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Cerebral Malakoplakia in a Patient with a Background of Common Variable Immune Deficiency Treated with Intravenous Antibiotics: A Case Report

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Abstract

Cerebral Malakoplakia is an extremely uncommon entity within the realm of neuroinflammatory disorders, characterized by the formation of distinctive Michaelis-Gutmann bodies within macrophages. Malakoplakia was first described in the genitourinary tract but has been sporadically reported in various extra genital sites, including the brain. These reports remain sparse due to the rarity of cerebral malakoplakia, making each documented case a valuable contribution to our understanding of this intriguing condition. It originates from the Greek words "malakos" (soft) and "plakos" (plaque) [1]. **Important Clinic Findings:** We present a 20-year-old patient with a background of Common Variable Immune deficiency, epilepsy and Evans Syndrome complicated with recurrent pancytopenia since early childhood who is on monthly treatment with IVIG and usually receives rituximab if his platelet dropped. The primary hospital presentation was a sudden and severe occipital headache, neck pain and vomiting. His clinical examination was insignificant. Routine blood, including inflammatory markers, ANA, ANCA, immunoglobulins, and C, C4, were all normal. CSF analysis failed to identify any organism. **Diagnoses and Management:** MRI brain revealed enhancing left cerebellar mass with surrounding oedema, mass effect with effacement of the fourth ventricle and acute hydrocephalus. Accordingly, he was referred to neurosurgery centre as a suspected metastatic versus primary cerebellar tumour for biopsy and further management. Craniotomy and biopsy were conducted and the histopathology was reported as leptomeningeal and cerebellar lesion, favour inflammatory, dominated by oncolytic histiocytic with central area of necrosis, suggestive of malakoplakia. Accordingly, he received treatment with different regimens of

intravenous antibiotics based on previous case reports with similar diagnoses and his repeated MRI brain showed initial debulking of the brain mass, which later became static in size. **Conclusion:** Although it is very rare, Cerebral Malakoplakia should be considered in patients who are immunocompromised and presented with symptoms, signs and brain imaging that are suggestive of intracerebral tumours with or without a mass effect. Several case reports, including this one, have demonstrated good response to antibiotics as treatment for this condition.

Keywords

Cerebral Malakoplakia, Common Variable Immune Deficiency, Evans Syndrome

1. Introduction

Cerebral Malakoplakia is a very rare chronic inflammatory condition that is not well understood. However, the main pathology represents abnormal lysosomal function in the macrophage in response to infectious triggers. Although it is not usually seen in early disease, Michealis-Gutmann bodies are the hallmark of the disease, which represent the presence of eosinophilic, basophilic and laminated cytoplasmic inclusions, which consist of calcium and iron deposits. These inclusions reflect an impaired immune response and defective phagocytosis by macrophages, leading to characteristic histopathological appearance [1]. The disease usually involves the genitourinary system, but it was also rarely reported to involve the gastrointestinal tract, skin, Lungs, bones, endometrium and the brain [2] [3]. Regardless of the disease location, the presentation could mimic symptoms and signs of tumours in the involved organ [4] [5]. In most of the cases, history of immunosuppression diseases such as HIV, post-transplant, TB, IBD or background of treatment with immunosuppressant medication might be presented [3]. In this work, we present a case of Cerebral Malakoplakia who responded well to intravenous antibiotics.

2. Case Report (Patient Information and Clinical Findings)

A 20-year-old Caucasian male presented to the emergency department with a one-week history of constant generalized headache, vomiting, and neck pain on flexion. He had a background medical history of combined variable immunodeficiency (CVID), Evans syndrome, and childhood epilepsy. He was receiving monthly intravenous immunoglobulin (IVIG) for CVID and had been treated with rituximab for Evans syndrome when required. He had been seizure-free for ten years and was not on antiepileptic therapy. He denied systemic symptoms such as fever, chills, or night sweats and did not report photophobia, visual disturbances, altered consciousness, focal weakness, sensory deficits, or gait disturbances.

On examination, his vital signs were stable. Neurological examination was unremarkable, with no focal deficits or signs of raised intracranial pressure, Routine investigations were normal (Table 1).

