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Spinal and cranio-cervical mycetoma: a difficult surgery, with poor prognosis

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Running title: Actinomycetoma dissemination

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Abstract

Background: Few central nervous systems (CNS) cases of actinomycetoma have been recorded in the literature, and most were reported in tropical and subtropical regions. The management of this invasive infection is difficult, especially when it affects the spine and the cranio-cervical regions.

Case: We report an unusual case of a cranio-cervical junction actinomycetoma, in a patient presenting a cerebellar syndrome from brainstem compression. The CT scan showed a compressive solid osteolytic lesion in the cranio-cervical junction. The patient underwent cranio-cervical decompression and lesion resection. The diagnosis of actinomycetoma was confirmed on immune-histochemistry and molecular analysis. At 4 months' follow-up, the patient presented a fatal recurrence disseminating within the cerebellum and the spine.

Conclusion: The surgical treatment of CNS actinomycetoma presented poor prognosis and a disseminating recurrence. We believe that clinicians and surgeons must be informed about these "new" infectious pathologies that are so difficult to treat, especially with the arrival of migrant patients from endemic countries in conflict.

Keywords: Actinomycetoma; brain; spine; invasive; fungal

INTRODUCTION

Mycetoma is commonly described as a tropical and subtropical disease, which mostly affects patients in the region known as the "mycetoma belt"[1]. This morbid chronic progressive inflammatory disease is caused by certain fungi (Eumycetoma) or bacteria (Actinomycetoma) [2]. The organisms are usually present in the soil under the form of grains.

The infecting agent is implanted into the host's tissue through a breach in the skin. These invasive infections may cause severe soft tissue, bone and even adjacent organ damage [1,3,4]. It is characterised by devastating distortions, disabilities, its high morbidity and has various negative impacts on patients and communities in terms of health and socio-economics [3,5]. Initial treatment consists in administrating trimethoprim-sulfamethoxazole for bacteria or Amphotericin B for fungi.

The treatment of patients with mycetoma remains perplex and challenging and outcomes are unsatisfactory. The follow-up of this disease is characterized by low cure rates, high rates of dramatic recurrences and consequently high rates of radical debridement followed by amputation.

The most impacted organs are hands [8%] and feet [76%] [3], whereas cranio-cervical and spine localisations are rarely reported [1,3,6,7]. The most reported pathologic entity of the nervous system is the brain, with an abscess presentation [1,3,7], due to spreading via an initial skin lesion on the scalp.

We reported a rare case of cranio-cervical mycetoma causing brainstem compression and secondary CSF dissemination to the spinal cord. We highlighted the difficulties in managing a CNS mycetoma infection, with the need of expansive surgeries to carry out the dissection of mycetoma spores, which have a very important sowing power. We believe that clinicians and surgeons must be informed about these "new" infectious pathologies especially considerning the arrival of migrant patients from endemic countries in conflict.

CLINICAL CASE

We reported the case of a 42-year-old man referred to our hospital for cervical pain and dizziness associated with dysphagia and significant weight loss. He reported only one previous surgery, five years before in Tchad for a subcutaneous occipital lipoma and no immunodeficiency was recorded.

A swelling of the fossa posterior scar was observed during local examination, the skin was stretched, smooth and shiny, with areas of hyper-pigmentation. Subcutaneous masses were felt during the palpation of this cutaneous sinus (figure 1A).

His clinical examination revealed asthenia, dysphagia with an abolition of the nauseous reflex as well as a cerebellar syndrome and tetra paresis.

Brain and cervical CT scans were performed and showed a heterogeneous solid lesion in the cranio-cervical region causing significant compression on the medullar cord (figure 1B-D). This lesion mimicked a metastasis or an aggressive tumor with skull bone lysis. The thoraco-abdominal CT scan was normal. Unfortunately, brain explorations by MRI were no longer possible since his posterior fossa surgery due to a history of ocular trauma with metallic impaction. We performed a decompressive surgery of the cranio-cervical junction with aid of the initial occipital craniectomy and an opening of the posterior arch of C1 (figure 2A-D). Then we removed the lesion (figure 2B-F). Per-operative constatation was unusual with a slim lesion, surrounded by inflammatory tissues, with multiple black grains disseminated in the soft tissue and the bone (figure 2E-F). The dura mater was inflammatory, invaded by black grains and there was CSF leakage during lesion resection.

