

Case Based Learning Infection



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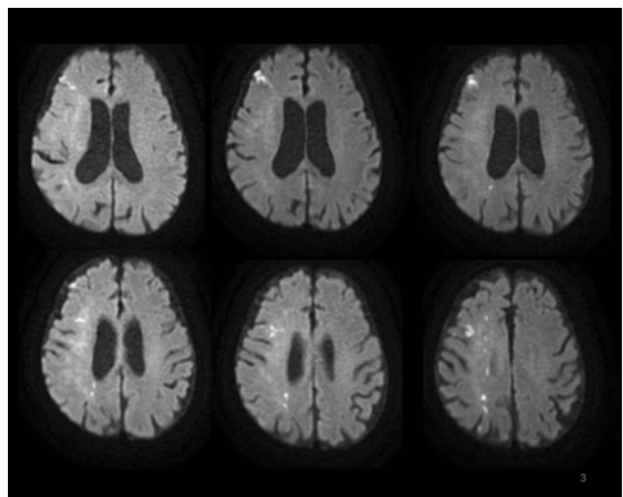
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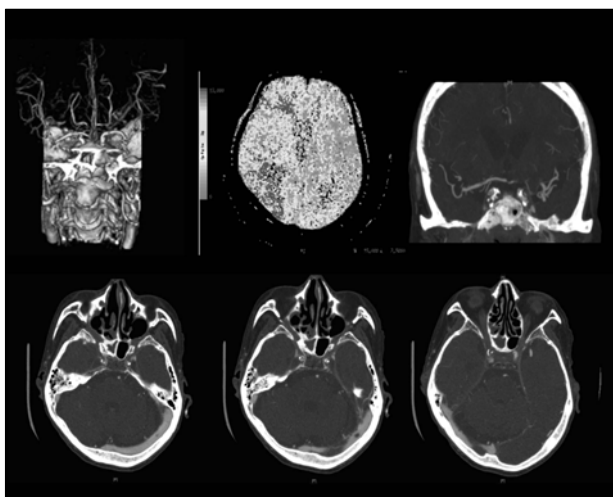
Case

- M/76 with altered consciousness
- Known DM, HT, prostatic cancer (stage IV)
- Herpes zoster (18 MA)
- 내원 5일전 침대에 앉아 있다 갑자기 왼쪽으로 넘어짐. 이후 왼쪽으로 **limping gait**가 있었다.
- 내원 1시간전 식사 중 서서히 고개를 떨구고 의식 저하, 자극에 대한 반응이 떨어짐.
- N/E 상 painful stimuli 에 대한 response 저하 (Lt > Rt)

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Hospital Course

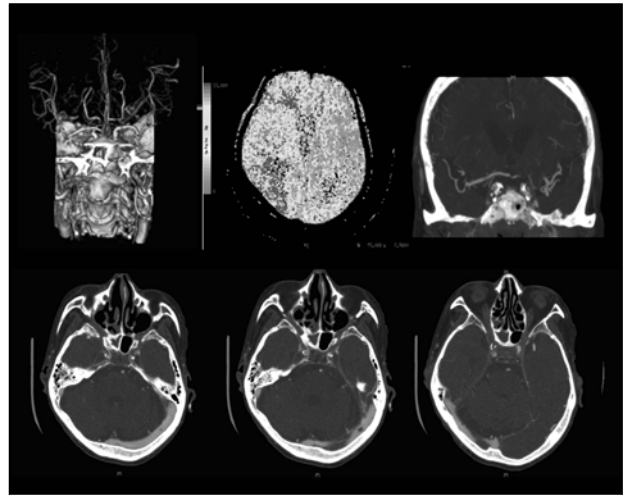
- NIHSS: 12
- EKG: sinus tachycardia only
- MMSE: uncheckable due to stupor consciousness
- Treatment plan
 - Anticoagulation > antiplt drug
 - Hydration
 - Stent insertion 고려

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Hospital Day 2

- Fever, pneumonia
 - WBC: 12,900 ESR: 73 CRP: 6.75
- 수개월 전부터 코에서 뽕뽕 소리가 났다.
- CT 판독
 - R/O invasive fungal sinusitis

