CASE 8: ASPERGILLUS INFECTION – A. ASPERGILLOMA/ B. INVASIVE ASPERGILLOSIS
(Slide 8A, B, C: H&E, PAS, GMS = Aspergilloma; 8D, E, F: H&E, PAS, GMS = Invasive Aspergillosis)

**HISTOLOGY: Aspergilloma**

The section from the case shows granulomatous response enclosing multiple fragments of hyphae with significant stromal response. The lesion is located deep, covered by a cap of cerebral cortical tissue. On the surface, cerebral tissue shows reactive astrocytosis. The granulomatous pathology is seen extending along the Virchow Robin space reaching to the surface leptomeninges. Some of the circumscribed granulomas located close to perivascular spaces, show foreign body giant cell reaction with cytoplasmic vacuolation.

The lesion has numerous granulomas with giant cells, some of the giant cells being singly and randomly distributed, with minimal lymphoplasmacytic reaction. The giant cells in their cytoplasm have unstained spaces, some of them appearing branched/lobulated. PAS and GMS staining have revealed these unstained spaces to be septate acute angle branching hyphal forms of the fungus of Aspergillus species. None of the fungi are found in the vascular lumen or found invading the vessel wall. The intervening space between the granulomas is densely hyalinised, reflecting the chronicity of the pathology.

**DIAGNOSIS: ASPERGILLOMA - CEREBRAL**

**HISTOLOGY: Invasive Cerebral Aspergillosis**

The section through the cerebral cortex showed focal dense meningeal inflammation around a medium sized muscular artery and in the surrounding subarachnoid space. The branch of this vessel has a cluster of branching, septate, hyphal form of fungus, suggesting hematogenous spread of a fungal embolus. The surrounding vessels are enclosed in hemorrhagic exudates. Along the walls of the sulcus on both side and in the depth, numerous fungal hyphae are found in the small branching arterioles. This pathology has extended deep into the subcortical white matter. Many of the arterioles and veins showed fibrin deposition on the vessel wall and thrombosis of the vessel extending into capillaries. Many of the capillaries are plugged by thin fungal hyphae. These septate hyphae have granular bluish cytoplasm reflecting active metabolic state and proliferation. The parenchyma around is edematous, demyelinated and has dense polymorphonuclear leukocyte infiltration admixed with lymphocytes.

There is no granulomatous or stromal response, suggesting acute inflammatory pathology to the fungal invasion, via hematogenous route. The probable primary source could be lung.

**DIAGNOSIS: INVASIVE CEREBRAL ASPERGILLOSIS**

**COMMENT:**

**INVASIVE ASPERGILLOSIS:** common in debilitated/immunosuppressed host

Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger – common species.

- Found in soil, plants, decaying tree bark
- Septate, acute angle branching hyphae, spore forming
- Initial infectionsite – Lung, Paranasal sinuses, GIT, Ears, Skin, Head Trauma, Open heart surgery, Major vascular surgery
- Hematogenous dissemination to brain
Common Infections of the Nervous System

- Contiguous spread by destroying bone; Cribriform plate, orbital roof
- Lymphatic spread via air ways
- Organs most frequently involved by metastatic spread – Heart, Brain, Kidney, GIT, Liver, Thyroid, spleen.
- CNS areas commonly involved – ACA, MCA territories
- Neurological signs – often nonspecific, raised ICT, headache, hemiparesis, seizures, fever, cranial nerve palsy, blurring of optic disc
- **CSF:** Pleocytosis (<600 cells/cmm), moderate elevation of Protein, Glucose – normal. Fungus is not usually found in CSF. PCR is available for diagnosis

ELISA test on serum developed. Test on CSF to be validated.

**Diagnosis established**

- Mostly after death.

