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Case report article: Fatal Cryptococcal Meningitis Complicated by Hydrocephalus in an Apparently Immunocompetent Farmer: A Case Report

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Case Report

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Abstract

Introduction:

Cryptococcal meningoencephalitis is an opportunistic fungal infection that predominantly affects immunocompromised individuals. However, an increasing number of cases have been reported in apparently immunocompetent hosts, posing important diagnostic and therapeutic challenges.

Case presentation:

We report the case of a 64-year-old previously healthy farmer living in a rural area who presented with a 10-day history of severe diffuse headache, fever, photophobia, and phonophobia followed by horizontal binocular diplopia. Neurological examination revealed neck stiffness and bilateral grade IV papilledema. Brain MRI demonstrated early active tetraventricular hydrocephalus with transependymal cerebrospinal fluid resorption. CSF analysis showed lymphocytic meningitis with markedly elevated protein levels, profound hypoglycorrhachia, and positive multiplex PCR, India ink staining, culture for Cryptococcus neoformans. Despite prompt induction therapy with liposomal amphotericin B plus fluconazole, progressive hydrocephalus developed, requiring neuronavigation-guided external ventricular drainage. An extensive immunological workup, including repeated HIV testing and lymphocyte subset analysis, excluded persistent immunodeficiency, with the initial transient lymphopenia resolving during treatment. The patient improved clinically, cerebrospinal fluid cultures became sterile, and he was discharged on oral fluconazole. Unexpectedly, he died at home one month later from an undetermined cause.

Conclusion:

This case illustrates that in cryptococcal meningoencephalitis, successful antifungal therapy and cerebrospinal fluid sterilization do not invariably predict neurological recovery. Vigilant monitoring for intracranial complications and persistent inflammatory injury remains crucial throughout the disease course.

Introduction

Cryptococcal meningitis (CM) is the most severe manifestation of cryptococcosis, an invasive fungal infection caused primarily by Cryptococcus neoformans and Cryptococcus Gattii [1]. These encapsulated yeasts are widely distributed in the environment, particularly in soil contaminated with bird droppings and decaying organic matter [2].

CM predominantly affects immunocompromised individuals, especially patients with advanced human immunodeficiency virus (HIV) infection, organ transplant recipients, and those receiving immunosuppressive therapies [2].

Nevertheless, an increasing number of cases have been reported in apparently immunocompetent hosts, and epidemiological data suggest that approximately 20–22% of cryptococcal meningitis hospitalizations occur in HIV-uninfected individuals, emphasizing that the disease is not exclusively confined to severely immunocompromised hosts [3].

Importantly, despite the absence of overt immunodeficiency, immunocompetent patients remain at substantial risk of severe neurological complications and death, with outcomes comparable to those observed in immunocompromised populations [4]. Hydrocephalus represents one of the most serious complications and is associated with increased morbidity and mortality.

Herein, we report a fatal case of Cryptococcus neoformans meningitis complicated by hydrocephalus in an apparently immunocompetent farmer with no identifiable underlying immunodeficiency despite extensive investigations.

Case Presentation

A 64-year-old male farmer living in a rural area, with no significant past medical history, was admitted to our Neurology Department for the acute onset of severe headaches that had begun 10 days before admission. The headaches were diffuse, constrictive, and holocranial ("helmet-like"), associated with photophobia, phonophobia, and fever. Two days before admission, he developed horizontal binocular diplopia.

Upon general examination, the patient was alert and oriented, He had a blood pressure of 130/90 mmHg, respiratory rate of 20 breaths per minute, oxygen saturation at room air of 98%, heart rate of 88 beats per minute, and blood glucose level of 1.12g. There was no pallor, icterus, lymphadenopathy or cyanosis.

Neurological examination on admission was unremarkable except for neck stiffness. Ophthalmological assessment revealed bilateral grade IV papilledema. Given the suspicion of intracranial hypertension, brain magnetic resonance imaging (MRI) was performed on the day of admission and demonstrated mild tetraventricular enlargement with subtle signs of transependymal cerebrospinal fluid (CSF) resorption, suggestive of early active hydrocephalus **(**Fig. 1**).**

Lumbar puncture revealed a normal opening pressure of 27 cmH_2O. CSF analysis showed lymphocytic meningitis with marked hyperproteinorrachia (2.49 g/L) and profound hypoglycorrhachia (0.03 g/L). Multiplex polymerase chain reaction (PCR) detected Cryptococcus neoformans, a finding subsequently confirmed by India ink staining and culture on Sabouraud agar. The cryptococcal antigen titer was markedly elevated (> 1:1280). Based on these findings, a diagnosis of Cryptococcus neoformans meningoencephalitis complicated by early active hydrocephalus was established.