After the surgery, the patient felt immediate improvement, with significant symptom relief especially concerning his cervical pain and dysphagia.

The histopathological examination showed many branching and septate fungal filaments surrounded by inflammatory granuloma (Figure 3A-C). Supplementary Polymerase Chain reaction (PCR) analyses permitted the identification of *Actinomycetoma.* Actinomycetoma was identified on growth media of Loewenstein-free antibiotic in Agar media (Figure 3D).

After four months of clinical improvement, the patient presented an acute consciousness alteration with progressive tetraparesia. The CT scan showed an abscess in the cerebellum (Figure 4A) associated with hydrocephalus and spinal dissemination: behind C1-C2 and within the medullar cord at C4 level (Figure 4B). An emergency surgery to evacuate the abscess and perform a C2-C4 decompression was performed. Secondary histopathologic examinations confirmed that the cerebellum abscess and the spinal C2 and C4 lesions

represented an Actinomycetoma recurrence, which spread to the spine. The patient died three days later of septic shock.

DISCUSSION

Mycetoma has a definite geographic belt distribution that includes: Sudan, Mali, Senegal, Somalia, Tchad and Sahel although it is reported in many other African countries. The majority of these countries are impacted by armed conflicts and civil war, generating refugees and migration flows towards Europe. Therefore, there is no doubt that we will have to take care of more and more patients coming from these endemic areas of Mycetoma.

In the literature, cranial involvement in mycetoma is clearly uncommon and occurs in less than 4% of cases [8], mainly in brain, i.e frontal or parietal lobes [9]. In 1964, Lynch et al. reported the first historical series of 1860 mycetoma patients: only 18 patients (0.96%) developed head and neck mycetoma [10]. Over 23 years, Fahal et al. described a series of 6,792 patients treated for Mycetoma with rates of surgical intervention at 30.9 %. None of the patients were affected in the cranio-cervical region or the spine [3].

As evocated previously, the two forms of mycetoma are anaerobic filamentous bacterial mycetoma and fungal mycetoma; bacterial mycetoma is known as Actinomycetoma, whereas the fungal form is called Eumycetoma. However, it is important to distinguish Actinomycetoma and Eumycetoma for their treatments are completely different and the management of Actinomycetoma is longer with more uncertainty.

The characteristic MRI findings can help make an early noninvasive diagnosis of Actinomycetoma/Eumycetoma and allow differentiation from other hypointense lesions, to adapt the surgery. Typically, in MRI, the recently described characteristic “dot-in-circle” MRI sign in eumycetoma represents a T2-hyperintense granuloma, with central hypointense “dots” of fungal grains separated by hypointense fibrous walls. A conglomeration of multiple hypointense dots of fungal grains within the inflammatory granuloma was observed. The grains were identified as hypointense dots on both T1W and T2W images and their MRI signal was attributed to the magnetic-susceptibility effects of the paramagnetic elements of the grains [3,11]. On the contrary, upon MRI diagnosis of pyogenic abscess, the capsule of the abscess is hyperintense in T1W, partially hypointense in T2W with surrounding vasogenic oedema. The gadolinium-MRI injected shows a ring-enhancing mass. The central component of the lesion shows high signal intensity in DWI, and hypointense signal in ADC [12].

As summarized in table 1, few previous cases report cranial mycetoma caused by either actinomycetes: Streptomyces somaliensis, Actinomadura madurae, pelleterii. [7,8,13–

16] or by eumycetoma: Madurella mycetomatis [1,11,15,17–20] in majority (table 1). The organisms may reach the brain via traumatic inoculation or spread from surrounding infected structures. In the presented case, the infection probably came from the previous brain surgery [1,18]

We would like to highlight several key points in terms of the clinicopathology and management of cranial Actinomycetomas: Indeed, in a current review of 9 cranial Eumycetomas, 2 of the cases were considered inoperable, leaving an overall cure rate >50% [9]. The others were cured thanks to antifungal agents based on ketoconazole and Itraconazole.

For cases of brain or cranio-cervical Actinomycetoma infection, treatment and prognosis are darker and remain challenging: drug associations such as streptomycin sulphate and dapsone, or streptomycin and trimethoprim-sulfamethoxazole are used, but early surgical excision with wide margins offers the only chance of cure. Nonetheless, bacterial granulomas affecting the brain or the spine are associated with very high mortality even after surgical excision and antibacterial therapy. The reported mortality rates are around 50–63% in various series; with meningoencephalitis accounting for the majority of deaths [21,22].