Table 1. Serology, tuberculous screen, urine and stool analysis upon admission.

HIV 1 + 2 Ag/Ab CMIA	Negative
Hepatitis BsAg CMIA	Negative
Hepatitis C Antibody CMIA	Negative
Syphilis Antibody CMIA	Negative
Cytomegalovirus IgM CMIA	Negative
Cytomegalovirus IgG CMIA	Negative
Anti-EBV-CA IgG ELISA	Positive
Anti-EBV-CA IgM ELISA	Negative
Anti-EBNA-1 IgG ELISA	Positive
Herpes Serology Request	HSV antibody not processed
Toxoplasma Gondii IgM CMIA	Negative
Toxoplasma Gondii IgG CMIA	Negative
Cytomegalovirus IgM CMIA	Negative
Cytomegalovirus IgG CMIA	Negative
Galactomannan Index	0.1. This result is NOT suggestive of invasive aspergillosis.
Beta-d-Glucan	85.0 pg/mL. Elevated BDG result.
B. *burgdorferi* IgG (NVRL)	Negative
Faeces *C. difficile* toxin B GENE	NOT detected.
Quantiferon TB	Negative. *M. tuberculosis* infection unlikely.

Blood culture for TB: Negative. Specimen Comment after 3 samples of urine TB. Direct Microscopy: Acid-alcohol fast bacilli not seen. TB Culture at 37C Mycobacterium species: NOT isolated after 42 days incubation.

Initial treatment included analgesics, empirical antibiotics, and dexamethasone. A CT brain revealed left cerebellar hemisphere edema with a focal hemorrhagic component, potential underlying mass or infarct, and hydrocephalus secondary to raised intracranial pressure (Figure 1). Subsequent MRI confirmed an enhancing lesion in the left cerebellar hemisphere with perilesional edema and effacement of the fourth ventricle (Figure 2). The patient underwent an urgent craniotomy and biopsy, which confirmed cerebral malakoplakia, a rare neuroinflammatory condition associated with chronic CNS infections. His underlying CVID and immunosuppressive therapy likely contributed to his predisposition. Two weeks post-craniotomy, he re-presented with worsening headache. Imaging revealed left transverse venous sinus thrombosis and a hemorrhage near the biopsy site. Due to the hemorrhage, anticoagulation was not initiated. Over two months, his symptoms

resolved, and follow-up imaging (Figures 3-6) showed resolution of the venous sinus thrombosis.

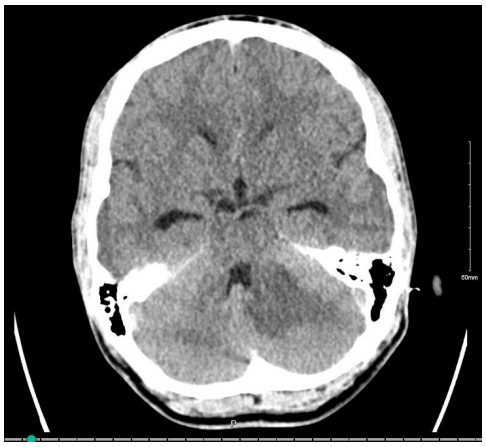

Figure 1. CT brain on admission.

