Cerebral histoplasmoma

Case report

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A 55-year-old man presented with dementia and seizures of recent onset. A computerized tomography scan revealed a ring-like lesion in the left occipital lobe, which on resection was found to be a histoplasmoma. Cerebral histoplasmoma is rare and simulates a metastatic brain tumor. Only eight cases of this entity have been reported.

KEY WORDS: cerebral histoplasmoma · histoplasmosis

Disseminated histoplasmosis is an uncommon manifestation of the common Histoplasma capsulatum infection. Less than 25% of patients with disseminated histoplasmosis have central nervous system (CNS) involvement. Three types of CNS involvement are recognized in the disseminated form: 1) miliary granulomas; 2) meningitis; and 3) solitary parenchymal granuloma or “histoplasmoma.” Review of the English literature disclosed reports of only eight patients with histoplasmoma. The rarity of this manifestation prompted our report.

Case Report

This 55-year-old cachectic man was admitted to our institution for evaluation of right-sided motor seizures and mental deterioration progressing over the previous 4 months. He had a history of systemic lupus erythematosi since 1961, when he presented with arthralgia and leukopenia. He was treated with prednisone and mercaptopurine (6-purinethiol) until 1977, when this therapy was discontinued due to the development of glaucoma. He was hospitalized at this center on several occasions for hypertension, alcoholism, inadequate nutrition, and peripheral neuropathy.

Examination. Physical examination was unremarkable except for a palpable mass in the left breast, bilateral atrophic testes, and condyloma acuminatum on the glans and shaft of his penis. White blood cell count was 3500/cu mm, hemoglobin 13.5 gm, and hematocrit 41%. Platelet count was 335,000/cu mm. Coagulation parameters were within normal limits. Chest x-ray films showed a diffuse patchy left-sided infiltrate, and a normal-sized heart. Electrocardiography was unremarkable. Computerized tomography (CT) of the head showed a ring-like lesion enhanced by contrast material in the left occipital lobe (Fig. 1). This was thought to be a metastatic neoplasm, and extensive work-up for a primary tumor was performed.

Bone marrow aspirate and biopsy, bronchoscopy, and bronchial washing for cytological analysis revealed essentially normal results, as did a liver-spleen scan, abdominal ultrasonography, and bone scan. Intravenous pyelography likewise failed to reveal any focal defect. Needle aspiration of the left breast mass showed gynecomastia. Sputum cultures for acid-fast organisms were negative. It was decided to treat the patient with steroids to reduce cerebral edema. Meanwhile, a left-sided pulmonary infiltrate noted at the time of admission eventually developed into a small abscess.

Operation. The patient was treated with antibiotics after appropriate cultures were performed, and underwent a left occipital craniotomy 2 weeks after admission. A circumscribed firm mass, 1.8 cm in diameter, was removed.

Postoperative Course. The patient was maintained on anticonvulsant drugs. Cultures of sputum, serum, and cerebrospinal fluid were negative for fungi, and bone marrow biopsy revealed no granuloma. Culture
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of the surgical specimen yielded *Histoplasma capsulatum*, and exo-antigen test for the identification of *Histoplasma capsulatum* by the immunodiffusion technique was positive. Serological studies were reactive at 1:16 for the yeast phase and 1:8 for the histoplasmin. The patient was treated with 2 gm of amphotericin-B intravenously for a period of 12 weeks, and showed progressive improvement.

**Pathological Examination.** On gross examination, the lesion was round and firm with central necrosis (Fig. 2 left). Touch imprint of fresh tissue revealed myriads of organisms in macrophages. Microscopic examination of the surgical specimen showed a caseous granuloma composed of a central necrotic area surrounded by sheets of macrophages, fibroblasts, blood vessels, and multinucleated giant cells. Innumerable round to oval organisms, approximately 2 to 4 μ in diameter, were present in the macrophages. Periodic acid-Schiff (PAS) and Gomori’s methenamine silver nitrate technique showed morphological and staining characteristics typical of *Histoplasma capsulatum* (Fig. 2 right).