**Pathology**

- **Hematogenous spread** – Multiple lesions, mycotic aneurysm
- **Acute stage** – purulent, necrotizing lesion in basal ganglia, thalamus, grey-white matter junctions.
- **Chronic** – fibrosis, granulomas

- **Fungus** – highly angiotropic, hemorrhagic lesions (mistaken for hemorrhagic infarcts)
- Small hemorrhagic lesion resemble septic infarcts, vascular thrombosis, cerebritis, abscesses; (necrotizing non suppurative lesions)
- Rarely intraparenchymal granulomas with fibrosis.

Aspergilloma: Contiguous spread from sinuses – pale, firm, fibrous lesions (mistaken for Basal menigioma, tuberculoma)

**HISTOLOGY**

- Abscesses with pus – polymorphonuclear leukocyte reaction
- Granulomatous lesions, fungal hyphae in giant cells
- Necrotising non suppurative lesion – Necrosis resembling caseous form as in tuberculoma

**DRUG**

- Amphotericin B, Fluocytosine

Aspergillosis is caused by Aspergillus fumigatus, A.niger, A.flavus and A.oryzae. The fungus is ubiquitous and consists of branching, septate hyphae with a diameter of 3-10µm. Most affected individuals are immunocompromised although immunocompetent individuals may also be affected. Infection is usually acquired by inhalation of air borne spores reaching the lung and paranasal sinuses. The invasive form of Aspergillosis shows the fungi in high metabolic state and proliferating potential evidenced by bluish fungal cytoplasm and distinct septation. These fungi can be seen diffusely in arterioles and capillaries. They are also found invading the media of the medium sized muscular arteries. They can elicit neutrophilic reaction similar to mucor mycosis.

There are three main types of Aspergillosis: Allergic Bronchopulmonary Aspergillosis which affects the paranasal sinuses and the lung, Aspergillomas occurring in the lung, paranasal sinuses or brain and Invasive Aspergillosis which is seen in debilitated or immunosuppressed patients. Intracranial Aspergillomas can arise in any location but are more frequent in the orbitofrontal and basal temporal lobes. They produce symptoms and signs of a slowly growing mass lesion. Histologically, aggregates of lymphocytes, plasma cells, epithelioid cells and multinucleated Langhan’s gaint cells associated with variable amounts of collagen, necrotic tissue and fungal hyphae are seen. Invasive Aspergillosis of the CNS is usually a secondary process
Fungal Infections

with the organisms spreading directly to the CNS from the paranasal sinuses or orbit or hematogenously from distant sites such as lung, liver and GIT. A variety of lesions may be produced in the CNS. Single or multiple hemorrhagic infarcts due to occlusion of intracranial arteries by the organism may result. These often evolve into septic infarcts associated with cerebritis and abscess formation. Necrotizing vasculitis and angioinvasion are the characteristic features of these lesions. Mycotic aneurysms and meningitis may also occur.

The species identification of Aspergillus is by culture and A.fumigatus and flavus are the most common offending organisms.
CASE 8 - ASPERGILLOMA – CEREBRAL

Fig A: Low magnification of the lesion showing multiple giant cells randomly distributed in fibrous stroma with sparse lymphocytic response. (H&E Obj X 1.6)

Fig B: Higher magnification shows intracytoplasmic hyphae of Aspergillus within the giant cells. (H&E Obj X 20)

Fig C: Elongated, hyphal forms of Aspergillus inside capillaries. The fungi are bluish reflecting high metabolic state and multiplication. Inflammation is minimal. (H&E Obj X 20)

Fig D & E: The hyphae forms of the fungi in the granulomas are PAS positive highlighting glycoprotein cell wall. (PAS Obj X 20)

Fig F: Branching hyphal forms of Aspergillus show branching and stained black by Methamine silver. (GMS Obj X 20)

Fig G: Aspergillus fungi are seen invading the vessel wall and projecting into lumen. (GMS Obj X 20)

Fig H: Higher magnification of the hyphal forms of Aspergillus showing septation and branching. (GMS Obj X 40)

Fig I: Electron micrograph of a hyphal form of Aspergillus fumigatus with a dense outside wall and a septum inside. (X 10,000)