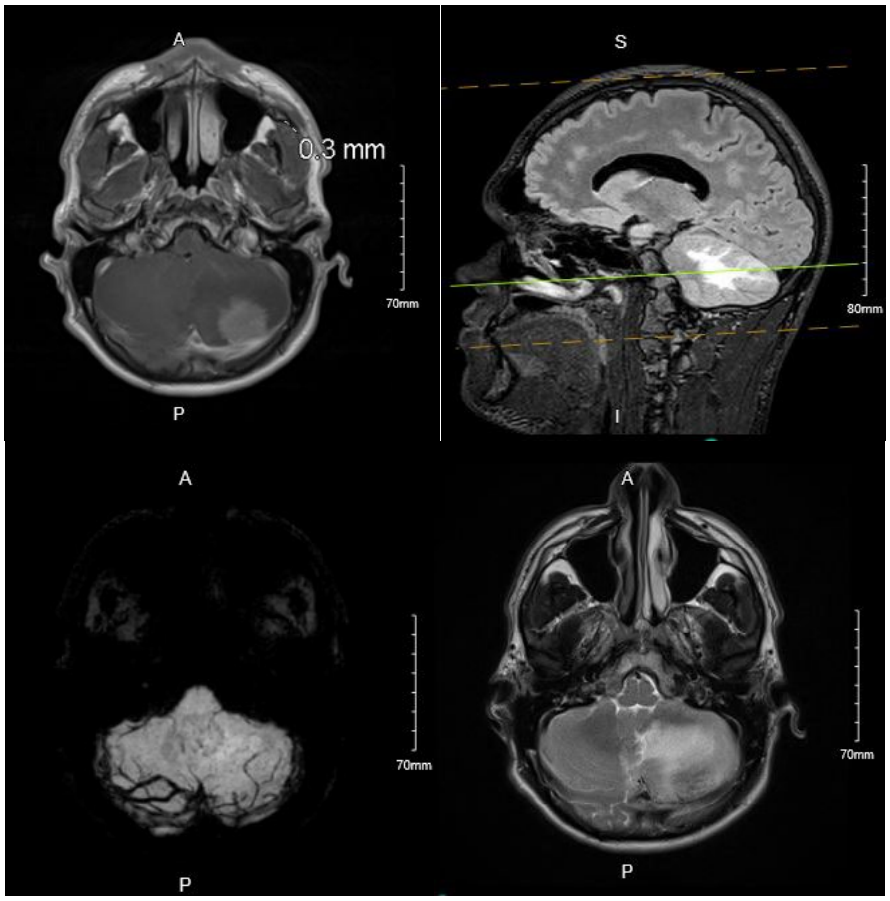

Figure 2. MRI brain on admission.

During his admission, he received tailored antimicrobial therapy for cerebral malakoplakia under infectious disease guidance. Adjustments were made due to side effects, including Redman syndrome and neutropenia (Table 2, Figure 7). Lumbar

puncture performed during a febrile episode suggested a bacterial CNS infection, although cultures were negative.

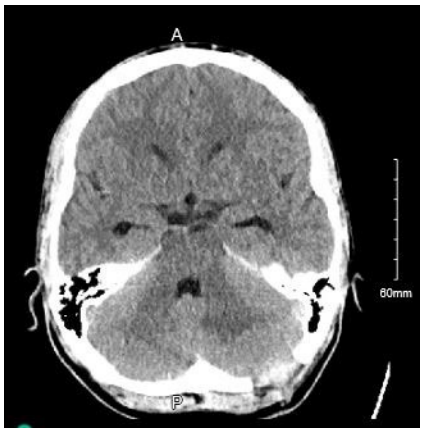

Figure 3. CT brain after craniotomy: There is more recent craniotomy with burr hole in the left occipital bone seen. Between the posterior surface of the left cerebellar hemisphere and the craniotomy there is a hemorrhage developed measuring 2.1 cm × 2.7 × 2.0 cm. There is some adjacent subarachnoid hemorrhage seen. There is remaining diffusely contrast-enhancing tumor in the left cerebellar hemisphere seen posteriorly. There is minimal parenchymal edema in the left cerebellar hemisphere seen.