The patient was initiated on intravenous liposomal amphotericin B (5 mg/kg/day) for 14 days combined with intravenous fluconazole (800 mg/day) as flucytosine was unavailable. This induction phase was

followed by oral maintenance therapy with fluconazole. Acetazolamide (2.5 g/day) was also administered as an adjunctive treatment for intracranial hypertension.

Despite appropriate antifungal treatment, the patient continued to experience persistent headaches and severe papilledema on follow-up ophthalmological examinations. Fifteen days after treatment initiation, he developed psychomotor slowing.

Consequently, on day 17 of hospitalization, the patient underwent stereotactic Brainlab-guided external ventricular drainage. Stereotactic guidance was used to optimize the accuracy of ventricular catheter placement despite only minimal ventricular enlargement on neuroimaging **(**Fig. 2**).** Ventricular puncture yielded clear, crystal-like CSF under high pressure with a forceful outflow. CSF samples were obtained for cytochemical, microbiological, and mycological analyses. The immediate postoperative course was marked by significant improvement in headache, recovery of the Glasgow Coma Scale score, and resolution of clinical signs of intracranial hypertension, supporting the pivotal role of external ventricular drainage in the management of symptomatic cryptococcal hydrocephalus. Postoperative CT imaging confirmed satisfactory ventricular catheter positioning and improvement of hydrocephalus **(**Fig. 3**).**

In parallel, an extensive investigation was undertaken to identify any underlying cause of immunosuppression. Initial laboratory testing revealed isolated lymphopenia ranging from 700 to 900 cells/mm³, with a nadir of 700 cells/mm³, while the remaining blood cell lines were normal. Liver and renal function tests were within normal limits. Serum protein electrophoresis with immunofixation demonstrated only an inflammatory pattern. HIV serology performed on two separate occasions was negative, and HIV RNA testing was also negative. Hepatitis B and C serologies, syphilis serology, and viral investigations including cytomegalovirus and Epstein–Barr virus were negative for active infection, with evidence of prior immunization only.

Lymphocyte immunophenotyping initially demonstrated a reduced CD8 + T-cell count. However, repeat testing performed after 20 days of antifungal treatment showed normalization of both the lymphocyte count (1,370 cells/mm³) and CD8 + T-cell levels. Following infectious diseases consultation, the transient lymphopenia was considered secondary to the acute infection rather than indicative of an underlying immunodeficiency. The patient was therefore classified as apparently immunocompetent. Given his occupation as a farmer and his prolonged exposure to soil and birds, environmental exposure was considered the most likely source of infection.

After 40 days of hospitalization, the patient's clinical condition had improved significantly. A follow-up CSF examination confirmed microbiological sterilization, and residual neurological deficits were limited to mild psychomotor slowing. He was discharged home on oral fluconazole (450 mg daily). Unexpectedly, one month after hospital discharge, the patient died suddenly at home despite his prior clinical improvement, documented microbiological CSF sterilization, and the absence of any identifiable underlying immunodeficiency.

Discussion

CM is an opportunistic neuro-infectious disease predominantly caused by the encapsulated yeasts Cryptococcus neoformans and Cryptococcus gattii, which exhibit distinct host tropisms and geographical distributions [5]. While Cryptococcus gattii is traditionally known to preferentially infect immunocompetent hosts, Cryptococcus neoformans remains the primary global pathogen, typically exploiting severe immunosuppression but occasionally infecting apparently healthy individuals following high-level environmental exposure, as observed in our patient [6]. Naturally acquired infections occur via the inhalation of environmental basidiospores or desiccated yeast cells from specific ecological reservoirs, most notably soil heavily contaminated with feral pigeon droppings and avian excreta. Once inhaled, Cryptococcus neoformans uses robust virulence factors and phenotypic plasticity to evade pulmonary macrophages, breach the blood-brain barrier, and proliferate within the nutrient-depleted CSF [7]. In our case, the patient's prolonged, close occupational exposure as a farmer with direct, repeated contact with pigeons highlights a critical professional hazard, demonstrating that massive, chronic inhalational exposure to these avian vectors can overcome normal host defenses and trigger a fulminant central nervous system infection.

