Case Report

Acanthamoeba meningoencephalitis

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Abstract

Report of a case of young immunocompetent male adult with autopsy proven acanthamoeba meningoencephalitis. The patient presented with a protracted febrile illness of 3 months duration with features of meningoencephalitis, this was followed by rapid deterioration while on anti tuberculous therapy and steroids and ended fatally. His magnetic resonance imaging showed features of hemorrhagic meningoencephalitis and magnetic resonance spectroscopy showed choline peak. Autopsy revealed necrotizing meningoencephalitis and intraocular colonization due to acanthamoeba.

Key Words

Acanthamoeba meningoencephalitis, immunocompetent, intraocular colonization, magnetic resonance imaging, magnetic resonance spectroscopy

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Introduction

Cerebral amoebic infections are caused by free living amoeba. These are invariably fatal and diagnosis is often made postmortem. We present the clinical, radiological and pathological findings of a case of acanthamoeba encephalomeningitis diagnosed at autopsy and highlight imaging features that might help to suspect a diagnosis antemortem.

Case Report

A 16-year-old boy from Orissa with complaints of non-pulsatile, holocranial headache and low-grade, intermittent evening rise of temperature for 3 months and was on anti-tubercular therapy with steroids and anti-edema measures for clinically suspected central nervous system tuberculosis. He reported transient improvement of constitutional symptoms over the next 15 days, following which he developed right hemiparesis, motor aphasia and altered sensorium and was referred to our hospital. There was no preceding history of seizures, myoclonus, history of dog bite or vaccination. No history of exposure to unsafe sexual practices or drug abuse. There was no recent history of travel or water related activities preceding this illness.

On admission, he was febrile, drowsy and unresponsive to commands. Neurological examination revealed neck rigidity, right-sided hemiplegia, with hypertonia, and bilateral extensor plantar responses. Routine investigations including serum biochemistry (liver and renal function tests) and hemogram were normal except for mild peripheral blood leukocytosis (total white blood cells count was 12,600/cubic milimeter with neutrophillic predominance). Serology for HIV, and venereal disease research laboratory test was non-reactive.

A cranial magnetic resonance imaging (MRI) [Figure 1] revealed multiple, coalescing, predominantly T1 and T2 hypointense lesions with ring enhancement located in left capsuloganglionic region, thalamus, brainstem and cortico-medullary junctions, also lesions involving left basal ganglia showed a characteristic peripheral thin rim of T1 hyperintensity with blooming on gradient-sequences and hyperdensity on plain-computed tomography (CT) scans indicative of bleed. Magnetic resonance spectroscopy (MRS) [Figure 2] from the lesions revealed elevated lactate and choline peaks. Fluid attenuated inversion recovery images sequences revealed sulcal hyperintensities with contrast enhancement, suggestive of leptomeningitis. The left caudate head and lentiform nuclei showed features suggestive of acute infarct, corresponding to recurrent artery of Huebner territory.

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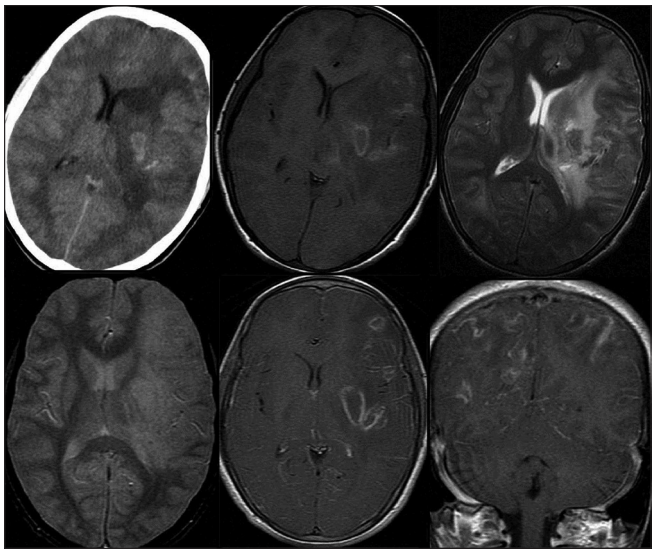