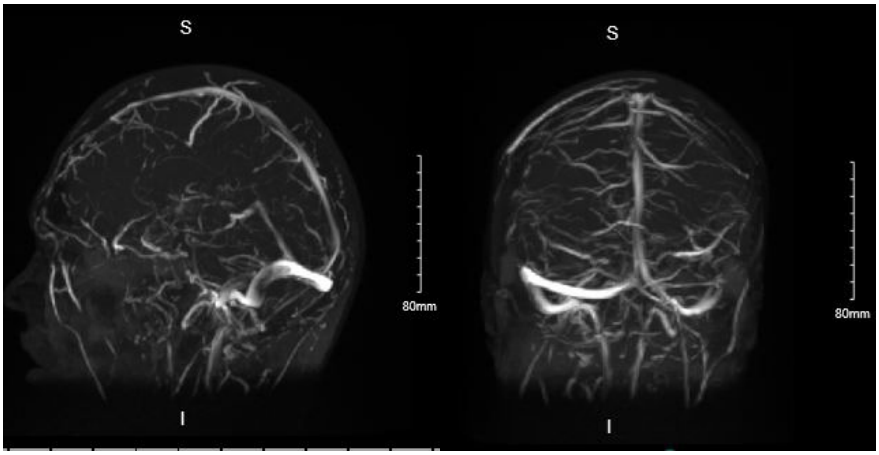

Figure 4. MRV brain after craniotomy: Showing the postsurgical change with disruption of the left transverse venous sinus suggestive occlusion. No evidence of residual tumor, assessment is limited in the immediate postsurgical setting.

Table 2. Full blood count upon admission.

	Day 1	Day 2	Day 3
WBCS	4.47	4.48	4.84
HGB	13.4	13.0	12.4
PLT	197	187	191
NEUT	3.35	2.96	3.62

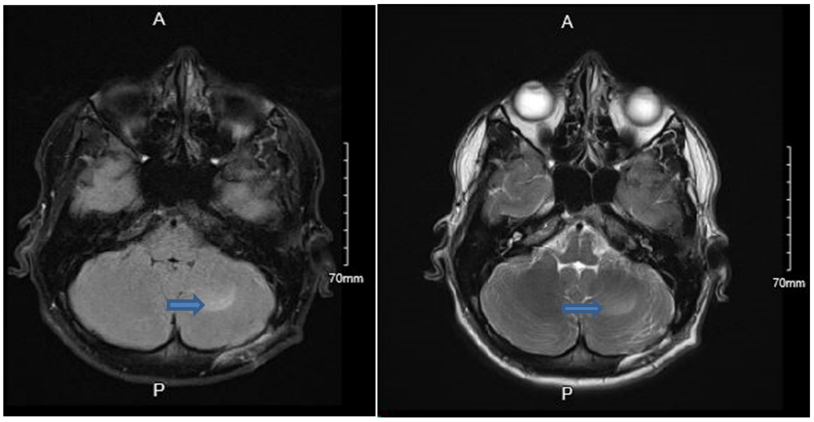

Figure 5. MRI brain after 4 weeks on IV antibiotics: Interval decrease in extent of abnormal T2/FLAIR hyper intensity in the left cerebellar hemisphere. Re-identified enhancing lesion demonstrating interval decrease in the extent of enhancement.

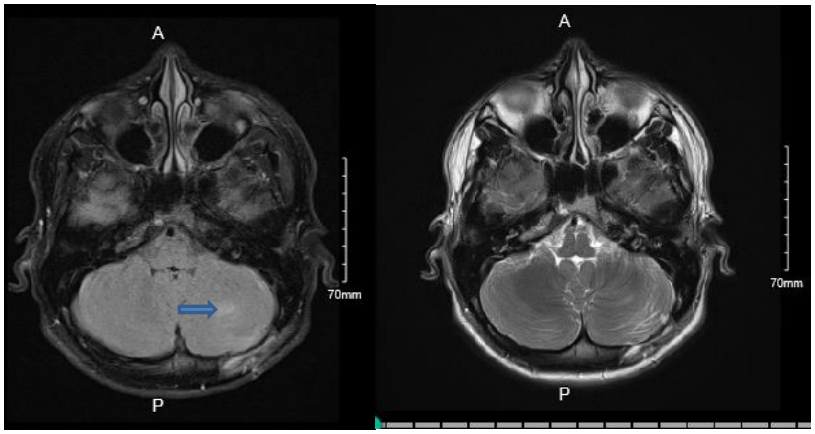

Figure 6. MRI brain 6 weeks on IV antibiotics: There is essentially no interval change compared to the last MRI scan, with post-operative changes in the left posterior fossa with small fluid collection and with minor high signal within the left cerebellum with no evidence of venous sinus thrombosis.