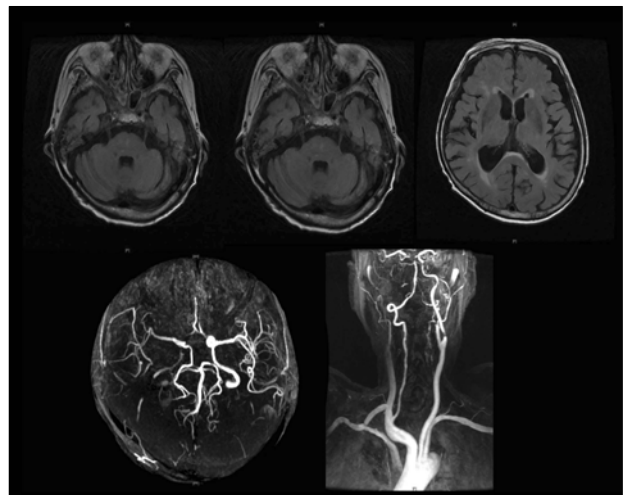
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Hospital Day 2

- Amphotericin B start
- CSF study
 - Pressure: 13mmH₂O
 - RBC: 0 WBC: 0
 - Protein 121.2mg/dL Glucose 107mg/dL (serum 188)
- Routine MRI

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Hospital Day 4

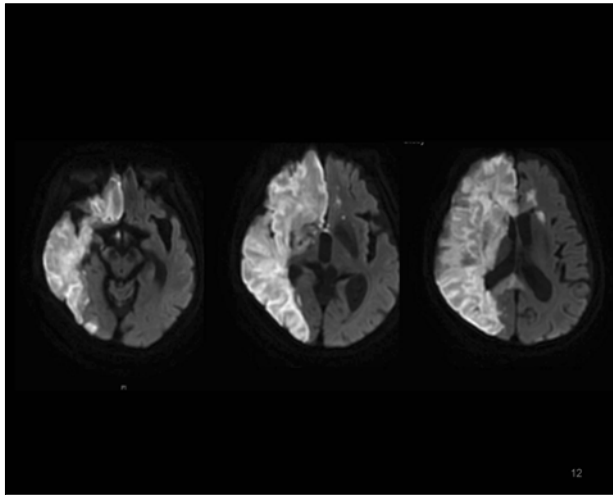
- CSF study
 - Aspergillus Ag (+)
 - Cryptococcus Ag (-)
- Endoscopic bx and Tx of sphenoethmoidal recess
 - Invasive fungal sinusitis < fungus ball
- Antifungal agent
 - Amphotericin B => Voriconazole

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Hospital Day 5

- Pathology
 - Consistent with aspergillosis
- Steroid 사용 여부 결정
- Clinically progressed

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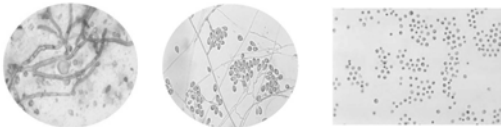
Hospital Course

- Fever, pneumonia improved
- 의식 상태는 eye contact 정도로 호전.
- 재활치료에 협조가 되지 않음.
- 요양병원으로 전원 (3 weeks later).

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Mold Infection of CNS

- Fungus
 - Mold: grows in the form of multicellular filaments called hyphae
 - Yeast: adopt a single celled growth habit (cryptococcus, candida Sp)
- Mold
 - Ubiquitous organisms found in soil, water, and decaying vegetation
 - All have septate, angular, branching hyphae in tissue



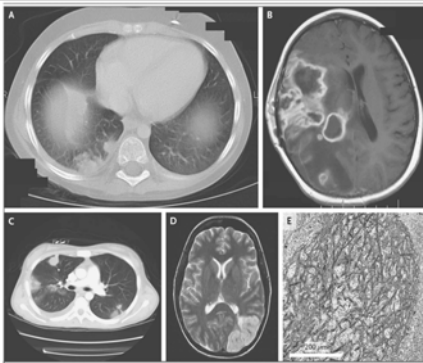
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Mode of CNS Infection

- Direct
 - As a result of surgery, trauma, IV drug use, and contaminated medical supplies
 - Even in immunocompetent persons
 - *Exophiala dermatitidis*, *E. rostratum*
 - Adjacent structures including sinuses, mastoids, and orbit
 - Ethmoid sinus => cavernous sinus thrombosis, brain
 - *Mucor circinelloides*, *aspergillus fumigatus*
- Indirect
 - Respiratory tract => hematogenous dissemination to CNS
 - Hyphal angioinvasion with thrombosis, hemorrhagic infarction
 - Common in immunocompromised patients (ChemoTx, leukemia)
 - *Aspergillus fumigatus*

