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Case Report

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# Plant Fungus Gloeotinia SP: A Rare Finding in a Case of Mesial Temporal Sclerosis with Medical Refractory Epilepsy

**Nur Nazleen Said Mogutham[1]*, Zamzuri Idris[1], Sanihah Abdul Halim[1], Anani Aila Mat Zin[2] and Siti Suraiya Md Noor[3]**

[1]Neurosciences Department, School of Medical Science, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

[2]Department of Pathology, School of Medical Science, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

[3]Department of Microbiology, School of Medical Science, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

**ABSTRACT**

We report a case of a 38-year-old gentleman who diagnosed since the age of 11 with medical refractory epilepsy. Semiology began with symptoms of automatism followed by deviation of eyes and unpurposeful movement of left hand. Patient would then experience loss of consciousness and generalised tonic seizure involving all four limbs. These episodes tend to last for 1-2 minutes and post ictal drowsiness frequently follows. Electroencephalography (EEG) displayed findings compatible with right temporal epilepsy with secondary generalisation. Magnetic resonance imaging (MRI) of brain confirmed right hippocampal sclerosis as culprit for the seizures while neuropsychological tests displayed poor memory. Otherwise, patient had no neurological deficit or any history of long-term infection. After a long history of anti-epileptic drug polypharmacy with poor control of seizures, surgical treatment was opted for. Right amygdala-hippocampectomy was performed by neurosurgeon which was uneventful. Histopathology of surgical specimen was reported as sections of neuronal loss, suggestive of sclerosis and diffuse fungal infiltration at brain surface and blood vessels. This was then confirmed as *Gloeotinia sp*. Via BLAST (basic local alignment search tool) method. Patient remains fit free after surgery.

***Corresponding author**

Nur Nazleen Said Mogutham Neurosciences Department, School of Medical Science, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

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## Introduction

Central Nervous System (CNS) infections are a leading cause for seizures and the World Health Organization (WHO) 2019 report claims that acquired epilepsy rates are climbing in developing countries due to this according to International League Against Epilepsy (ILAE), common aetiologies are bacterial such as meningococcus or pneumococcus causing meningitis, viral infections by herpes simplex virus (HSV), Cytomegalovirus (CMV); parasites such as cerebral toxoplasmosis and even tapeworm in neurocysticercosis [1]. CNS fungal infections are relatively rare but opportunistic cerebral mycosis has become more prevalent with dawn of AIDS pandemic, organ transplants and use of immunosuppressive agents. Common agents are Candida, Cryptococcus, Coccidioides Aspergillus, Blastomyces, and Histoplasma. They each have their own unique pattern of clinical presentation, but common route of entry is via inhalation or skin abrasions with regards to clinical presentation, clinicians need to be aware that fungal infections may not manifest as the regular meningitis triad of fever, nuchal rigidity and altered mental status while fungal brain abscess will cause focal neurological deficits and seizures [2,3]. This may be due to direct invasion of CNS due to underlying sinusitis, history of skull fracture due to trauma or previous neurological procedures [4]. Radiologically, magnetic resonance imaging (MRI) was diagnostically more sensitive in distinguishing fungal abscess and pyogenic abscess. Both of them demonstrate post-contrats ring enhancement with hypointense rim in T2-weighted imaging (T2WI). Highlights that previous studies had shown fungal abscess had lobulated contours while pyogenic or tuberculous abscess had smooth contours [5]. CNS infections could also lead to mesial temporal epilepsy with hippocampal sclerosis (MTLE-HS), which would be a possible reversible cause especially in third world countries with poor resources. According to a study conducted in Korea, CNS infections tend to present with clinical picture of encephalitis rather than meningitis, with seizure normally occurring in the acute phase of disease [6]. Reports positivity of mainly human herpes virus-6 (HHV-6) and small percentage of herpes simplex virus 1 (HSV-1) in cases of hippocampus sclerosis. There has also been reported cases of association between neurocysticercosis and intractable temporal epilepsy with the additional evidence of hippocampal atrophy. Unfortunately, there has been quite limited literature linking fungal infection and MTLE-HS.