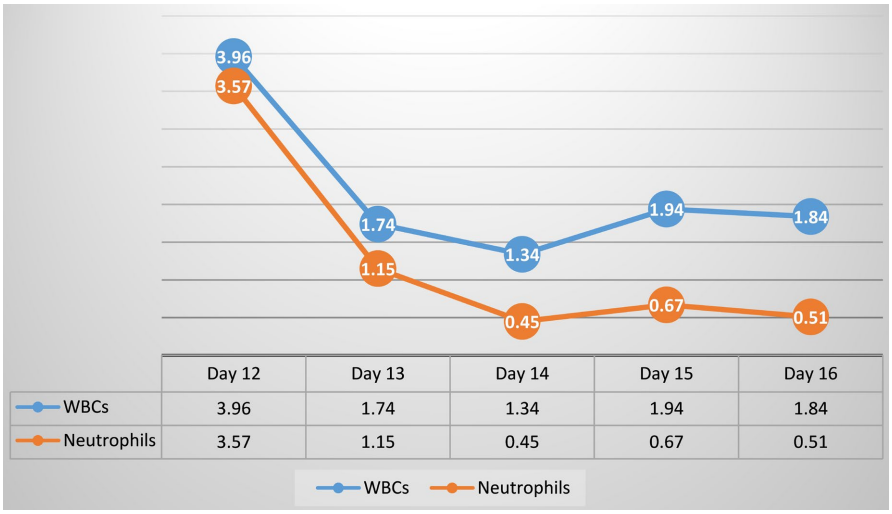

Figure 7. Meropenem induced neutropenia trend 12 days post initiation.

By discharge, the patient showed clinical improvement with stabilization of the cerebellar lesion on imaging (**Figures 3-6**). He was commenced on a long-term prophylactic antimicrobial regimen to prevent recurrence, with plans for careful monitoring and alternative options in case of side effects.

Left cerebellar hemisphere oedema with focal haemorrhagic component, potential underlying mass or infarct, and evidence of raised intracranial pressure and hydrocephalus.

3. Discussion

3.1. Scientific Discussion of the Strengths and Limitations Associated with This Case Report

Limitation of the case reports is that the patient received different courses of antibiotics during his treatment period, due to the fact that he developed complications as red man syndrome and neutropenia secondary to vancomycin and Meropenem respectively. These side effects necessitated the need to change antibiotics regimens under supervision of infectious disease team and guidance from previous case reports to select the appropriate treatments. Additionally, the fact that craniotomy biopsy was not cultured, as it would help to determine the exact causative organism, and help to guide the selection of appropriate antimicrobial for treatment. This case report represents one of the rare and typical presentations of Cerebral Malakoplakia as brain tumour clinically and radiologically in a patient who is immunocompromised, which was confirmed by biopsy. Also, it demonstrates the clinical and radiological response to IV antibiotics.

3.2. Discussion of the Relevant Medical Literature

Cerebral malakoplakia is incredibly rare, with just few cases were reported. Six of these cases occurred in neonates and infants aged 3 weeks to under 3 years, often linked to neonatal herpes simplex infection. Clinical symptoms and rising antibody titers pointed to herpes simplex virus (HSV) infection, but viral isolation was rarely successful. Two cases successfully cultivated HSV from various samples, yet cerebral tissue never contained the virus [3]. Unfortunately, in our case, brain biopsy culture that could help to determine the underlying causative organism was not done.

Herpes simplex infections exhibit eosinophilic inclusion bodies and necrosis prone to mineralization, resembling malakoplakia. Besides herpes-related cases, three instances of cerebral malakoplakia were found. Two occurred in adults after cerebral infarction, and one involved a 4-month-old infant with a brain hematoma. Unlike HSV-related cases, these instances lacked direct links to infections like *E. coli*, with no microorganisms found in tissue samples. This scarcity is seen in urinary tract malakoplakia as well, where bacterial evidence is rare [3].

In a specific case, a 53-year-old patient experienced a right-sided temporo-parietal intracerebral haemorrhage. After conservative treatment, the patient developed *E. coli* bacterial meningitis and subsequent encephalitic changes. Biopsies

conducted in July and August 1998 confirmed cerebral malakoplakia characterized by subacute to chronic intracerebral hematoma with the presence of Michaelis-Gutmann bodies. The patient's condition improved post-surgery, but he later died suddenly, suspected due to a pulmonary embolism [4].