The clinical presentation of CM is notoriously heterogeneous and frequently mimics less severe conditions, creating a diagnostic challenge in the emergency where classical signs of meningism occur in fewer than 20% of cases [7]. While immunocompromised individuals typically present with indolent symptoms due to a blunted inflammatory response, immunocompetent hosts mount a robust immune reaction that paradoxically leads to rapidly progressive neurological manifestations. This clinical dichotomy is vividly illustrated by our 64-year-old patient, whose initial symptoms, severe holocranial "helmet-like" headaches associated with photophobia, phonophobia, and subsequent binocular diplopia reflect an intense inflammatory response. Although multicenter data indicate that headache (73%), general symptoms (weight loss, fever and night sweats) (68%), and altered mental status (42%) are the predominant features in non-HIV cryptococcal meningoencephalitis, approximately 30% of these central nervous system infections occur in patients with absolutely no identifiable predisposing risk factors [8].

Cryptococcal meningoencephalitis classically occurs in patients with impaired cellular immunity, particularly those with HIV infection, solid organ transplantation, corticosteroid exposure, hematological malignancies, or primary immunodeficiencies such as idiopathic CD4 lymphocytopenia or anti-GM-CSF autoantibodies [8]. However, our patient underwent an extensive immunological evaluation that excluded these recognized causes of immunosuppression. Although an initial CD8 + lymphopenia was observed, its rapid normalization following antifungal therapy, together with recovery of the absolute lymphocyte count, strongly argues against a primary immunodeficiency and instead suggests transient infection-related lymphocyte redistribution or immune consumption. Increasing evidence indicates that Cryptococcus neoformans itself can modulate host immunity through multiple mechanisms, potentially inducing reversible alterations in cellular immunity during acute infection. Therefore, in apparently immunocompetent patients, transient lymphopenia should be interpreted cautiously and not be considered, by itself, evidence of an underlying immunodeficiency.

Hydrocephalus is one of the most severe complications of cryptococcal meningoencephalitis and is associated with increased morbidity and mortality. It is usually a communicating hydrocephalus resulting from impaired cerebrospinal fluid absorption due to obstruction of the arachnoid villi by cryptococcal organisms, capsular polysaccharides, inflammatory debris, and subsequent meningeal fibrosis [9]. This inflammatory process is thought to be more pronounced in apparently immunocompetent patients, predisposing them to elevated intracranial pressure and progressive hydrocephalus [10]. Current recommendations advocate CSF diversion when intracranial hypertension persists despite repeated lumbar punctures [10]. In our patient, despite appropriate antifungal therapy and acetazolamide, persistent headache, psychomotor slowing, and papilledema prompted external ventricular drainage, resulting in effective intracranial pressure control while allowing continuation of antifungal treatment. This case highlights the importance of early recognition of hydrocephalus and timely neurosurgical intervention as a crucial adjunct to antifungal therapy.

Current guidelines recommend liposomal amphotericin B combined with flucytosine as the preferred induction regimen for cryptococcal meningoencephalitis, followed by fluconazole consolidation and maintenance therapy. However, in many resource-limited settings, including ours, flucytosine remains unavailable, making amphotericin B and high-dose fluconazole the recommended alternative [1]. Our patient received this regimen, which resulted in microbiological clearance of the CSF after induction therapy. Several factors have been consistently associated with poor prognosis in cryptococcal meningitis, including delayed diagnosis, high cryptococcal antigen titers, elevated intracranial pressure, hydrocephalus, low CSF leukocyte count, and underlying immunosuppression [11]. Although our patient was apparently immunocompetent, he presented with a markedly elevated cryptococcal antigen titer and developed progressive hydrocephalus requiring neurosurgical intervention, both recognized markers of severe disease. Nevertheless, successful fungal eradication does not necessarily translate into favorable neurological outcomes, as mortality is frequently related to complications of intracranial hypertension rather than persistent infection. The unexpected death of our patient one month after discharge, despite CSF sterilization, illustrates this dissociation between microbiological and clinical outcomes. Although the exact cause could not be established, several mechanisms may be considered, including delayed hydrocephalus recurrence or shunt dysfunction, a post-infectious inflammatory (IRIS-like) phenomenon, or an unrecognized thromboembolic event. This case highlights the importance of prolonged clinical surveillance even after apparent therapeutic success, particularly in patients who develop hydrocephalus during the acute phase.