In addition, surgery is often precluded by the advanced stage of the disease at presentation, the deep anatomical location within the brain and the multiplicity of the lesions. The infection usually progresses slowly over many years and is commonly painless; this may contribute to the late presentation of many patients. However, progression rates are more rapid for Actinomycetoma than for Eumycetoma. In Eumycetoma, the lesion grows slowly with clear defined margins and remains encapsulated for a long period, whereas, in Actinomycetoma the lesion is more inflammatory, more destructive and invades the bone at an earlier stage [23]. Hussein et al. described the only case of spine mycetoma with extensive neck pyomyositis, epidural C4/C5 extension and spinal cord compression treated by surgical decompression [24].

As illustrated in our case, the lesions are usually characterized by suppuration, abscess formation, granulomas, and the formation of draining sinuses containing granules. These granules may range up to 2 mm, are rigid, and contain intertwined septate hyphae that are typically distorted and enlarged at the periphery of the granule. These granules mediate the dissemination power.

In Sudan, considered the homeland of mycetoma, Fahal et al. presented their experience managing 49 patients affected by mycetoma in the head and neck region. Only 1/49 (2.04%) had occipital and upper cervical bone involvement. Their series showed poor

treatment outcome: only five patients were cured (<10%) [6] and they all presented a convexity Actimycetoma.

Considering the poor prognosis of brain and spine Actinomycetoma, we recommend that a meticulous operative technique be used during the exposure and resection of cerebral lesions to prevent spillage and seeding of Acytomycetoma grains. Reccurences are almost inevitable, and fatal. When it is possible, the opening of the dura mater must be avoided, since meningeal dissemination adds difficulty to the treatment by disrupting the hematomeningeal barrier. This dissemination seems to be the one involved in our case resulting in an infectious epiduritis with spinal cord compression.

Less experience in tropical diseases can be a source of misdiagnosis. Several diagnoses were evocated in our case prior surgery, most opting for an osteolytic tumor. In the majority of cases, these lesions are operated on quickly, for they simulate brain tumors or a brain abcess. Even in endemic countries the diagnosis of CNS mycetoma is not stated first. A good clinical examination is therefore essential, by thorough skin inspection, looking for any entry point (breach, cut) or an initial skin infection with the presence of black or yellow grains.

In agreement with the previously reported series, Actinomycetoma was the prevalent type of mycetoma for tissue infections (limbs, brain, trunk) in migrant patients: the explanation for this prevalence remains unclear, but certain suggested that actinomycetes are resilient and able to survive in colder areas than Eumyceteces [8,25].

CONCLUSION

CNS Actinomycetes remains a very difficult diagnosis to evoke in first intention. Medical management of this infection should be preferred since resection surgeries still have poor outcome and are often deleterious. The prognosis of these infections remains dark. Due to global human conflicts generating large flows of Sub-Saharan African migrants, clinicians should be warned and educated about such infections.