Figure 1: Left putamen and thalamus showing hemorrhagic lesions with features of leptomeningitis

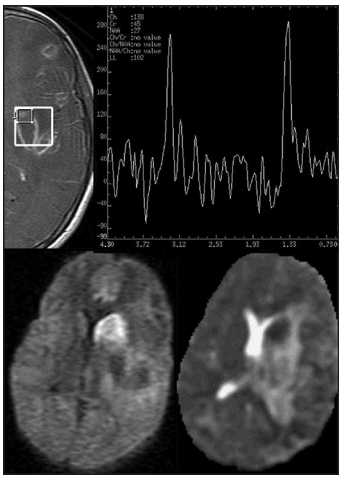

Figure 2: Multivoxel short TE MRS reveals raised choline (cho/cr-3) and lipid lactate with reduced NAA. DWI demonstrates acute infarct in left caudate head and anterior lentiform nucleus indicating occlusion of recurrent artery of Heubner due to arteritis

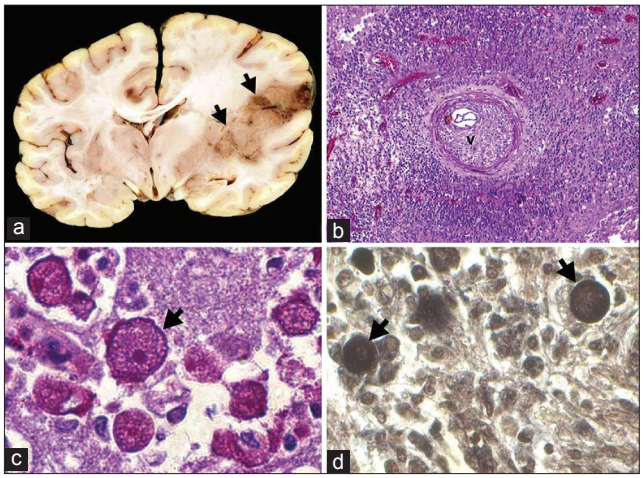

Figure 3: Large coalescing necrotizing hemorrhagic lesions are seen involving the insular cortex and putamen with extensive perilesional edema with compression of ipsilateral ventricle (a) on histology, dense vasculitis and inflammation is noted (b) large trophozoite forms with prominent nucleoli (c) is seen aggregating around vessels in addition to thick walled cyst forms of acanthamoeba (d)

Based on MRI features, possibility of a hemorrhagic meningoencephalitis either of viral or fungal origin was suspected. He succumbed to his illness on the second day of admission. A complete autopsy was performed following informed consent from close relatives of the deceased. At autopsy, the brain was diffusely edematous and revealed large necrotizing lesions with yellowish center surrounded by zones of hemorrhage involving parietooccipital lobes bilaterally, left orbitofrontal and inferior occipital regions [Figure 3]. On coronal slicing, multiple hemorrhagic, necrotic lesions were seen along the cortical ribbon mostly located in the crown of gyrus/depth of sulcus in left middle and inferior frontal lobe. At the level of optic chiasm, the left insular cortex showed large nodular confluent coalescing necrotic lesion [Figure 3] with central zones of yellowish xanthomatous areas with peripheral rim of hemorrhage [Figure 3a], extending along the sylvian fissure following the gyral pattern and superiorly into the left putamen compressing the ipsilateral ventricle. The surrounding white matter was edematous. Distinct pale necrotic lesions were seen in the left head of caudate, left uncus, left anterior hippocampus and anterior thalamic nucleus. The cingulate gyrus on the right also showed a hemorrhagic lesion involving the cortical ribbon.

