Patients with orbital aspergillosis commonly present with unilateral proptosis and associated sinus disease. However, neither of these manifestations was observed in a 62-year-old woman who had an orbital apex syndrome with visual loss, complete ophthalmoplegia, and corneal hypoesthesia. Pathologic examination of a specimen from a granulomalike mass removed at left frontotemporal craniotomy showed branching hyphae with the characteristic appearance of Aspergillus.

Parasellar and orbital apex syndrome caused by aspergillosis

THOMAS R. HEDGES, M.D., and LAI-SUNG E. LEUNG, M.D.

Aspergillosis involving the orbit and cranial contents is rare; only 47 cases have been reported in the literature. The predominant clinical manifestations in such patients are proptosis and associated sinus disease. Loss of vision or paresis of extraocular muscles is less common. We report here a unique case of aspergillosis in which the orbital apex and the parasellar area were involved without proptosis or known sinus disease.

The orbital apex syndrome consists of involvement of the optic nerve and structures in the apex of the orbit within the superior orbital fissure, including the nerves to the extraocular muscles and the first division of the trigeminal nerve. It is usually associated with proptosis, but if the responsible lesion is contiguous with the cavernous sinus, proptosis may be absent and symptoms and signs present primarily as a parasellar lesion.

Case report. In March 1973, a 62-year-old previously healthy woman experienced a mild headache at the vertex and nuchal region 2 days after she had been hit on the head by a light plastic picture frame. She did not report significant pain or loss of consciousness at the time of the accident; subsequently, however, increasing pain developed in the forehead and the left eye and ear. She was first admitted to Friends Hospital voluntarily because of excess use of drugs for pain, but was then transferred to St. Mary's Hospital, Philadelphia, for investigation, which included a skull x-ray, a brain scan, an electroencephalogram (EEG), and routine blood work. All were within normal limits. She was discharged with the diagnosis of headache of unknown origin.

After she was discharged, pain in the left ear increased, with tinnitus, and she was admitted to Frankford Hospital, Philadelphia. Examination showed hand movements vision in the left eye, ptosis of the left lid, and an almost complete left external ophthalmoplegia. The left pupil was amaurotic, with no direct light reaction, but consensual and near reactions were intact. Results of fundus examination were normal in both eyes. Cerebrospinal fluid examination on April 10 showed opening pressure 140 mm Hg, fluid clear, glucose 73 mg per 100 ml, two white blood cells, 62 red blood cells, protein 37 gm, and a nonreactive VDRL. No culture was done. The workup included a skull x-ray, a brain scan, an EEG, a complete blood count, serology, and sedimentation rate determination; all were normal. A left carotid arteriogram was read as normal; however, on subsequent review, minimal narrowing of the carotid siphon was noted. The patient was given 40 mg prednisone per day and remained on this dosage for 2 weeks. She was then referred to us for consultation.

The patient was seen by one of us (TRH) in consultation for the first time on May 4. Visual acuity was left eye 6/7.5 and right eye no light perception; 90% ptosis of the left eye and an almost complete left external and internal ophthalmoplegia were seen. Only slight medial and superior movements were present. Corneal reflex was normal in both eyes. Results of slit lamp and fundus examination were normal. Visual field in the right eye was full. Anterior cavernous sinus and orbital apex syndrome of unknown etiology was diagnosed.

The patient was admitted to the Hospital of the University of Pennsylvania on May 12 with increasing pain in the left eye and a fever of 101.4° F. Results of physical and neurologic examinations were normal except for the eye examination, which, in addition to the blindness, showed a complete third, fourth, and sixth nerve paralysis. The corneal reflex in the left

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eye was now absent. The working diagnosis was an orbital apex
tumor, probably metastatic, versus an indolent infection. Again
skull x-rays and a brain scan were normal, and a bone marrow
biopsy specimen was negative for occult neoplasm. Cerebrospinal fluid examination now showed an
opening pressure of 110 mm Hg, 333 polymorphonuclear leukocytes,
220 red blood cells, protein 64 gm, and glucose 73 mg per 100
ml. Routine multiple blood cultures were negative. An orbital
venogram revealed a relative dilation of the left superior orbital
vein (figure 1) suggestive of an abnormality in the region of the
left superior orbital fissure of the cavernous sinus. Repeated
cerebrospinal fluid cytology and multiple routine cultures were
negative except for two positive cultures of streptococci, which
were thought to be contaminations. Cultures for yeast or fungi
were not done.

