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Mental status changes in an immunocompromised patient

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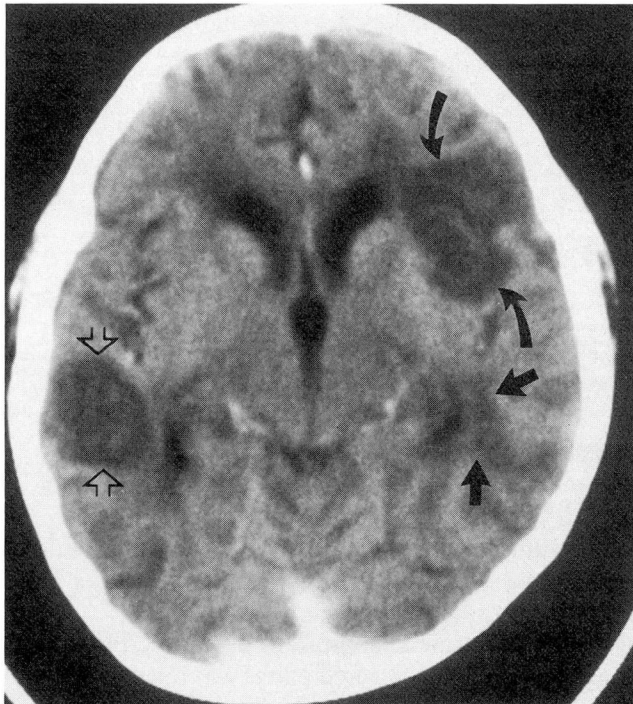


FIGURE 1. Contrast-enhanced axial computed tomography scan of the brain demonstrates multiple low-attenuation lesions involving the gray-white junction within the left frontal lobe (curved solid arrows), right posterior temporal lobe (open arrows), and left posterior temporal lobe (straight solid arrows), without significant enhancement.

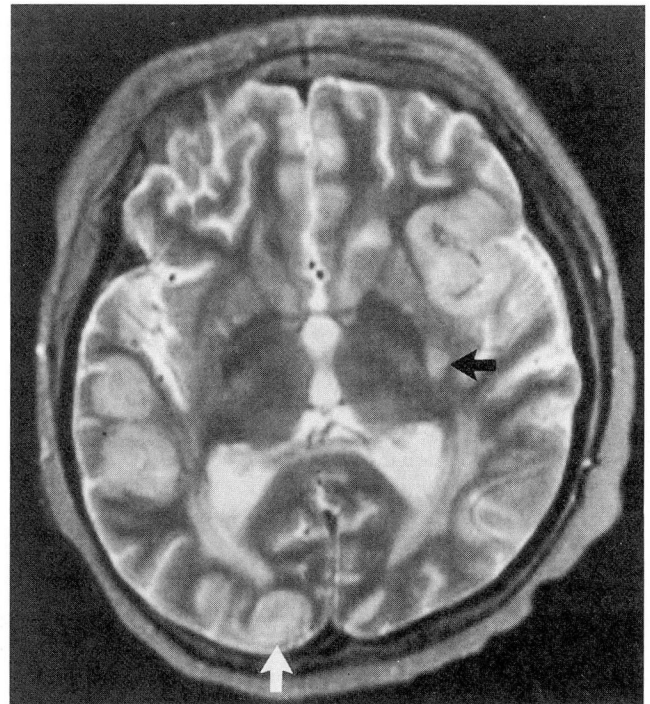


FIGURE 2. Spin-echo T2-weighted (TR 2500, TE 90) axial magnetic resonance imaging through the level of the third ventricle at a slightly different angulation than *Figure 1* also demonstrates the left frontal and right posterior temporal lobe lesions, with additional lesions noted in the right occipital lobe (white arrow) and in the posterior aspect of the left lentiform nucleus (black arrow).