Electroencephalogram (EEG) should display the hallmark findings of "interictal anterior temporal spikewave discharges which phase-reverse at temporal region" [7]. On the other hand, classical radiological findings would be hippocampal atrophy based on volumetric measurements on coronal plane with ipsilateral dilatation of temporal horn of lateral ventricle, best appreciated on T1-weighted imaging (T1WI) sequence [8]. Increased signal on T2-weighted imaging (T2WI) and FLAIR sequence indicates increased free tissue water which validates sclerosis [9]. Here we report an interesting case of hippocampal sclerosis secondary to a plant fungal infection, a first reported case in Malaysia.

## Case Report

We report a 38 year old gentleman, under neurology follow up for

a longstanding case of medical refractory epilepsy. He initially presented with seizures at the age of 11 and had no significant history of neonatal or febrile seizures as a child. Born at term via vaginal delivery, he had no significant paediatric medical history and was up to date with vaccinations. He has had previous admissions for his recurrent seizures and several episodes of sinusitis. His initial semiology was sudden onset of giddiness pre-ictally, followed by generalized tonic movement of all four limbs and loss of consciousness. There was associated tongue biting, up rolling of eyeballs and each episode would last 1-2 minutes before it would abort spontaneously.

Over the years, his semiology evolved as patient became more aware of specific details of his seizure episodes. With confidence, patient would describe his pre-ictal symptoms as tingling sensation like "ants crawling down his back" and palpitations. Ictally, patient would have loss of consciousness where he would be unaware of his surroundings and the typical post-ictal drowsiness would follow. Trigger factors could be epigastric pain, fatigue or even simple stress at home. A significant change of events was in 2007, when patient was undergoing a routine video electroencephalography (EEG). Immediately, after a seizure, patient had visual hallucinations of an 'evil entity' in the room that meant to cause harm to himself and his surroundings. This episode lasted several hours after his seizure and psychiatrist concluded this event to be an interictal psychosis with underlying right temporal lobe epilepsy.

Patient has been thoroughly investigated throughout these years. There had been no long term history of infection which was supported by erythrocyte sedimentation rate (ESR) value of 13 mm/hour and C-reactive protein (CRP) value of 7.2 mg/L. Viral screening, tumour markers and inflammatory markers were negative which ruled out immunocompromised state(Figure 1). Magnetic resonance Imaging (MRI) of brain (Epilepsy protocol) had consistent findings of right hippocampal complex atrophy with prominence of temporal horn, best appreciated on T1-weighted imaging (T1WI). There is hyperintensity at right hippocampal area on both T2-weighted imaging (T2WI) and on Fluid attenuation Inversion Recovery (FLAIR) sequence which is in keeping with diagnosis of sclerosis. However, there was no contrast enhancement (Figure 2A-D). To conclude, video EEG also successfully displayed frequent spikes and wave complexes with phase reversal over right temporal region. Intermittent theta slowing was seen over the same right middle temporal region. Interestingly, neuropsychological assessment revealed borderline cognitive function with very limited verbal activities, poor verbal IQ and impaired recent and short-term memory.

This patient went through a grueling polypharmacy process and despite that, his seizures were still uncontrolled. Several attempts were made to counsel family for surgical intervention and vagus nerve stimulation (VNS) but to no avail. Finally, in 2019, both patient and family were agreeable and underwent right selective amygdalo-hippocampectomy which was uneventful. Patient recovered swiftly and has been fit free ever since. A striking finding from the histopathology was the evidence of marked fungal infiltration of the glial tissue which is predominantly in form of yeast/spore found at the brain surface and around blood vessels. These organisms are highlighted by Periodic acid-Schiff (PAS) and Grocott methenamine silver (GMS) stains. Against the possibility of contamination was the presence of microglial and lymphocytic reaction in surrounding brain parenchyma. (Figure 3 A-H).

