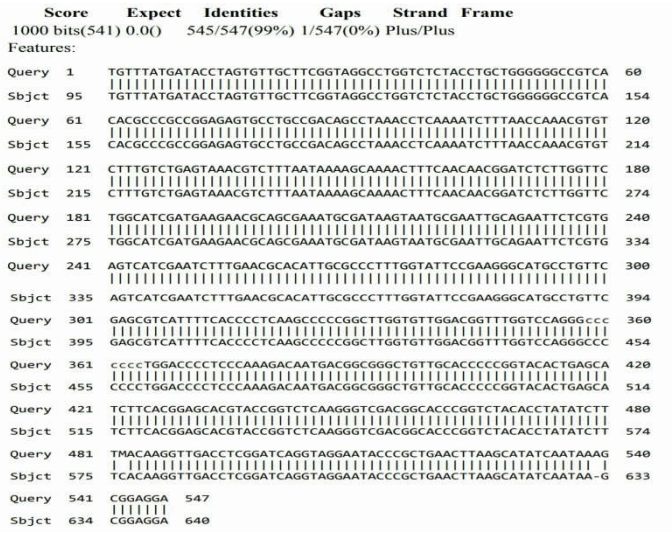
Table 2 Cycle sequencing conditions with corresponding time and temperatures

Steps	Temperature	Time
Initial Denaturation	96ºC	1 Minute
25 cycles	96 ºC, 50 ºC, 60 ºC	10 Sec, 05, Sec, 1 Minute
Hold	4 ºC	-


Sequences producing significant alignments:

Select for downloading or viewing reports	Description	Max score	Total score	Query cover	E value	Ident	Accession
1 Select seq gb|KC254071.1|	Rhinocladiella similis strain UOA/HCPF 11700 isolate ISHAM-ITS_ID MITS2166 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, complete sequence; and 26S ribosomal RNA gene, partial sequence	1000	1000	100%	0.0	99%	KC254071.1
2 Select seq gb|FJ914711.1|	Rhinocladiella sp. HSAUP074099 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, complete sequence; and 28S ribosomal RNA gene, partial sequence	1000	1000	100%	0.0	99%	FJ914711.1
3 Select seq gb|KF811429.1|	Rhinocladiella sp. 137/143/155x214wat 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, complete sequence; and 28S ribosomal RNA gene, partial sequence	998	998	99%	0.0	99%	KF811429.1
4 Select seq emb|HE608796.1|	Rhinocladiella sp. MS-2011-F27 genomic DNA containing ITS1, 5.8S rRNA gene and ITS2, strain F27	996	996	100%	0.0	99%	HE608796.1
5 Select seq gb|KX958040.1|	Exophiala oligosperma isolate 29R-2-F02 internal transcribed spacer 1, partial sequence; 5.8S ribosomal RNA gene and internal transcribed spacer 2, complete sequence; and large subunit ribosomal RNA gene, partial sequence	994	994	100%	0.0	99%	KX958040.1
6 Select seq gb|KY657562.1|	Rhinocladiella similis strain 02-124 internal transcribed spacer 1, partial sequence; 5.8S ribosomal RNA gene and internal transcribed spacer 2, complete sequence; and large subunit ribosomal RNA gene, partial sequence	990	990	98%	0.0	99%	KY657562.1
7 Select seq emb|AJ279469.1|	Ascomycete sp. 6/97-36 ITS1, 5.8S rRNA gene and ITS2	990	990	98%	0.0	99%	AJ279469.1
8 Select seq gb|AY040855.2|	Rhinocladiella atrovirens 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene and internal transcribed spacer 2, complete sequence; and 28S ribosomal RNA gene, partial sequence	989	989	100%	0.0	99%	AY040855.2
9 Select seq gb|KF811431.1|	Rhinocladiella similis strain 152wat 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, complete sequence; and 28S ribosomal RNA gene, partial sequence	989	989	98%	0.0	99%	KF811431.1
10 Select seq dbj|AB488492.1|	Exophiala spinifera genes for 18S rRNA, ITS1, 5.8S rRNA, ITS2, 28S rRNA, partial and complete sequence	985	985	98%	0.0	99%	AB488492.1
11 Select seq dbj|AB701674.1|	Exophiala sp. NH738 genes for 18S rRNA, ITS1, 5.8S rRNA, ITS2, 28S rRNA	983	983	98%	0.0	99%	AB701674.1
12 Select seq gb|KY680425.1|	Rhinocladiella similis isolate CMRP1259 internal transcribed spacer 1, partial sequence; 5.8S ribosomal RNA gene and internal transcribed spacer 2, complete sequence; and large subunit ribosomal RNA gene, partial sequence	981	981	99%	0.0	99%	KY680425.1
13 Select seq gb|KP132562.1|	Rhinocladiella similis strain PWO2355 isolate ISHAM-ITS_ID MITS2180 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, complete sequence; and 28S ribosomal	974	974	96%	0.0	99%	KP132562.1