The brainstem showed a nodular, hemorrhagic, necrotic circumscribed lesion in the upper pons on left side. No lesions were seen in mid-brain or cerebellum. Histologically these lesions revealed florid meningoencephalitis with mixed infiltrate of lymphocytes and histiocytes flooding the subarachnoid space. The larger leptomeningeal vessels were thrombosed with dense inflammation [Figure 3b]. The inflammatory infiltrates were seen invading the underlying cortex. The smaller parenchymal venules entrapped in the inflammation were ruptured forming small pools of fresh hemorrhage. Parenchymal necrosis and hemorrhage was prominent with venulitis. Foci showed ill-formed granulomas with histiocytic aggregates and multinucleate giant cells. Special stains for fungal hyphae and acid fast bacilli were negative. Periodic acid Schiff stain highlighted several large trohphozoite form of amoeba surrounding penetrating venules and filling the Virchow Robin spaces in continuity with subarachnoid space [Figure 3c]. In addition scattered cysts morphologically resembling Acanthamoeba were detected perivascularly by silver stains [Figure 3d]. The trophozoites were large (25 microns to 40 microns), with thick cell wall and prominent nucleoli. The cysts were multinucleate with thick cell walls. Trophozoites and cysts were also found in necrotizing lesions in pons. The posterior half of eye ball with optic nerves removed at autopsy revealed dense inflammation expanding the subarachnoid space surrounding the optic nerve, particularly on the left side with scattered trophozoites detectable in the perioptic space and within the substance of the optic nerve.

The lungs were boggy, subcrepitant and revealed bilateral consolidation with evidence of bronchopneumonia on histology. No trophozoites were detectable. The liver and spleen were enlarged and revealed multiple small abscesses and necrotizing granulomas with scattered trophozoite forms of acanthamoeba. Cysts were not detectable in the organs. Dot polymerase chain reaction for acanthamoeba was positive in serum and in vitreous of the left eye and brain tissue [Figure 4] but negative in Cerebro spinal fluid. Dot blot is the simplification of conventional method, a mixture containing the molecule to be detected is applied directly on a membrane as a dot and is then spotted through circulate templates on to the membrane. No electrophoresis is applied and hence saves time, it confirms the presence of the biomolecules which can be detected by DNA probes or antibody. The principle is that a single oligoprobe can hybridize to a second DNA molecule that contains the target sequence. So, it is speculated that, following primary parasitemia secondary to poor host defenses, the parasite might have seeded the choroid of the left eye, spread through the lamina cribrosa into the peri-optic subarachnoid space, and extended along the subarachnoid space into basal cisterns, along sylvian fissure and into the parenchyma. We were handicapped with the absence of history and a very brief stay of the patient at our hospital, it is likely that he harboured the organism as a normal commensal probably in his nasal mucosa. Parasitemia would have occurred following breakdown of the local barriers secondary to viral infection.

Discussion

Pathogenic free-living amoebae include Naegleria fowleri, Acanthamoeba spp., Balamuthia mandrillaris and Sappinia diploidea. While Acanthemeba and Balamuthia cause granulomatous amebic meningoencephalitis, Naegleria causes primary amebic meningoencephalitis, an acute fulminant rapidly fatal disease affecting healthy children and young adults. These two entities have distinct clinical profiles, pathologies, imaging, treatment and prognosis.[1]

Acanthamoebae is distributed ubiquitously in air, soil, water, chlorinatedwater in swimming pools, contaminated contact lens solutions, dialysis units, sewage and air-conditioning units.[2] Despite their ubiquitous presence, they hardly cause disease in the immunocompetent. It usually infects debilitated and immunocompromised individuals. Conditions predisposing include diabetes mellitus, renal failure, bone marrow failure, lymphoproliferative and hemato proliferative disorders, splenectomy, dysproteinemias, radiotherapy, corticosteroids, chemotherapy, and acquired immunodeficiency syndrome.[3-5] Infections have been reported to occur with rituximab (anti CD20 monoclonal antibody),[6] after autologous peripheral stem cell use for leukemia or lymphoma and also in immunocompetent individuals from low socio-economic status.[7]