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AN 11-YEAR-OLD boy with Burkitt's lymphoma and acute lymphoblastic leukemia was admitted to the Cleveland Clinic after he was found unarousable by his parents following 3 days of forgetfulness and expressive nominal aphasia. His diagnosis was made 15 months prior to

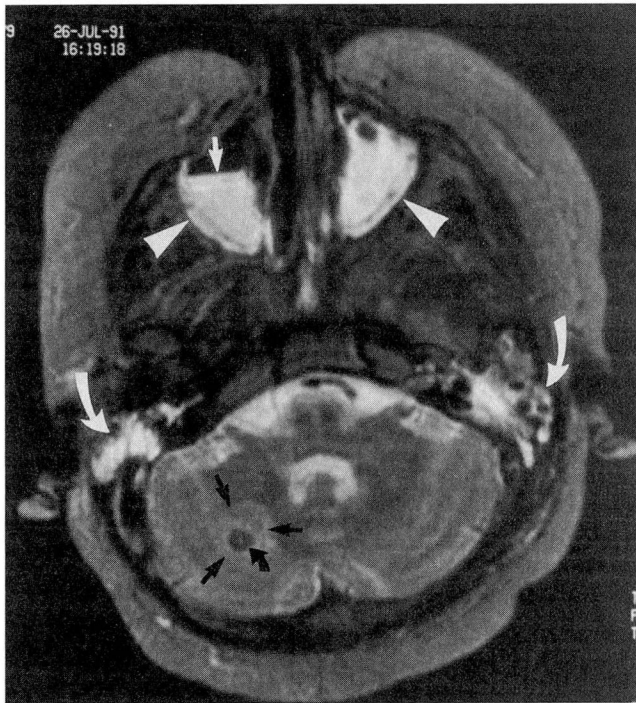


FIGURE 3. Spin-echo T2-weighted (TR 2500, TE 90) axial magnetic resonance imaging through the posterior fossa demonstrates an abnormal lesion of high signal intensity within the right cerebellar hemisphere (straight black arrows), with evidence of acute hemorrhage (curved black arrow). Also note evidence of inflammatory change within both mastoid sinuses (curved white arrows) and both maxillary sinuses (white arrowheads) with an air-fluid level in the right maxillary sinus (straight white arrow).

this admission. He had undergone autologous bone marrow transplantation 7 months after the initial diagnosis. He also received multiple courses of chemotherapy, including vincristine, methotrexate, daunorubicin, cyclophosphamide, leucovorin, and methylprednisolone sodium succinate. He had developed graft vs host disease and was put on a continuous regimen of cyclosporine and methotrexate.

Following intubation and stabilization, a computed tomography (CT) scan of the brain with intravenous contrast was performed, demonstrating multiple low-attenuation lesions involving the gray-white junction without significant enhancement (Figure 1). The patient's clinical condition did not improve. Magnetic resonance imaging (MRI) of the brain with contrast material was performed 2 days later, demonstrating the lesions noted on the CT scan, as well as multiple additional lesions, including a cerebellar lesion with evidence of acute hemorrhage (Figures 2 and 3). In