| SEQUENCE PRIMER |
| --- |
| Internal transcribed spacer 1(ITS1) (forward) :5'-TCC GTA GGT GAA CCT GCG G-3' |
| Internal transcribed spacer 4(ITS4) (reverse) :5'-TCC TCC GCT TAT TGA TAT GC-3' |

**Figure 1:** Internal transcribed spacer(ITS) /5.8S ribosomal DNA (rDNA) primer sequence (Ferrer et al., 2001)

Sample was then sent to a microbiologist for further assessment and via Basic Local Alignment Search Tool (BLAST) method, was concluded to have the sequence primer of:

These sequences were amplified via real time-polymerase chain reaction (RT-PCR) method, amplified DNA sequenced and aligned against sequences in GenBank at the National Institutes of Health. Sequence was compatible with Gloeotinia sp., a type of plant fungi that was responsible for blind seed disease, attacking germinating seeds of Lolium perenne (perennial rye-grass), initially found in Germany, Netherlands and United Kingdom and now predominantly in Australia and New Zealand [10].

**Discussion**

It has been reported that there are approximately 1.5 million fungal species but thus far, only 70000 of them have been officially described. Out of this number, only 10-15% have the capability to cause central nervous system (CNS) infections in humans but this has increased in the past decade due to increasing number of reported individuals who are immunosuppressed [11]. They can be grouped as moulds, yeasts and dimorphic fungi and their pathogenesis involves penetration across the blood brain barrier (BBB) which is further weakened by low immunity. This happens due to involvement of tumour necrosis factor-alpha (TNF – α) in disrupting tight junctions of BBB.

Gloeotinia sp. which was detected from intra-operative specimen is a plant fungus in the Helotiales order and has two distinct species, Gloeotinia temulenta & Gloeotinia granigena [10]. G. temulenta hails from Germany, Netherlands, Norway, Scotland, and the United States while its counterpart, originated from France. Their existence was reported since 1920s when they were found to be responsible for 'blind seed disease', mostly by G.temulenta, involving attack of ovary of Lolium perenne (perennial rye-grass) which seizes germination. explained about its essential role in improving grass and rice and was distributed to Malaysia in 2013 for

this purpose. It is rather interesting, to figure out how exactly our patient has been exposed to this particular organism as he has never had exposure in agriculture. Possible route of such infection could possibly be via inhalation of spores as patient has reported several episodes of sinusitis, but imaging did not display mucosal thickening at sinus cavities to support this [12].

Another intriguing point would be the lack of an inflammatory reaction in this patient which would be expected in immunosuppressed individuals. CNS infections can cause two types of seizures, either "acute symptomatic or unprovoked". Acute symptomatic occurs in 31% of cases, occurring within 7 days of infection but normally subsides after the infection is treated. On the other hand, unprovoked seizures tend to occur way outside the acute window and has higher tendency to recur this draws a possible argument there might have been an acute phase of infection for our patient which resolved but led to recurrent seizures [1].

There have been no reported cases linking this plant fungi to CNS infection in humans. Fungal CNS infections tend to occur in patients with risk factors of immunocompromised status, who have undergone chemotherapeutics, prolonged use of corticosteroids, haematological disorders and chronically ill patients [13]. Our work up indicated patient had none of the above risk factors and was never exposed to rye-grass. In conclusion, this is a first reported case of plant fungus CNS infection possibly causing medical refractory epilepsy in a young immunocompetent individual with no previous agriculture exposure [14,15].