This patient was presumed to be not immunocompromised primarily as he did not suffer from frequent infections in the past; however, we could not do the laboratory confirmation. History of swimming could not be obtained as he was in altered sensorium. Acanthamoeba spreads hematogenously from a primary lung or skin infection causing primary parasitemia. However, hematogeneous spread from Acanthamoeba keratitis has not been reported to occur.[8] Clinically, granulomatous amebic encephalitis has a gradual onset with a subacute to chronic course with low grade fever, headache, seizures, focal neurological deficits and altered mentation.[4,9] Cerebrospinal fluid (CSF) analysis shows mild to moderate pleocytosis with lymphocytes and neutrophils, decreased glucose and moderately elevated total protein.

Hanging drop technique can be used to identify the trophozoites which show characteristic movement in fresh CSF samples.[10] H and E, and immunohistochemistry in particular are used to identify the organisms on histology. Even when amoebae cannot be visualized, PCR can identify the type of amoebae causing the disease.

On gross examination, brain shows necrosis, edema and hemorrhage. Microscopically, chronic granulomas with multinucleated giant cells, lymphocytes, neutrophils and

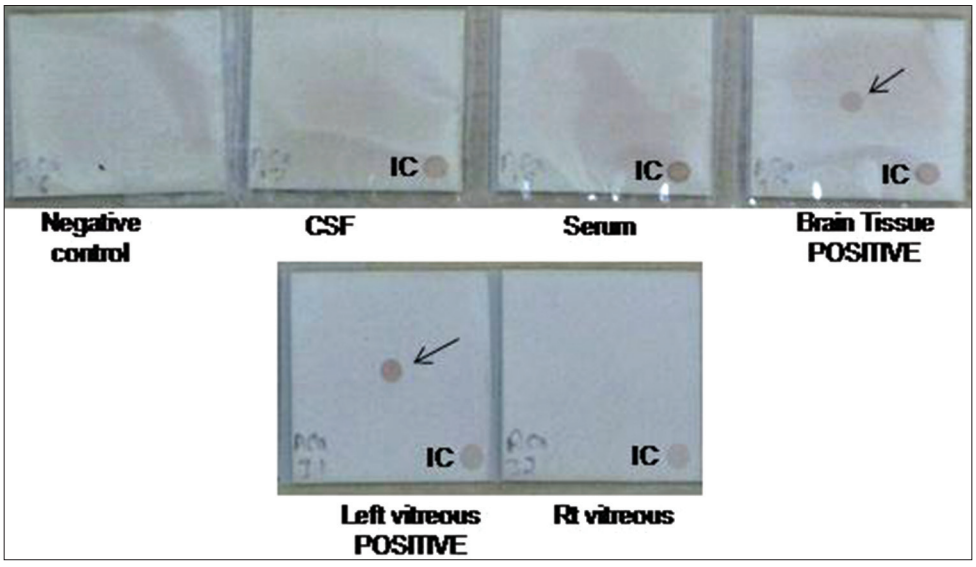

Figure 4: Dot blot hybridization of PCR product shows positivity in serum, brain tissue and left vitreous samples tested (arrows). The CSF and right vitreous was negative (IC: Internal positive control included in each)

eosinophils will be present with the trophozoite and cyst forms of acanthamoeba. Trophozoites are similar in morphology to macrophages but are larger and contain phagocytosed red blood cells. Only acanthamoeba presents with both the trophozoite and cyst forms in the tissue. The rest of free-living amoebae present with only trophozoite forms.[11] Parasites will be found in plenty in the perivascular spaces indicating hematogenous spread to the tissue. They release toxins which cause direct tissue destruction and severe necrotizing vasculitis which leads to hemorrhage, thrombosis and infarction. Our patient also had necrotic foci with peripheral rim of punctate hemorrhages and left caudate head acute infarct, which are the results of vasculitis. Cerebellum, brainstem and diencephalon are the sites ofpredilection.[3] However, in the present case, though brainstem was involved, cerebral hemispheres were predominantly affected. Leptomeningitis was also present. Severely immunologically suppressed patients may not exhibit granulomatous reaction.[3]