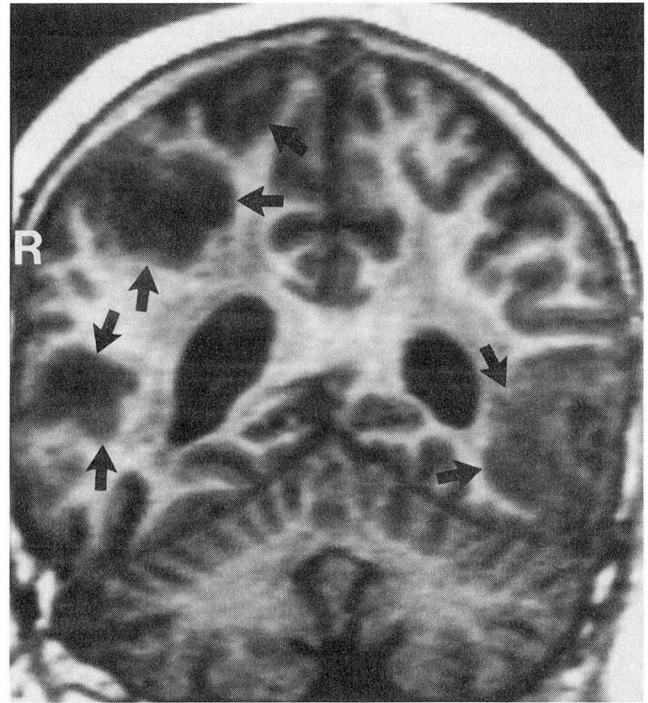


FIGURE 4. Low flip-angle gradient echo (TR 10, TE 4, 10° flip angle) coronal magnetic resonance imaging demonstrates the previously seen low-signal-intensity lesions (arrows) at the gray-white junction.

addition, inflammatory changes involving the mastoid and maxillary sinuses were noted, with evidence of an air-fluid level in the right maxillary sinus, indicative of acute sinusitis (Figure 3). Minimal enhancement of several of the cerebral lesions was noted (Figures 4 and 5).

Diagnostic tracheal aspiration was performed. A mold that grew on cultured plates was initially flat and gray, but the upper surface became powdery and dark green; the reverse side was white. Microscopically, the phialides were uniseriate and covered the upper two thirds of the vesicle. The mold was identified as *Aspergillus fumigatus*.

DIAGNOSIS: DISSEMINATED *ASPERGILLUS FUMIGATUS* INFECTION WITH BRAIN ABSCESSES

The patient was put on a regimen of high-dose amphotericin B. However, he continued to worsen rapidly and died on the sixth day after admission. At autopsy, *A fumigatus* was cultured from abscesses in both brain (Figures 6 and 7) and lung tissue. Fungi consistent with *Aspergillus* sp were also identified microscopically from

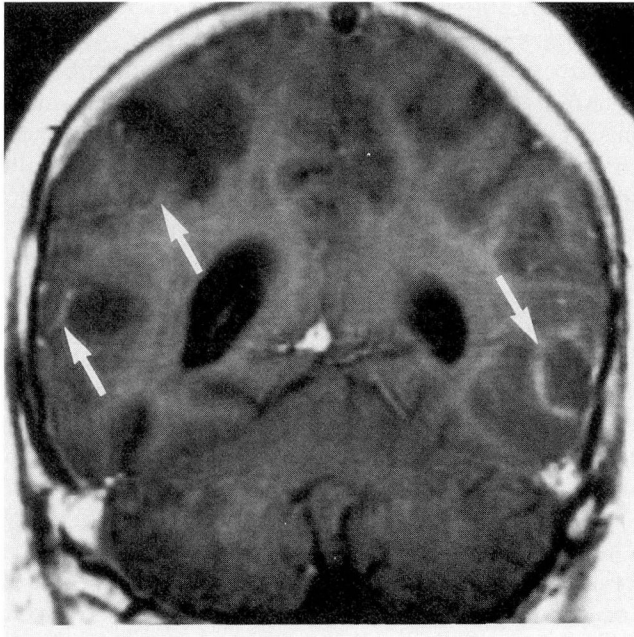


FIGURE 5. Spin-echo T1-weighted (TR 550, TE 15) coronal magnetic resonance imaging following the administration of intravenous gadolinium-DTPA at the same level as Figure 4 shows minimal enhancement (arrows) of the peripheral low-signal-intensity lesions.

abscesses in the kidney, thyroid, heart, stomach, and trachea.

DISCUSSION

The more than 350 species of *Aspergillus* are ubiquitous in the environment. "Aspergillosis" refers to disease such as allergy, colonization, or tissue invasion caused by *Aspergillus* sp. The conidiophores of *A fumigatus*, the species most often associated with aspergillosis, range from 2.5 to 3 μm and, when inhaled, can lodge in the alveoli or enter the paranasal sinuses. Despite the frequency of exposure, disease is uncommon in persons well armed with phagocytes (neutrophils, monocytes, and macrophages).¹