Samples for electron microscopic examination were recovered from fresh tissue and were fixed in phosphate-buffered 3% glutaraldehyde, followed by 1% osmium tetroxide. Thin sections were stained with uranyl acetate and lead citrate, and examined in a Philips EM 300 transmission electron microscope. Ultrastructural findings of the organisms were similar to previously reported electron microscopic studies of *Histoplasma capsulatum*. Organisms were round or oval, and composed of an electron-dense cell wall lying directly over a serrated plasma membrane. Cytoplasm showed few ellipsoid mitochondria. Numerous ribosomes were distributed freely in the cytoplasm. Some organisms showed vacuoles containing dense granular material or tubulo-vesicular structures. The nucleus was large and eccentric, and contained a nucleolus. Chromatin was evenly distributed or showed peripheral aggregate (Fig. 3 left). The fungi were present in the macrophages (Fig. 3 right). The latter possessed large cytoplasm where numerous swollen mitochondria, abundant rough endoplasmic reticulum, microvesicles, and dense bodies of lysosomal types were prominent. Organisms were present in phagosomes or vacuoles lined by a single membrane (Fig. 4). Some phagosomes contained cytoplasmic elements as well as fungi.

**Discussion**

Histoplasmosis is a systemic fungal infection caused by *Histoplasma capsulatum* and is most common in the Ohio, central Mississippi, and St. Lawrence River valleys. The primary portals of infection are the respiratory tract, mouth, gastrointestinal tract, and skin.

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**Fig. 1.** Computerized tomography after administration of contrast material showing enhancement in a ring-like pattern in the left occipital lobe.

**Fig. 2.** _Left:_ Gross photograph of the bisected granuloma with central caseous necrosis. _Right:_ Photomicrograph showing many *Histoplasma capsulatum* fungi in a macrophage. PAS, x 400.
Histoplasmosis usually presents as acute pulmonary infection, chronic cavitary infection, or progressive disseminated infection. The great majority of infections fall into the first category, and present as respiratory infections of varying intensity. These have a self-limited course, and symptoms include fever, cough, and chest pain. The chronic cavitary form is clinically and radiologically very similar to tuberculosis. The disseminated form is seen most frequently in infants, elderly men, and immunosuppressed adults. It presents a fulminating systemic illness with severe constitutional symptoms. There is frequently a fatal outcome or a very chronic course in which focal lesions produce dominant clinical symptoms. Fever, chills, anorexia, and weight loss are common. Hepatosplenomegaly, anemia, leukopenia, thrombocytopenia, interstitial pneumonia, intestinal ulceration, and oropharyngeal ulcers constitute the clinical picture. Adrenal glands, meninges, and brain are the organs most commonly involved in the disseminated form. Schulz reported involvement of brain or meninges in 10% of a series of autopsied patients. In a series of 26 patients with disseminated histoplasmosis, published by Smith and Utz, six patients (23%) had evidence of CNS involvement. Cooper and Goldstein reported CNS involvement in 24% of cases of disseminated histoplasmosis. Histoplasmosis of the CNS can be classified into three categories: miliary granulomas, meningitis, and histoplasmoma. The last is a granuloma, which attains a size sufficient to suggest an intracranial neoplasm by causing increased intracranial pressure and destruction of brain tissue, clinically manifested by sensory and motor deficits. Miliary granulomas are very similar to those seen in tuberculosis.

The clinical features of the nine known cases of cerebral histoplasmoma are summarized in Table 1. Eight of the patients were male and one female. The predominance of males was likely due to greater occupational exposure. Solitary masses were noted in seven cases and multiple histoplasmomas were present in two cases. Two patients showed pulmonary histoplasmosis. Disseminated histoplasmosis may occasion-
TABLE 1
Clinical data from patients with cerebral histoplasmoma