Fig.1 NCBI Blast presenting sequences producing significant alignment


Score Expect Identities Gaps Strand Frame
1000 bits(541) 0.0() 545/547(99%) 1/547(0%) Plus/Plus
Features:

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Query  1    TGTTTATGATACCTAGTGTTGCTTCGGTAGGCCTGGTCTCTACCTGCTGGGGGGCCGTCA  60
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  95   TGTTTATGATACCTAGTGTTGCTTCGGTAGGCCTGGTCTCTACCTGCTGGGGGGCCGTCA  154

Query  61   CACGCCCGCCGGAGAGTGCCTGCCGACAGCCTAAACCTCAAAATCTTTAACCAAACGTGT  120
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  155  CACGCCCGCCGGAGAGTGCCTGCCGACAGCCTAAACCTCAAAATCTTTAACCAAACGTGT  214

Query  121  CTTTGTCTGAGTAAACGTCTTTAATAAAAGCAAAACTTTCAACAACGGATCTCTTGGTTC  180
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  215  CTTTGTCTGAGTAAACGTCTTTAATAAAAGCAAAACTTTCAACAACGGATCTCTTGGTTC  274

Query  181  TGGCATCGATGAAGAACGCAGCGAAATGCGATAAGTAATGCGAATTGCAGAATTCTCGTG  240
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  275  TGGCATCGATGAAGAACGCAGCGAAATGCGATAAGTAATGCGAATTGCAGAATTCTCGTG  334

Query  241  AGTCATCGAATCTTTGAACGCACATTGCGCCCTTTGGTATTCCGAAGGGCATGCCTGTTC  300
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  335  AGTCATCGAATCTTTGAACGCACATTGCGCCCTTTGGTATTCCGAAGGGCATGCCTGTTC  394

Query  301  GAGCGTCATTTTCACCCCTCAAGCCCCCGGCTTGGTGTTGGACGGTTTGGTCCAGGGccc  360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  395  GAGCGTCATTTTCACCCCTCAAGCCCCCGGCTTGGTGTTGGACGGTTTGGTCCAGGGCCC  454

Query  361  ccccTGGACCCCTCCCAAAGACAATGACGGCGGGCTGTTGCACCCCCGGTACACTGAGCA  420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  455  CCCCTGGACCCCTCCCAAAGACAATGACGGCGGGCTGTTGCACCCCCGGTACACTGAGCA  514

Query  421  TCTTCACGGAGCACGTACCGGTCTCAAGGGTCGACGGCACCCGGTCTACACCTATATCTT  480
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Sbjct  515  TCTTCACGGAGCACGTACCGGTCTCAAGGGTCGACGGCACCCGGTCTACACCTATATCTT  574

Query  481  TMACAAGGTTGACCTCGGATCAGGTAGGAATACCCGCTGAACTTAAGCATATCAATAAAG  540
            | ||||||||||||||||||||||||||||||||||||||||||||||||||||||||| |
Sbjct  575  TCACAAGGTTGACCTCGGATCAGGTAGGAATACCCGCTGAACTTAAGCATATCAATAA-G  633

Query  541  CGGAGGA  547
            |||||||
Sbjct  634  CGGAGGA  640
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Fig 2 Rhinocladiella similis strain UOA/HCPF 11700 isolate ISHAM-ITS_ID MITS2166 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, complete sequence; and 26S ribosomal RNA gene, partial sequence.

DISCUSSION

Dematiaceous fungi are a group of molds characterized by the presence of melanin-like pigment within the cell wall that is pale brown to black. These organisms can be pathogens to plants or livestock. These agents are responsible for chromoblastomycosis and phaeo-hypomycosis. They may also produce black-grain mycetoma. Dematiaceous fungi cause

deeply invasive infections (phaeo-hyphomycosis), including infections of the central nervous system. Most of the agents causing phaeohyphomycosis grow very slowly on routinely used fungal culture media. Conventional mycologic identification can take around 3 weeks or longer. In comparison with aspergillus, mucorales, and fusarium, dematiaceous molds commonly cause infections of the CNS in immunocompetent hosts. Some dematiaceous molds within a narrow geographic range cause cerebral phaeohyphomycosis. Clade Exophialia spinifera contains several morphologically and genetically identical species, being Rhinocladiella similis one of them as an agent of cerebral phaeo-hypomycosis and chrmoblastomycosis. With recent advances in the molecular biology techniques, it has been possible to identify and characterise these pathogenic molds based on DNA-DNA hybridization[7, 8]. Conventionally, fungal identification is based on observation of microscopic characteristics, morphological identification on slide culture, pigment production and temperature variation. This has led to incorrect and prolonged fungal identifications[9]. It is not always possible to identify the fungus at a species level based on morphological characteristics. Some of the fungi are common laboratory contaminants leading to under or overestimation of the number of infective cases as there is lack of confidence in reporting such fungi in routine clinical practice. Panfungal DNA detection is a PCR based test for detection of fungi by panfungal PCR followed by fungal identification by DNA sequencing. The assays targets multicopy genes, the ribosomal DNA (rDNA) genes (18S, 28S, and 5.8S) and the intervening internal transcribed spacer (ITS) regions (ITS1 and ITS2).