The conidia of *Aspergillus* sp are rarely seen in tissue; more commonly seen are the 5- to 10- μm -wide septate hyphae which branch dichotomously at a 45° angle. Although the histologic morphology can give good evidence for an infection caused by *Aspergillus* sp, it is important to confirm histologic suspicions with culture because in the absence of conidiophores the hyphae of *Aspergillus* sp resemble the hyphae of many other molds, including *Penicillium* sp, *Fusarium* sp, and even

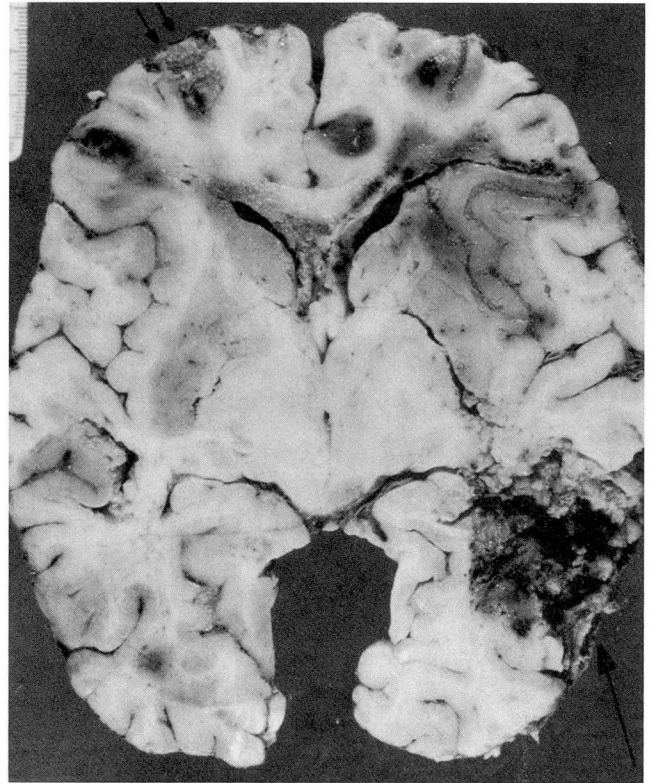


FIGURE 6. A 3.5- × 4.5-cm soft necrotic mass occupies the inferoposterior part of the left temporal lobe (single arrow). The right frontal pole (double arrow) contains a second necrotic area.

the Zygomycetes.

Definitive ante mortem diagnosis of invasive aspergillosis can be difficult. These infections most often occur in immunosuppressed patients, and their underlying diagnosis in concert with a frequently concomitant thrombocytopenia can make tissue biopsy risky. In patients such as this who have acute leukemia, fungal infections are often a complication of both antileukemic chemotherapy and other immunosuppression. Invasive aspergillosis is second only to candidiasis as the most common fungal infection in patients with acute leukemia. The most common presentation is with pulmonary involvement; autopsy studies have documented extrapulmonary dissemination in 10% to 25% of patients.² Of patients with disseminated aspergillosis, about one third will have central nervous system (CNS) involvement.³ CNS involvement can result from either hematogenous dissemination or direct spread from adjacent areas. In immunosuppressed patients *Aspergillus* sp can occlude the cerebral