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Indirect CNS Involvement



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Four Cornerstones of Management

- Early diagnosis
- Administration of antifungal chemotherapy
- Neurosurgical assessment and intervention
- Management of immunologic impairment

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Early diagnosis

- Early diagnosis
 - Early CT and MRI in patients who are at risk or who have documented invasive mold infection of the lungs and sinuses
 - Two distinctive patterns
 - **Direct invasion** causing a single abscess or a few abscesses in frontal or temporal lobe
 - **Hematogenous infection**, which may lead to solitary or multiple small abscesses that are often seen at the junction of cerebral gray and white matter junction and in the putamen-striatal artery distribution, or cause mycotic aneurysm
 - Detection of CSF Antigen and 1,3- β -D glucan in aspergillosis or other mold infection (Sensitivity, Specificity; 40 - 90%)
 - PCR assay for aspergillosis, but standardized platforms are lacking

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Mold	Mold Taxon and Common Features Used for Identification	Common Host Factors	Common Symptoms and Signs	Diagnostic Tests	Neuroimaging
	Aspergillus fumigatus Calcofluor-white potassium hydroxide fluorescent stain: Thin, septate hyphae of <i>A. fumigatus</i> are seen on this direct smear of a brain-biopsy sample.	Neutropenia, solid-organ or hematopoietic stem-cell transplantation	Focal deficits	Galactomannan in serum, bronchoalveolar-lavage specimen, or CSF; 1,3- β -D-glucan in serum or CSF; positive PCR assay	Cerebral infarcts, parenchymal hemorrhage, mycotic aneurysms, abscess
	Mucor circinellus LPCB: The hyphae are broad, ribbonlike, and hyaline. Two large, round sporangia (arrows) contain many spores. Rhizoids are absent.	Diabetes mellitus, neutropenia, solid-organ or hematopoietic stem-cell transplantation, iron-overload conditions	Sino-orbital mucormycosis; cranial-nerve palsies, cavernous sinus infection, focal deficits	Positive PCR assay	Cerebral infarcts, parenchymal hemorrhage, mycotic aneurysms, cavernous sinus thrombosis
	Scedosporium apiospermum Front of inhibitory mold agar plate showing dark, "mossy-green" colonies.	Drowning, trauma, neutropenia, solid-organ or hematopoietic stem-cell transplantation	Focal deficits	1,3- β -D-glucan in serum or CSF; positive PCR assay	Cerebral infarcts and abscesses
	Scedosporium prolificans LPCB: Hyphae are septate, and the conidogenous cell has a swollen base (arrow) and elongated neck. Conidia with truncated bases form in clusters at the apex of the conidogenous cell.	Trauma, neutropenia, solid-organ or hematopoietic stem-cell transplantation	Focal deficits	Positive blood culture; 1,3- β -D-glucan in serum or CSF; positive PCR assay	Cerebral infarcts and abscesses
	Fusarium species Sabouraud dextrose agar showing yellow-orange colonies.	Neutropenia, hematopoietic stem-cell transplantation	Focal deficits, nodular cutaneous lesions, bilateral endophthalmitis	Positive blood culture; galactomannan in serum, bronchoalveolar-lavage specimen, or CSF; 1,3- β -D-glucan in serum; positive PCR assay	Cerebral infarcts, parenchymal hemorrhage, mycotic aneurysms

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Issues in Diagnosis

- The morphology and size determine the phenotype
 - Small size (up to 20 μ m)
 - Cryptococcus, candida, blastomyces, etc
 - Access to microcirculation => subarachnoid space => meningitis, subpial ischemic change
 - Larger size
 - Aspergillus, zygomycetes
 - Obstruct large and intermediate arteries and vein, resulting in large infarction
 - Mild CSF abnormality
- Laboratory studies
 - 1,3- β -D glucan
 - A cell wall component, aspergillosis, but nonspecific
 - Fungal antigens
 - CSF > serum, can be detected within 5-8 days before the development of clinical symptoms and signs

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Antifungal Therapy

- Three classes of drugs
 - Polyenes (amphotericin B formulations)
 - Triazoles (voriconazole, itraconazole, and posaconazole)
 - Echinocandins (caspofungin, micafungin, anidulafungin)
- Clinical usage
 - **Voriconazole** is the primary agent for CNS aspergillosis
 - **Amphotericin B** is the first line for mucormycosis
 - The roles of other triazoles and echinocandins in CNS infection have not been defined for low CSF concentrations
 - The administration of antifungal agents through a ventriculostomy or by the intrathecal route is not recommended because of local toxic effects and a lack of proven efficacy
 - Steroid?