Conclusion

This report illustrates the complex relationship between fungal eradication, host immune response, and intracranial pressure in cryptococcal meningoencephalitis. Our patient achieved CSF sterilization after appropriate antifungal therapy, yet developed progressive hydrocephalus requiring neurosurgical intervention and ultimately experienced an unexpected fatal outcome. Importantly, in apparently immunocompetent patients, neurological complications secondary to an exaggerated inflammatory response may become the main determinant of outcome once fungal clearance has been achieved.

These findings emphasize that microbiological cure should not be regarded as the endpoint of management and support the need for prolonged neurological follow-up in patients with complicated cryptococcal meningoencephalitis.

Declarations

Ethics approval and consent to participate

Ethical approval

was waived because this is a single case report. Written informed consent was obtained from the patient's next of kin

Consent for publication

Written informed consent for publication of this case report and the accompanying images was obtained from the patient's next of kin.

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Competing interests

The authors declare that they have no competing interests.

Author Contribution

ZB and FZM conceived the study, collected the clinical data, performed the literature review, and drafted the manuscript. LE critically revised the manuscript for important intellectual content.MSA, NH, and MA performed the microbiological investigations, contributed to the diagnostic workup, and reviewed the manuscript.AA performed the neurosurgical procedure, contributed to the neurosurgical section, and reviewed the manuscript. MB and SEA participated in patient management and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Figures

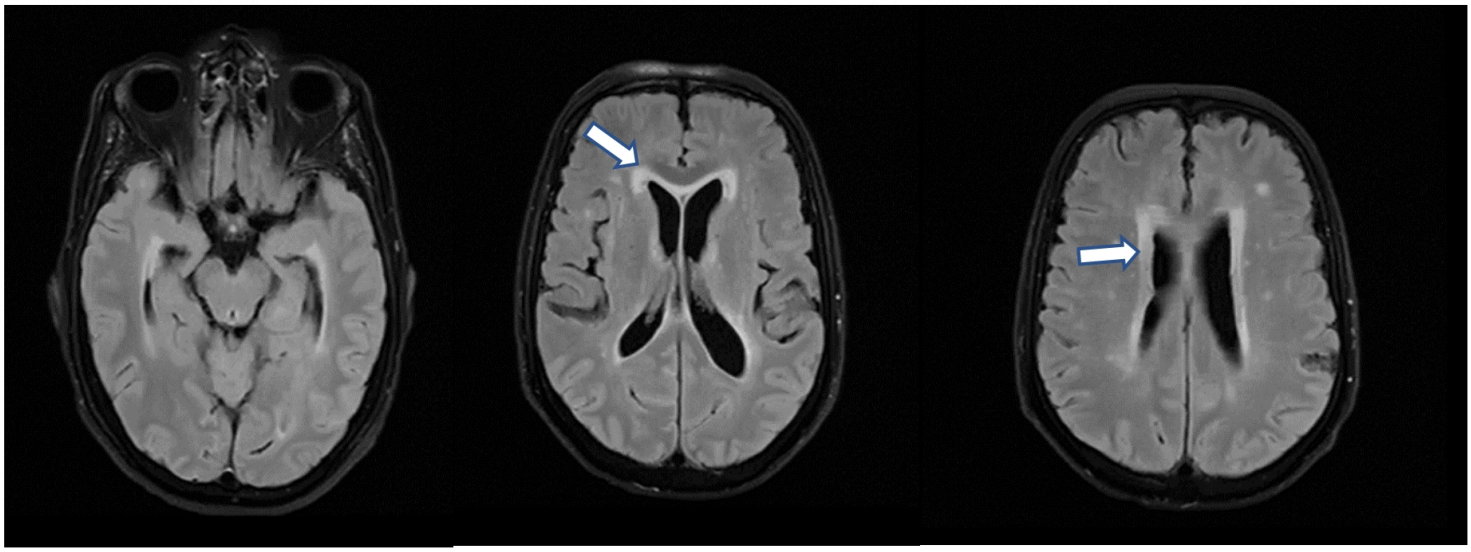


Figure 1

Axial FLAIR brain MRI showing mild tetraventricular enlargement associated with subtle transependymal CSF permeation (white Arrows), consistent with early active hydrocephalus.