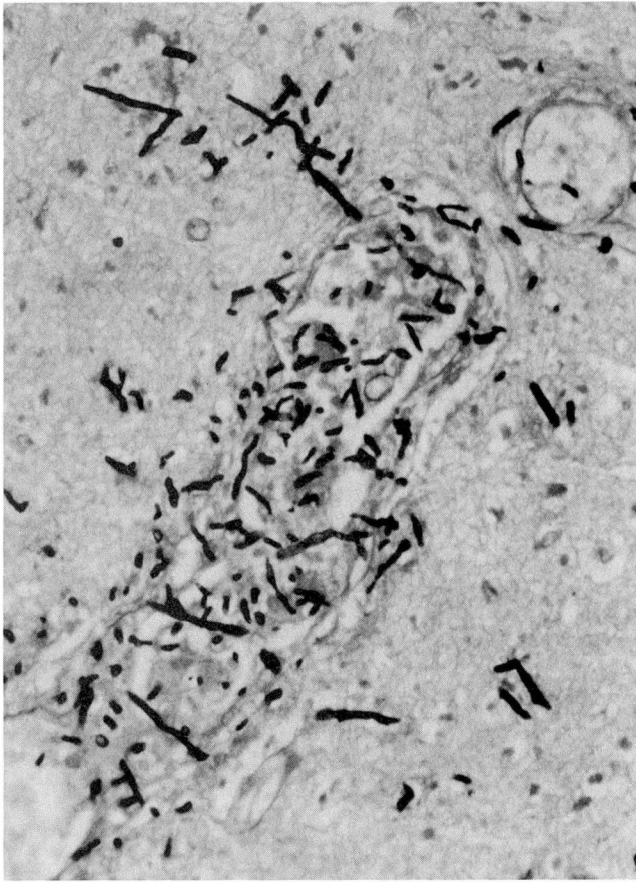


FIGURE 7. The darkly staining hyphal forms of *Aspergillus* sp invade through the blood vessel wall into the brain parenchyma (Gonori methanamine silver, original magnification $\times 60$).

vessels causing cerebral infarction. In non-immunosuppressed patients, the clinical signs and symptoms are like those of an abscess, and on histologic exam one sees necrotic tissue with many hyphae.¹

Infections in granulocytopenic patients are not only fungal. In fact, during initial chemotherapy infections are most often bacterial. The causative agents can be gram-negative (especially *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*) or gram-positive bacteria (*Staphylococcus* sp, especially *S aureus* and *S epidermidis*). Patients requiring a second dose of chemotherapy are susceptible to the same infections; in addition, these patients often have been in the hospital for longer periods, have received prolonged administration of broad-spectrum antibiotics, and have had shifts in their normal flora to gram-negative resistant rods. Many of these patients are colonized by

Candida sp; a significant number are colonized with *Aspergillus* sp, and in many patients latent viruses such as herpes simplex and cytomegalovirus reactivate.⁴

Among all patients with brain abscesses, most abscesses are bacterial in etiology. The yeast and dimorphic fungi are responsible for about 15% of brain abscesses, and most fungal abscesses occur in immunosuppressed patients. Among patients with neutropenia, the most common agents are *Candida* sp, *Aspergillus* sp, and the fungi causing zygomycosis (*Absidia*, *Rhizopus*, *Mucor*, and *Rhizomucor*). In patients with T-cell or mononuclear phagocytic defects, the organisms implicated most commonly are *Toxoplasma gondii* and *Nocardia asteroides*, as well as *Cryptococcus neoformans*, *Mycobacterium* sp, and *Listeria monocytogenes*.⁵

The radiologic evaluation of a patient with acute changes in mental status begins with a CT scan of the brain. An examination without contrast may be useful for excluding the presence of hemorrhage, mass effect, or hydrocephalus. If warranted, a contrast examination may be useful to look for abnormal enhancement. Following stabilization of the patient, MRI of the brain may be useful for further evaluation, as it has been shown to be more sensitive than CT in the evaluation of most CNS pathology. Advantages of MRI include its increased tissue contrast, superior anatomic localization, and the ability to image in multiple planes. However, its disadvantages include increased length of time per exam, greater sensitivity to patient motion, difficulty in imaging critically ill patients due to effects on life-support equipment and monitors, and the inability of some patients to complete the examination due to claustrophobia or the presence of a permanent pacemaker or other implantable medical device.

Factors influencing the differential diagnosis in the patient with mental status changes include patient age, medical history, clinical findings, and imaging findings. A focal or multifocal process, its anatomic distribution, its imaging characteristics, and its pattern of enhancement are all considered to develop a limited differential diagnosis. In this young patient with a history of Burkitt's lymphoma and acute lymphoblastic leukemia who was additionally immunocompromised due to bone marrow transplant and chemotherapy, the differential diagnosis of multiple intracranial lesions involving the gray-white junction included infection, infarctions, and lymphoma or leukemic infiltrates.