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LEGENDS

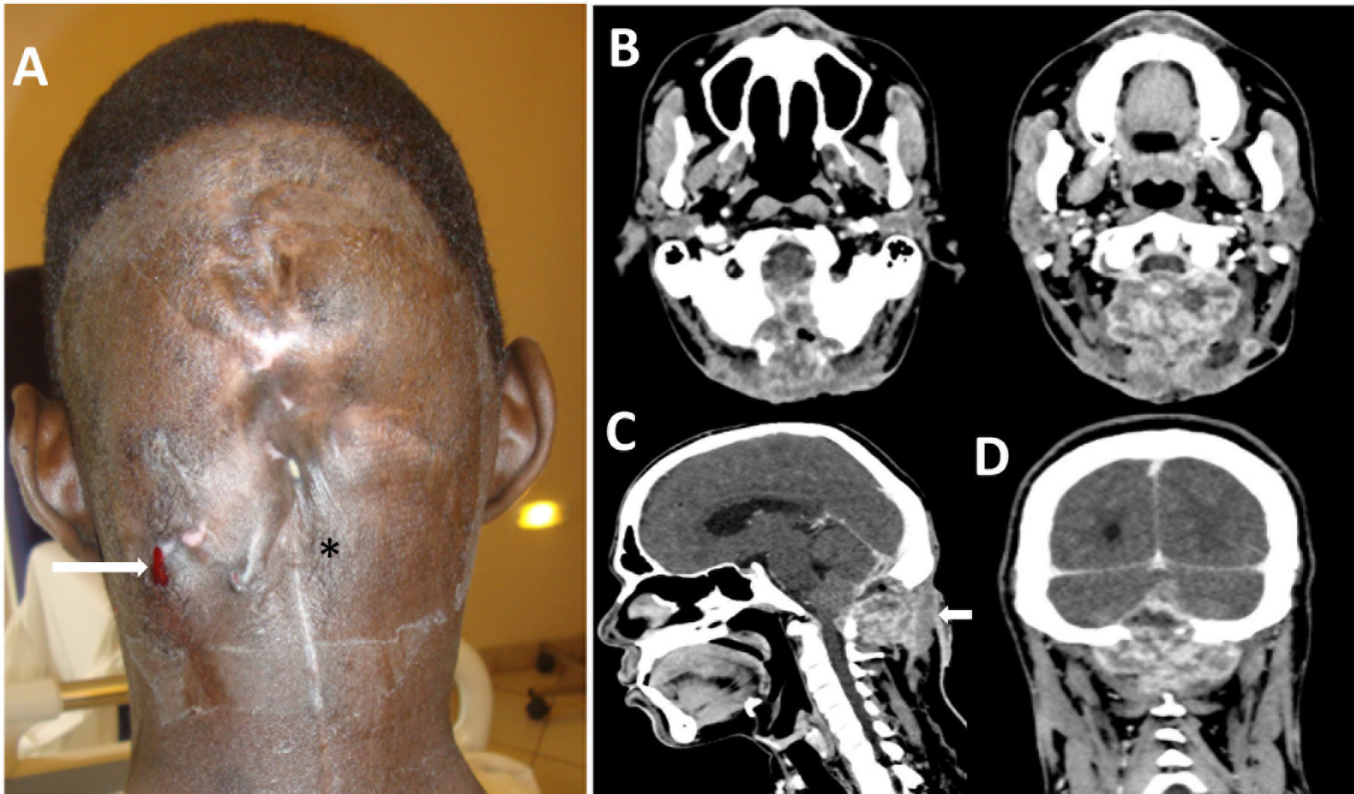
Figure 1: (A) Cranio-cervical subcutaneous mass with cutaneous sinus (white arrow) of deep Actinomycetoma infection and previous posterior fossa scar (black star); B) Axial CT scan showing fossa posterior polylobar lesion with brainsteam compression; (C and D) sagittal/coronal CT scan with previous craniectomies sequalae and deep-cutaneous (sinus) fistula (white arrow)

Figure 2: Postoperative cranio-cervical CT scan: A) 3D-model bone window with fossa posterior craniectomy and C1 laminectomy; B) Axial CT scan demonstrating complete decompression and lesion resection but C-D) dural and intradural enhancement (blue arrow) corresponding to infiltration. E) Intraoperative photograph of the posterior surgical approach showing the Actinomycetoma lesion with black grains (white star) through the craniotomy; F) the lesion appeared as friable tissue with interspersed necrotic areas (white star) and black-colored hard granules measured 1–2 mm (white arrow)

Figure 3: A) Low magnification (20X) of Periodic Acid-Schiff staining showing fungal masses (black arrowhead) borderered by an inflammatory granuloma (white arrowhead) and infiltrating the connective adipose-subcutaneous tissue; B) High magnification (X400) of Grocott's staining showing branching and septate fungal filaments (black arrowhead); C) High magnification (x400) of the inflammatory granuloma containing numerous neutrophils and eosinophils; D) The black grains of lesion during a Loewenstein free antibiotics culture test showed actinomyctema growth in Agar media.