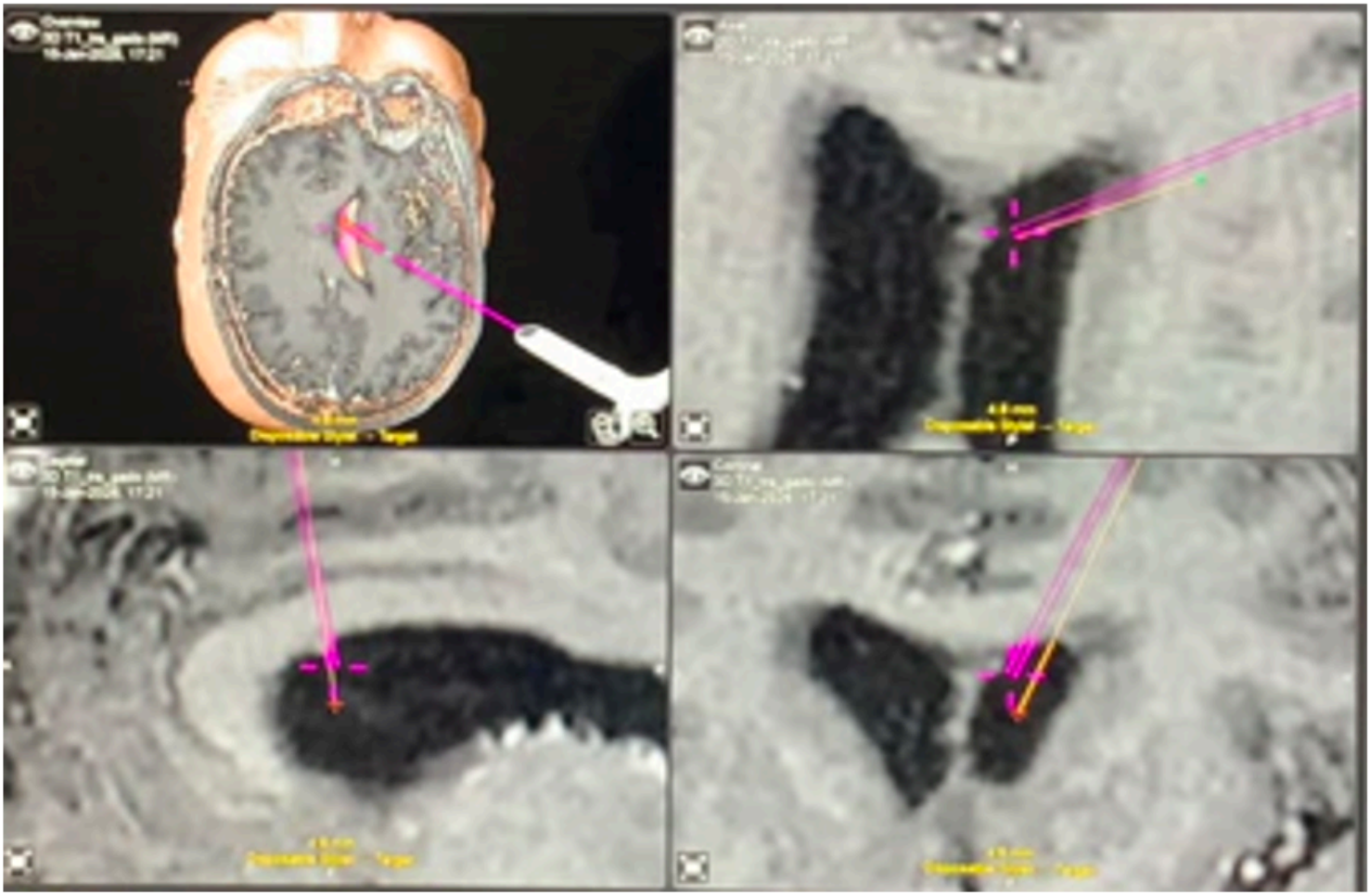


Figure 2

Brainlab® stereotactic neuronavigation used during external ventricular drain placement, demonstrating the planned ventricular trajectory and accurate catheter targeting despite only mild ventricular dilatation