Imaging

Multifocal hemorrhagic lesions are noted in the cortico-medullary junction, ganglio-capsular region, thalamus and brainstem indicating hematogenous spread of the organism, with extensive perilesional edema and mass effect. Smaller lesions were present with punctate foci of hyperdensity (CT) and enhancement [Figure 1] indicating early stage of the lesions (cerebritis with hemorrhage). As lesions enlarge, they give a central region of non-enhancement indicative of necrosis with a peripheral thin rim of enhancement suggestive of inflammatory zone. The peripheral rim showed hyperdensity on CT, hyperintensity on T1 weighted images and blooming on gradient images indicating bleed, which was a characteristic feature. Intralesional hemorrhage has also been considered an important diagnostic feature.[12]

The organism causes necrotizing vasculitis which initially bleeds. This is responsible for the peripheral rim of hemorrhage which indicates the spreading front of the infection. Progression of vasculitis leads to vessel thrombosis resulting in tissue necrosis-the central nonenhancing T2 hypointense portion of the lesion. As lesions enlarge, adjacent lesions coalesce.

Involvement of meninges leads to exudates in the subarachnoid space which appear hyperintense on FLAIR and enhance on contrast. These enhancing exudates along with enhancement of subjacent cortex and medulla give a curvilinear gyriform (striated) enhancement (pseudo tumor appearance). Lesions have also been reported in spinal cord.[13] Necrotizing arteritis can lead to ischemic infarcts especially in the perforator territories. Our patient had acute infarction due to left recurrent artery of Heubner involvement. On T2 weighted images, hyperintense lesions have been described. However, in this case, lesions consistently showed central T2 hypointensity.

Multivoxel short TE magnetic resonance spectroscopy revealed raised choline (cho/cr-3) and lipid lactate with reduced N acetyl aspartate in the lesion of suggestive tissue destruction and anaerobic metabolism.[14] Differential diagnosis on imaging includes tubercular, fungal and toxoplasma infections. MRS in aerobic bacterial infection show acetate, succinate, lipid, alanine, glycine and lactate peaks, in anaerobic infections acetate and succinate peaks are not found. In tuberculosis choline and lipid peaks are prominent. MRS in viral infections, e.g., AIDS dementia complex inositol and choline peak is increased and NAA becomes reduced with the onset of dementia. Jacob Creutzfeldt virus show a better prognosis if there is increase in inositol to creatinine ratio. Subacute sclerosing pan encephalitis shows increase in inositol and decreased in NAA as disease advances. In herpes simplex encephalitis significant increase in lipid and lactate, moderate increase in choline and decrease in NAA is noted. Parasitic fungal and syphilitic gumma are difficult to differentiate from glial tumor.[15] Acanthamoeba infection was proved by the presence of both trophozoites and cysts in the tissue and by the PCR. However, the species specific typing of the acanthamoeba was not performed due to lack of the required facility. No effective treatment exists for Acanthamoeba meningoencephalitis.[16] Surgical excision along with intrathecal amphotericin is lifesaving. Fluconazole, rifampicin and pentamidine are also known to be effective.[11,17]

Conclusion

Cerebral amoebic infections are rare and fatal. On imaging, the characteristic marginal hemorrhage appearing as a ring of hyperintensity on T1WI and hyperdensity on CT stands out. This feature along with leptomeningitis and subacute to chronic constitutional symptoms with headache, vomiting and altered sensorium must prompt a differential diagnosis of acanthamoebic infection and institution of appropriate therapy at the earliest. Our case is unique in the sense that he had intraocular colonization and was not proved to be immune compromised.

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