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Mold	First-Line Therapy		Second-Line Therapy		Adjunctive Therapy and Comments†
	Adults	Children	Adults	Children	
Aspergillus species	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr Liposomal amphotericin B: 5-7.5 mg/kg/day IV	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr Liposomal amphotericin B: 5-7.5 mg/kg/day IV	Amphotericin B lipid complex: 5 mg/kg/day IV Caspofungin: loading dose, 70 mg/m ² /day IV; maintenance dose, 50 mg/m ² /day IV Posaconazole: 200 mg 4 times a day orally, then 400 mg PO twice a day Itraconazole: dosage depends on formulation	Amphotericin B lipid complex: 5 mg/kg/day IV Caspofungin: loading dose, 70 mg/m ² /day IV; maintenance dose, 50 mg/m ² /day IV	Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy. Combination therapy with voriconazole plus echinocandins may be more effective than voriconazole alone in pulmonary aspergillosis, but its effectiveness has not been determined for CNS aspergillosis.
Mucorales	Liposomal amphotericin B: 5-7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV	Liposomal amphotericin B: 5-7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV			Reversal of neutropenia, surgical resection, discontinuation of glucocorticoids, and control of diabetes mellitus should be used as adjunctive therapy; use of hyperbaric oxygen remains controversial. Combination therapy with liposomal amphotericin B and echinocandins may be synergistic, but its role in CNS disease is not well defined.
Scedosporium apiospermum	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr	Posaconazole: 200 mg orally 4 times a day initially, then 400 mg orally twice a day Itraconazole: dosage depends on formulation		Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy. This organism is resistant to all licensed antifungal agents.
Scedosporium prolificans	Surgical resection	Surgical resection			

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Table 1. Therapeutic Options for Mold Infections of the Central Nervous System (CNS).¹⁴

Mold	First-Line Therapy		Second-Line Therapy		Adjunctive Therapy and Comments
	Adults	Children	Adults	Children	
Fusarium species [†]	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV	Posaconazole: 300 mg orally 4 times a day initially, then 400 mg orally twice a day		Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy
Dematiaceous molds					
<i>Cladophiala berrisii</i>	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr	Liposomal amphotericin B: 3–5 mg/kg/day IV	Liposomal amphotericin B: 3–5 mg/kg/day IV	No single antifungal agent or combination of agents has proved to be effective; surgical resection is critical for a successful outcome
<i>Onychomycetes gallopava</i>	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV			Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy. Interpretive breakpoints for <i>in vitro</i> antifungal susceptibility tests have not been established for this organism
<i>Exophiala rostratum</i>	Initial therapy — voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr For severe or refractory infection, add liposomal amphotericin B: 5 mg/kg/day IV	Initial therapy — voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr For severe or refractory infection, add liposomal amphotericin B: 5 mg/kg/day IV			Decompression of spinal epidural abscess should be used as adjunctive therapy

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Neurosurgical Assessment & Intervention

- For diagnosis
 - Biopsy with prompt inspection of the specimen
 - Wet-mount preparation with calcofluor white stain, culture, and histologic analysis (with Gomori methenamine silver stain and periodic acid-Schiff stain)
 - In situ hybridization & immunohistochemical analysis may be helpful
 - Brain biopsy may be invasive, lung or sinus biopsy can be used
- For treatment
 - Early selective decompressive hemicraniectomy
 - Selective stereotactic decompression
 - Localized meningitis & arachnoiditis should be treated conservatively

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Management of Immunologic Impairment

- Innate host defense play a critical role in protection from and eradication of mold infection
- Strategies
 - The use of growth factors
 - Provision of granulocytes transfusion
 - Discontinuation or reduction in the dose of glucocorticoids
 - The correction of metabolic acidosis and hyperglycemia

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Summary

- Mold is a type of fungus, has septate, angular, branching hyphae
- Mold can invade CNS via direct or hematogenous involvement especially in the immunocompromised patients
- Amphotericin B is the drug of choice for mucormycosis and voriconazole is the drug of choice for aspergillosis
- Surgical intervention and immunologic consideration is important for the management for the patients

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