Figure 4: 4-month FU cranio-cervical CT scan. A) obstructive hydrocephalus due to Actinomycetoma abcess recurrence: B) Posterior C1/C2 (white arrow) and antérior C4 medullar cord (black star) Actinomycetoma spreading. C) Cerebellar abcess evacuation and a C2-C5 laminectomy were performed, histopathological analyses confirmed Actinomycetoma lesion

Table 1: review of the literature on CNS Mycetoma (1970-2020); legends: years (Y), Cerebellopontine angle (CPA)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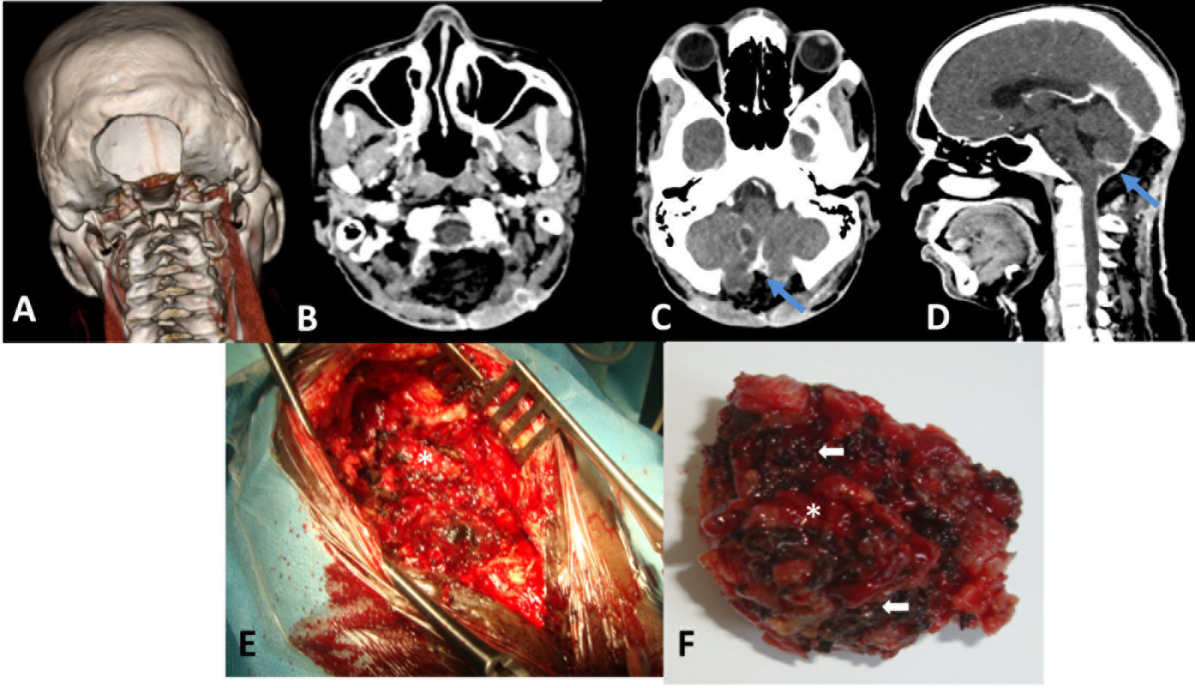
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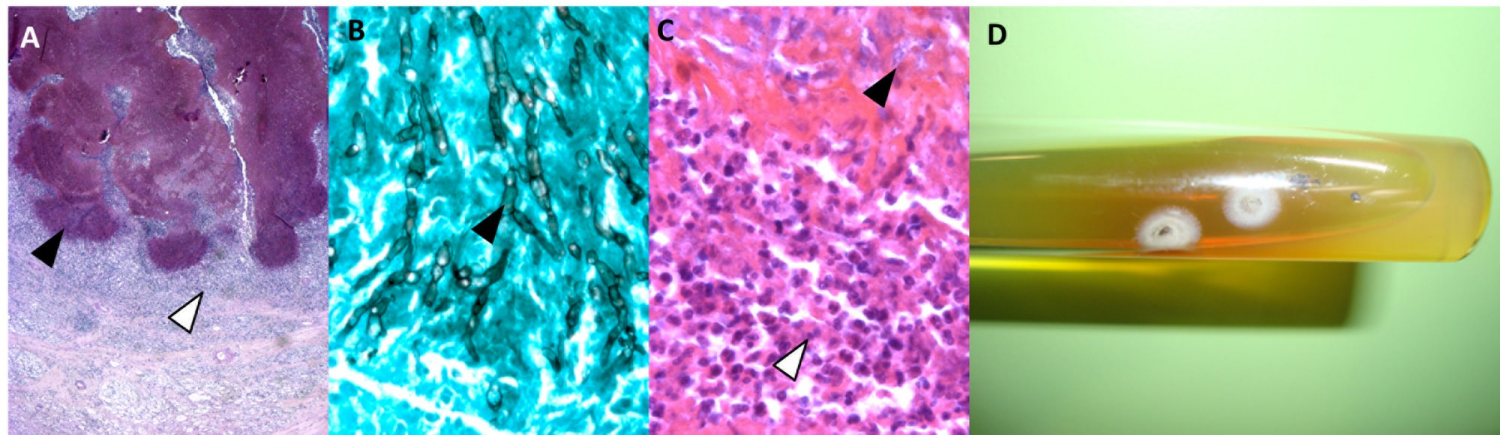
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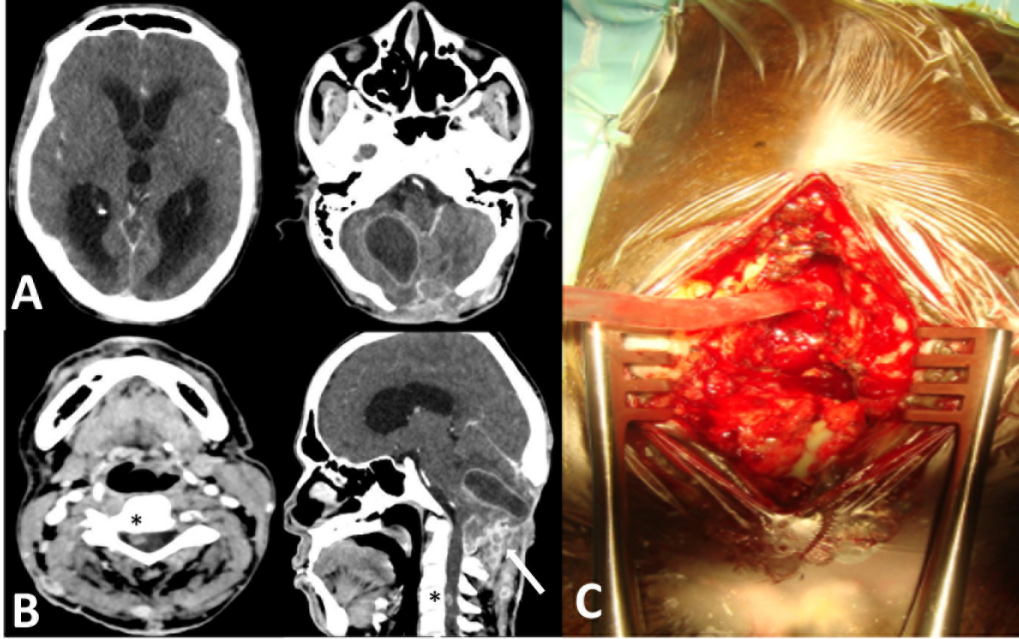
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Authors	Year	Age	Gender	Symptoms	Localisation	Outcome
Muyunga et al. [15]	1971	4,5	Male	Epistaxis Vision loss Left III/VI nerves palsy	Temporal lobe	Dead
Natarajan et al. [12]	1975	25	Male	Parietal scalp swelling Convulsions Left Hemiplegia	Parietal lobe	Left hemiparesis No recurrence 5y F.U