Conventional PCR: Polymerase Chain Reaction (PCR) is a molecular biology technique that allows for quick replication of DNA. With PCR, minute quantities of genetic material can be amplified millions of times within a few hours allowing for the rapid and reliable detection of infectious agents. The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers (short DNA fragments) containing sequences complementary to the target region along with a DNA polymerase (after which the method is named) are key components to enable selective and repeated amplification. To check whether the PCR has generated the anticipated DNA fragment, agarose gel electrophoresis is employed for size separation of the PCR products. The size(s) of PCR products is determined by comparison with a DNA ladder (a molecular weight marker), which contains DNA fragments of known size, run on the gel alongside the PCR products.

DNA Sequencing: DNA sequencing is the determination of the precise sequence of nucleotides in a sample of DNA or PCR product. DNA sequencing has been performed using the chain termination method developed by Frederick Sanger. It involves addition of dideoxy nucleotides (ddNTPs- synthetic nucleotides that lack the -OH at the 3′ carbon atom), which gets incorporated along with ddNTPS to a growing DNA strand and stops elongation because there is no 3′ -OH for the next nucleotide to be attached to. At the end of the cycling reaction, there are various products of different lengths tagged to fluorescently labeled ddNTPs. The fragments are separated by length from longest to shortest on a DNA sequencer. Presence of amplified product in the range of 350bp –880 bp indicates detection of fungal DNA. Fungal identification is done by sequencing of amplified product followed by BLAST analysis with the sequences in the GeneBank Database. Absence of amplimer indicates absence of Fungal DNA in the given specimen. Absence of an internal control as well as fungal DNA indicates an invalid result. The frequency of invasive fungal infections (IFIs) in critically ill and immunocompromised patients is continuing to increase and the spectrum of fungal pathogens has expanded well beyond *Aspergillus fumigatus* and *Candida* species. Early, rapid, and accurate identification of pathogenic fungi is important in order to guide the selection of appropriate antifungal therapy and thus improve patient outcomes, as well as for epidemiologic purposes. Culture -independent methods such as PCR can offer sensitive and specific diagnosis of viable and nonviable fungal pathogens in a variety of clinical specimens. The assay can detect clinically important fungi such as Candida, Cryptococcus, Aspergillus, Saccharomyces etc. Currently, in research, the identification based on sequencing of the Internal Transcribed Spacer (ITS) region of ribosomal DNA has been considered a reliable source of identification for this clade, but it has not been frequently used in clinical practices. Using the cutoff proposed by clinical laboratory standard institute (CLSI)[10] the isolate was considered sensitive to posaconazole and itraconazole. Itraconazole was considered to be drug of choice in such cases of invasive fungal infections. Amphoteicin B is considered to have higher MFCs, not used for rhinocladiella species. The studies which have isloated *R. Similis* and *R. aquaspora* as an agent of cutaneous chromoblastmycosis have reported that the response was intermediate to voriconazole and resistant to amphotericin B. For terbinafine and ketoconazole, there is no reference of cutoff to estimate minimum fungicidal concentrations (MFC). The MICs of posaconazole and voriconazole against R. similis were similar to those of both antifungals against R. Aquaspersa[11, 12]. In the present case, itraconazole was chosen as the initial treatment of choice in a dose of 10 mg/kg/day in three divided doses along with caspofungin in the loading dose of 70 mg followed by 30 mg four times a day for 21 days of inpatient admission. With this treatment there was improvement in both clinical and lab parametres. On discharge patient has been prescribed oral iatraconazole 200 mg twice day for 6 months with follow up every month till 6 months. The duration of treatment with itraconazole is variable, but a range from 8 to 10 months has been reported in many case studies[13]. This case report present *R. similis* as a agent an of chronic recurrent lymphocytic meningitis. This species could be more resistant to antifungals such as amphotericin B. The duration of treatment in such cases is prolonged and combination of antifungals should be considered in view of drug resistance following monotheray. In addition, this report also stress the importance of species level identification by using pangungal DNA PCR and DNA sequencing as conventional methods lack sensitivity.

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Conflict of Interest

Author declares no conflicts of interest

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Consent

Written informed consent has been taken

Guarantor

First (corresponding) and Second author

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