## Appendix

**Figure 1**

| SPECIAL INVESTIGATIONS | RESULTS | REFERENCE RANGE |
|---|---|---|
| C-reactive protein (CRP) | 7.2 mg/L | <10 |
| Erythrocyte sedimentation rate (ESR) | 13 mm/hour | 0 – 15mm/hour |
| Viral screening<br>a) Hepatitis Bs Antigen<br>b) Hepatitis Bs Antibody<br>c) HIV Ag/Ab screening<br>d) Venereal Disease Reseacrh Laboratory (VDRL) test | <br>Non-reactive<br>Non-reactive<br>Non-reactive<br>Non-reactive | |
| Endocrine:<br>a) Thyroid stimulating hormone (TSH)<br>b) Glyclated haemoglobin (HbA1c) | <br>1.62 mIU/L<br>5.7% | <br>0.35 – 4.55 mIU/L<br>5.6- 6.2% (pre-diabetes) |
| Tumour markers:<br>a) Alpha-feto protein<br>b) Carcino-embryogenic Antigen (CEA)<br>c) CA 19- | <br><1.3 µg/L<br>0.7 µg/L<br>26.9 U/mL | <br>0.0-8.1 µg/L<br><5.0 µg/L<br>0.0 – 37.0 U/mL |

**Figure 1:** Table of Summary of Special Blood Investigations

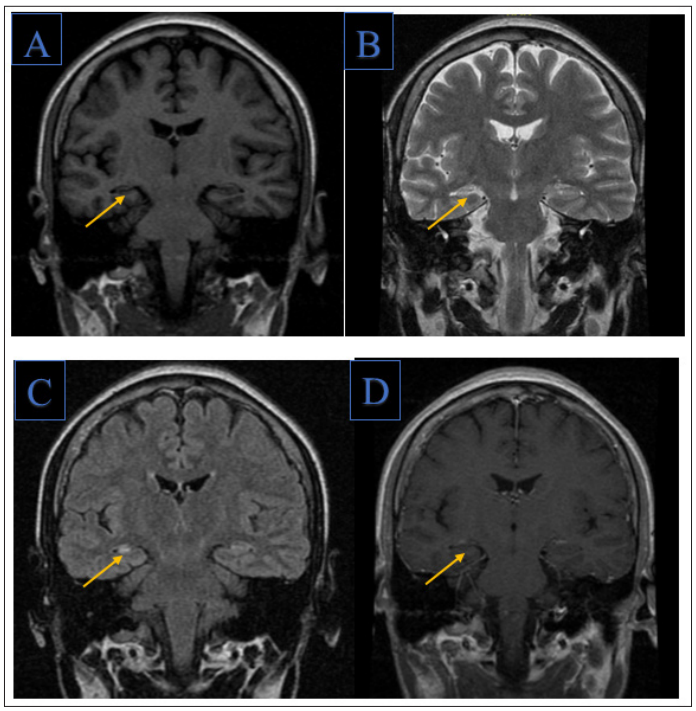
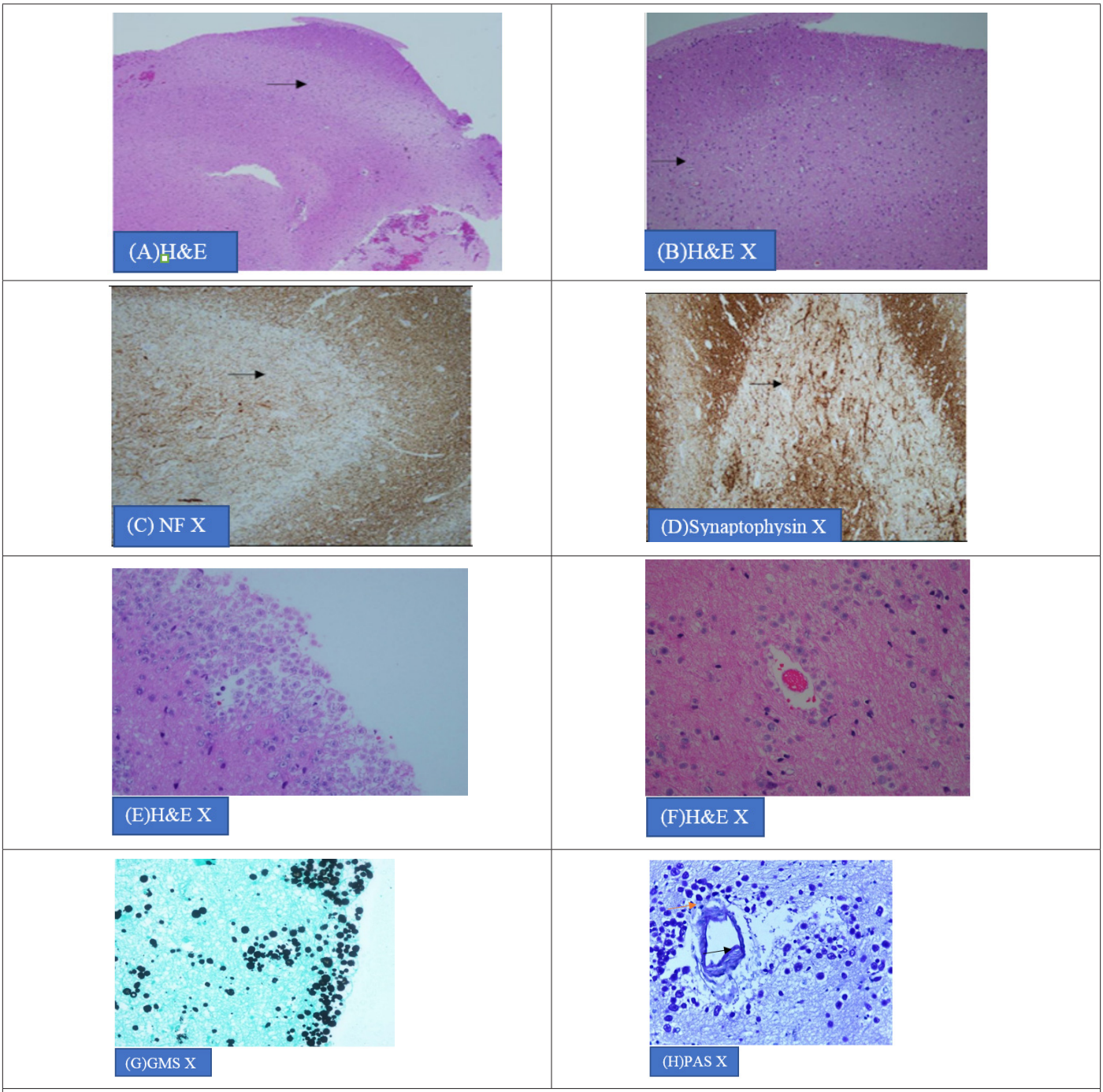



**Figure 2A-D:** MRI Brain (epilepsy protocol) Findings of the Tumor. (A) Coronal T1-weighted image. Bilateral hippocampus appears hypointense with bulk of right hippocampus appearing smaller (yellow arrow) (B) Coronal T2-weighted image: Bilateral hippocampus

appear hyperintense in comparison with grey matter and bulk of right hippocampus appearing smaller and mild dilatation of right temporal horn. (C) Coronal FLAIR sequence shows hyperintensity at right hippocampal region reflecting sclerosis (D) Coronal Gadolinium-enhanced T1-weighted images shows no enhancement of lesion.

**Figure 3 A-H: Histopathological Images of the Specimen from the Right Amygdala-Hippocampectomy**




A&B: Hematoxylin & Eosin (H&E) stain: Brain tissue exhibit neuronal loss, indicative of sclerosis
C&D: Neurofilament (NF) and synaptophysin stain highlighted neuronal loss area (⟶)
E&F: fungal infiltration in yeast/ spore forms at the brain surface and around blood vessels.
G&H: Periodic Acid Schiff (PAS) and Grocott's Methenamine Silver (GMS) highlighted the yeast/spores (⟶) which organized around blood vessel (⟶).

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