Fungal infection of the CNS results in a granulomatous reaction, producing findings similar to those of tuberculosis, pyogenic abscesses, or tumors.

CT and MRI demonstrate findings suggestive of meningitis, granuloma formation, abscess, or vasculitis with infarction and hemorrhage, with a general lack of specificity for the different fungal infections. Aspergillosis may involve the CNS, most commonly by hematogenous dissemination, and less commonly by direct extension from nasal cavity, orbit, or paranasal sinus infection, or by direct inoculation during surgery. Hematogenous spread usually is from a pulmonary focus, with the *Aspergillus* hyphae lodging in cerebral vessels and causing occlusion. Growth through the vessel walls produces hemorrhagic infarction which converts to septic infarction, resulting in associated cerebritis and abscess formation, usually in an anterior and middle cerebral arterial distribution. Case reports in the literature describe poorly defined areas which are initially focal and which later become widespread; these areas have low attenuation on CT, prolonged T1 and T2 relaxation times on MRI, variable mass effect, and minimal contrast enhancement.⁶⁻⁹ If direct extension occurs from the nasal cavity or paranasal sinuses, there is invasion of blood vessels, especially the Circle of Willis and the cavernous sinus, which results in angiitis, thrombosis, and infarction. Extension to the

subarachnoid space may also occur, resulting in meningitis and meningoencephalitis.¹⁰

In this case, the enhanced CT scan demonstrated multiple low-attenuation lesions involving the gray-white junction without significant enhancement (Figure 1). MRI demonstrated additional lesions with decreased signal on T1-weighted images (prolonged T1) (Figure 4) and increased signal on T2-weighted images (prolonged T2) (Figures 2 and 3). MRI also demonstrated a hemorrhagic lesion of the right cerebellar hemisphere (Figure 3). Minimal enhancement of a few lesions was demonstrated following the administration of gadolinium-DTPA (diethylenetriaminepentaacetic acid) (Figure 5). As this patient had evidence of mastoiditis and pansinusitis (Figure 3) and evidence of pulmonary infection by *Aspergillus*, the source of CNS infection is uncertain, although statistically and by anatomic distribution it was most likely caused by hematogenous spread from the lungs.

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REFERENCES

- Bennett, JE. *Aspergillus* species. In: Mandell GL, Douglas RG Jr, Bennett JE, eds. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990:1958-1962.
- Burch PA, Karp JE, Merz WG, Kuhlman JE, Fishman EK. Favorable outcome of invasive aspergillosis in patients with acute leukemia. *J Clin Oncol* 1987; 5:1985-1993.
- Barrios N, Tebbi CK, Rotstein C, Siddiqui S, Humbert JR. Brainstem invasion by *Aspergillus fumigatus* in a child with leukemia. *N Y State J Med* 1988; 88(12): 656-658.
- Schimpff SC. Infections in the compromised host—an overview. In: Mandell GK, Douglas RG Jr, Bennett JE, eds. Principles and practice of infectious disease. 3rd ed. New York: Churchill Livingstone, 1990:2258-2265.
- Wispelwey B, Scheld WM. Brain abscess. In: Mandell GL, Douglas RG Jr, Bennett JE, eds. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990:1958-1962.
- Grossman RI, Davis KR, Taveras JM, et al. Computed tomography of intracranial aspergillosis. *J Comput Assist Tomogr* 1981; 5:646-650.
- Jenkins JR, Siqueira E, Al-Kawi MZ. Cranial manifestations of aspergillosis. *Neuroradiology* 1987; 29(2):181-185.
- Nov AA, Cromwell LD. Computed tomography of neuraxis aspergillosis. *J Comput Assist Tomogr* 1984; 8:413-415.
- Mikhael MA, Rushovich AM, Ciric I. Magnetic resonance imaging of cerebral aspergillosis. *Comput Radiol* 1985; 9:85-89.
- Atlas SW, ed. Magnetic resonance imaging of the brain and spine. New York: Raven Press, 1991:523-525.