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Age (yrs), Sex</th>
<th>Underlying Condition</th>
<th>Clinical Presentation</th>
<th>Location of Lesion</th>
<th>Specific Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>White &amp; Fritzlen, 1962</td>
<td>63, M</td>
<td>tuberculosis, diabetes</td>
<td>spastic hemiparesis, homonymous hemianopsia</td>
<td>rt frontoparietal region</td>
<td>surgery</td>
<td>death</td>
</tr>
<tr>
<td>Cooper &amp; Goldstein, 1963</td>
<td>67, M</td>
<td>none</td>
<td>ataxia, coma</td>
<td>4th ventricle, pons, midline of cerebellum</td>
<td>none</td>
<td>death</td>
</tr>
<tr>
<td>Greer, et al., 1964</td>
<td>46, M</td>
<td>none</td>
<td>seizure, headache</td>
<td>lt frontoparietal region</td>
<td>surgery &amp; amphotericin B</td>
<td>survival</td>
</tr>
<tr>
<td>Tvetan, 1965</td>
<td>48, F</td>
<td>myelomatosi</td>
<td>headache, confusion, coma</td>
<td>lt cerebellar region</td>
<td>none</td>
<td>death</td>
</tr>
<tr>
<td>Bridges &amp; Echols, 1967</td>
<td>42, M</td>
<td>post-hepatic cirrhosis; histoplasmosis of tongue &amp; gingiva</td>
<td>headache, ataxia</td>
<td>lt cerebellar region</td>
<td>surgery &amp; amphotericin B</td>
<td>survival</td>
</tr>
<tr>
<td>LeBourgeois, 1979</td>
<td>63, M</td>
<td>none</td>
<td>rt hemiparesis</td>
<td>lt cerebellar region, pons</td>
<td>surgery</td>
<td>death</td>
</tr>
<tr>
<td>Schochet, et al., 1980</td>
<td>53, M</td>
<td>pulmonary histoplasmosis</td>
<td>seizure, rt hemiparesis</td>
<td>rt parietal region</td>
<td>surgery &amp; amphotericin B</td>
<td>survival</td>
</tr>
<tr>
<td>Duber &amp; Schnitzer, 1982</td>
<td>54, M</td>
<td>pulmonary histoplasmosis</td>
<td>seizure</td>
<td>lt frontal region</td>
<td>surgery &amp; amphotericin B</td>
<td>survival</td>
</tr>
<tr>
<td>Vakili, et al., 1983</td>
<td>55, M</td>
<td>systemic lupus erythematosus treated with prednisone &amp; mercaptopurine</td>
<td>seizure, dementia</td>
<td>lt occipital region</td>
<td>surgery &amp; amphotericin B</td>
<td>survival</td>
</tr>
</tbody>
</table>

Common ring-enhancing lesions on CT include primary brain neoplasms (particularly glioma), metastases, abscess, resolving intracerebral hematoma, cerebral infarction, and contusion (including recent surgery). Less common lesions are demyelinating process and radiation necrosis. In the vast majority of cases, a correct diagnosis can be suggested by the CT appearance and clinical presentation. Peripheral contrast enhancement on CT can be due to blood-brain barrier breakdown, luxury perfusion secondary to loss of autoregulation, or local metabolic changes resulting in hypervascularity or neovascularity associated with granulation tissue and gliosis. The exact mechanism responsible in each case is determined by the pathological process. In fungal infections, the mechanism is probably similar to that seen in tuberculomas in which the focal tissue reaction is related to the cell-mediated immune response incited by the fungus. In a series of immunocompromised patients with opportunistic CNS infections, Enzemann, et al., demonstrated that the intensity of the contrast enhancement and the extent of the “ring-like” appearance correlated with the patient’s ability to mobilize an adequate defense and contain the infection. The CT findings in our patient would indicate that his immune system is relatively competent and that he should have a good prognosis. Although not present in our patient, fungal infections of the brain are frequently associated with meningeal involvement. On CT, this would show up as obliteration of the basilar cisterns or sulci with contrast enhancement of the leptomeninges.

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References
6. Enzmann DR, Brant-Zawadski M, Britt RH: CT of cen-
S. T. Vakili, J. N. Eble, B. D. Richmond and R. A. Yount

central nervous system infections in immunocompromised patients. AJR 135:263-267, 1980
1978

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