Sundaram et al. [13]	2006	18	Male	Scalp swelling Discharging sinus	Skull base Temporal lobe	Dead
Sai Kiran et al. [18]	2007	21	Female	Intracranial hypertension Left V/XII nerves palsy Right hemiparesis Cerebellar signs Hydrocephalus	Left PCA lobe	Dead
Beeram et al. [14]	2008	18	Male	Scalp swelling Convulsions	Parietal	No recurrence 1y F.U
Maheshwari et al. [16]	2010	31	Male	Left hemifacial palsy	Paranasal air sinus Left cavernous sinus	Recurrence
Ahmed et al. [19]	2011	35	Male	Pain Diplopia VI nerve paresis"	Parietal bone Dural-based mass	No recurrence
Goel et al. [1]	2012	17	Female	1-year seizures Left scalp swelling Right hemiparesis Aphasia GCS 10/15 Right facial palsy Right spastic tone	Parietal bone	No recurrence
Mir et al. [7]	2013	7	Male	Right parietal scalp Generalised sewelling seizures	Parapharyngeal Infratemporal fossa Temporal lobe	Dead
Rao el al. [17]	2020	26	Male	Left mandible swelling	Parieto-occipital bone Dural lesion	Recurrence
Current case	2020	42	Male	Generalised seizures Blurring of vision Headache	Cranio-cervical junction	Recurrence Dead

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