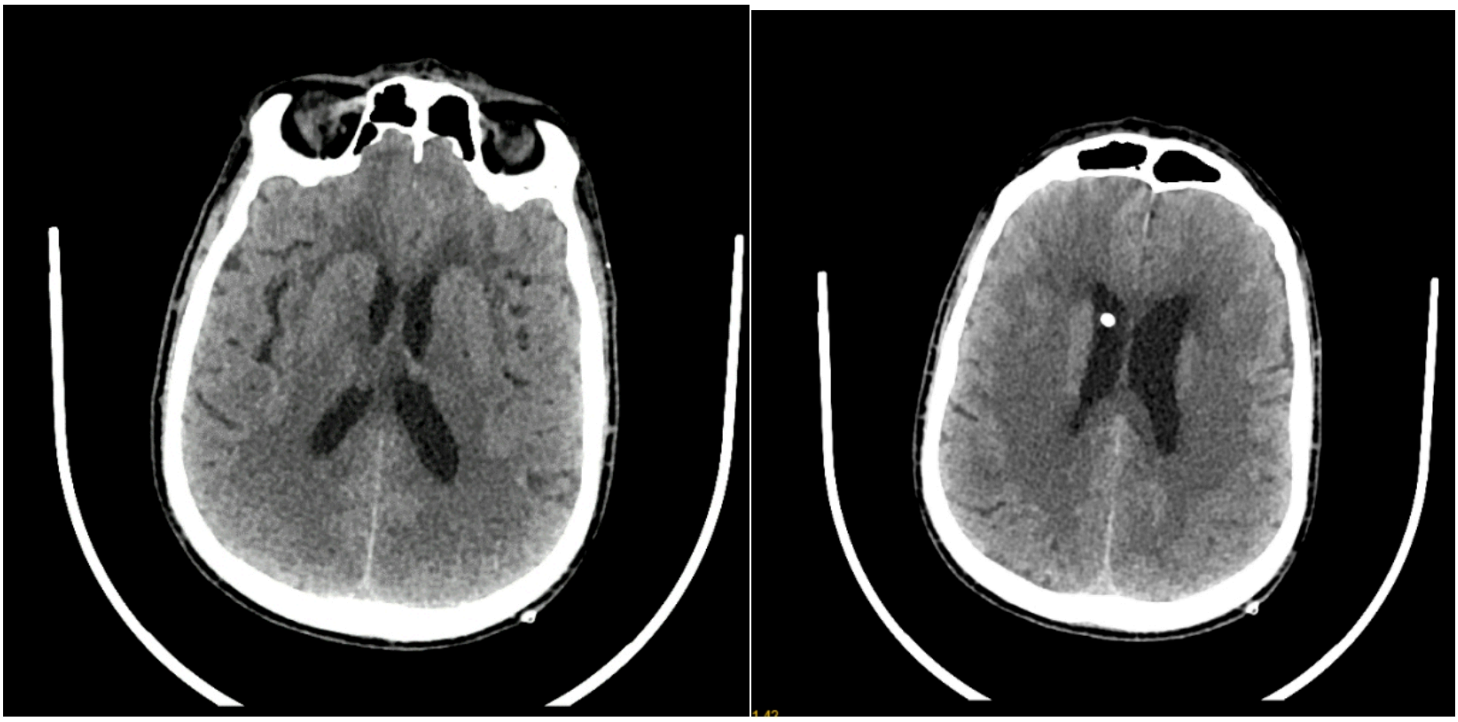


Figure 3

Postoperative non-contrast axial brain CT demonstrating satisfactory positioning of the external ventricular drain within the frontal horn of the lateral ventricle, with radiological improvement of hydrocephalus.