In 2013, Fudaba *et al.* reported a case of 49 years old female presented with slowly progressive speech disturbance and right-sided hemiparesis. MRI brain revealed irregular strong enhanced lesions in the left insula, thalamus and basal ganglia with moderate frontal and cerebral peduncle edema. Similar to our case, their patient was initially diagnosed with brain tumor. However, biopsy results confirmed cerebral malakoplakia. They used Doripenem for two weeks initially, which was effective and had the progressive course of cerebral malakoplakia stopped with slight improvement. This was replaced by ceftriaxone in view of high penetrance to blood brain barrier and the broad-spectrum activity against gram positive and negative bacteria, in addition to oral Bethanicol and ascorbic acid (in view of acting as a choline agonist, Bethanicol elevates cGMP levels. Ascorbic acid decreases cAMP levels and triggers the formation of a hexose monophosphate shunt, ultimately enhancing the bactericidal activity of phagosomes. This process leads to more effective bacterial elimination and the development of M-G bodies). Two weeks after that, ceftriaxone was replaced by Levofloxacin by the treating team. Repeated CT scan and MRI brain showed decrease in area of calcification and shrunk of the irregular enhancing lesion after the courses of the previous antibiotics [5].

In our case, the patient presented primarily with a feature suggestive of increase intracranial pressure in form of headaches, vomiting and neck pain. The MRI finding suggested cerebellar tumor with surrounding edema and mass effect. However, biopsy pointed to the diagnosis of cerebral malakoplakia. Unfortunately, the biopsy was not cultured to help determine the culprit organism. His serological test was positive for some viral infections that might be considered as causative agent for his disease. But as the patient was on regular treatment with IVIG monthly to aid in control of his common variable immunodeficiency, these positive serological results were likely secondary to chronic administration of IVIG rather than he was actually infected with one of the viruses that predispose him to Cerebral Malakoplakia. Repeated MRI after administration of IV antibiotics and antiviruses showed decrease in mass size pointing to good response to antimicrobial.

3.3. Scientific Rationales for Conclusions

The patient's initial symptoms, including headache, vomiting, and neck pain, raised concerns about increased intracranial pressure and neurological issues. His complex medical history, featuring combined variable immunodeficiency (CVID), Evans syndrome, and epilepsy, heightened his vulnerability to neurological complications and immune-related challenges. CT Brain revealed edema with hemorrhagic component, and hydrocephalus in the left cerebellar hemisphere, indicative of a focal lesion causing mass effect, possibly stemming from infection, infarction,

or a mass. The patient's immunodeficiency and immunomodulator use predisposed him to cerebral malakoplakia, an unusual neuroinflammatory disorder linked to chronic infections in immunosuppressed patients. Biopsy results supported this, showing an inflammatory reaction due to persistent infection. Initial treatment involved dexamethasone for inflammation, and empirical use of broad-spectrum antibiotics started with ceftriaxone 2 g BD for almost two weeks in addition to 600 mg TDS IV of acyclovir in view of previously published case reports. Then, ceftriaxone was switched to Meropenem 2 g TDS IV and Vancomycin 1 g BD IV, which was increased to 1.75 BD IV based on advice from infectious disease team. The development of Redman Syndrome after vancomycin and the Meropenem-related neutropenia (**Table 2**, **Figure 7**), which was complicated with meningitis of unknown causative organism on the CSF analysis, led to switching treatment to Flucloxacillin 2 g QDS IV, Ceftazidime 2 g TDS IV, and acyclovir. Septrin (trimethoprim-sulfamethoxazole) is commonly used to prevent bacterial and opportunistic infections in individuals with compromised immune systems, thus it was commenced on discharged as prophylactic agent, in addition to acyclovir as a second prophylactic agent against HSV as this virus was reported in previously published case reports to cause cerebral malakoplakia [6]. Alternatively, Linezolid can be used to serve as a viable substitute for Septrin, offering effectiveness against a broad spectrum of pathogens. However, the choice of Levofloxacin as an alternative should be cautious due to its potential to lower the seizure threshold, a concern particularly relevant to this patient with background of epilepsy.

Patient Consent

The patient consented (written) to publish this case report.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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