At this point, the patient had a bleeding gastric ulcer. On June
18, after the bleeding had been controlled and the ulcer
stabilized, a left carotid arteriogram was done. This showed an
occlusion of the left internal carotid artery, presumed to be
recent since the arteriogram had been normal 2 months
previously. There was presumed retrograde thrombosis from the
intracranial (cavernous) portion of the internal carotid down
almost to the carotid bifurcation (figure 2).

On June 20, the patient underwent a left frontotemporal
craniotomy. A yellowish-white, granulomalice mass was seen
under the left anterior clinoid process causing an upward bowing
and compression of the left optic nerve just as it entered the optic
canal. The optic canal was unroofed, showing that the mass had
invaded and destroyed the optic nerve. The optic nerve was
severed and the mass was excised. Exploration showed that the
carotid artery was necrotic and occluded. As much of the mass
was excised as possible, and the carotid artery was clipped
intracranially. Some hemorrhage, which occurred during the
dissection, was controlled.

Figure 1. Orbital venogram showing dilation of left superior
orbital vein (arrow).

Figure 2. Presumed retrograde thrombosis from the intracranial
(cavernous) portion of the internal carotid down almost to the carotid
bifurcation (arrow).
Pathologic examination of the excised specimen showed a marked amount of chronic inflammation with necrotic tissue around it. Special stain for fungus revealed the presence of branching hyphae with the characteristic appearance of *Aspergillus* (figure 3).

Postoperatively, the patient was treated with intravenously administered amphotericin B, which was increased by 5 mg per day over a 15-day period to a maintenance dosage of 45 mg per day. A mild right hemiparesis developed, and she remained lethargic and continued to run a fever between 100° and 103° F. Her course continued downhill despite amphotericin therapy, and she died on July 10. Autopsy was not performed. The cause of death was thought to be *Aspergillus* meningitis and left cerebral ischemia.

**Discussion.** Table 1 summarizes the findings in the 47 previously reported cases of orbital aspergillosis. The geographic distribution of cases is of interest. Localities with a warm and humid climate appear to predominate. Of 47 reported cases, 38 were from such climate, including 17 cases from Sudan, 13 from the southern United States, and eight from the Indian subcontinent (table 2).

It is well known that *Aspergillus* infections elsewhere in the body occur in debilitated patients, in patients with immune deficiencies, or in those under immunosuppressive therapy. A breakdown in a focus of an old infection in the lung is a common source of the organism. However, *Aspergillus* infections often occur in the orbit in healthy individuals without an apparent distant source. Seventy-seven percent of the reported cases were secondary to a contiguous infection in the paranasal sinuses, 9 percent were primary orbit infections, 6 percent were primary central nervous system infection with secondary orbital involvement, and only one case was a reinfection from an old fungal abscess (table 2).

Unilateral proptosis was the most common mode of presentation, occurring in three-fourths of the reported cases. Decreased vision, pain in the involved eye, and central nervous system involvement, respectively, occurred in approximately one-fourth of the cases, while paresis of the extraocular muscles occurred in only four cases.

The overall mortality was 28 percent, but in patients in whom the central nervous system was involved, the mortality increased precipitously to 80 percent. On the other hand, of 32 patients without central nervous system involvement, only one patient died, and this was because of an unrelated disease. Therefore, the major factor for a better prognosis seems to be early diagnosis and prompt treatment with appropriate therapy before the central nervous system becomes involved.

Two important aspects of the patients with central nervous system involvement were:

**Table 1. Manifestations and prognosis of orbital aspergillosis**

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proptosis</td>
<td>35</td>
<td>74</td>
</tr>
<tr>
<td>Associated sinus disease</td>
<td>36</td>
<td>77</td>
</tr>
<tr>
<td>Central nervous system involvement</td>
<td>15</td>
<td>32</td>
</tr>
<tr>
<td>Decreased vision</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Pain</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Extraocular muscles palsy</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Orbital apex syndrome</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality in all cases</td>
<td>13 of 47</td>
<td>28</td>
</tr>
<tr>
<td>Mortality with central nervous system involvement</td>
<td>12 of 15</td>
<td>80</td>
</tr>
</tbody>
</table>
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Table 2. Geographic distribution and primary source of infection in orbital aspergillosis

<table>
<thead>
<tr>
<th>Geographical distribution</th>
<th>Cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudan</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>Southern United States</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>India-Pakistan</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary source of infection</th>
<th>Cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus</td>
<td>36</td>
<td>77</td>
</tr>
<tr>
<td>Orbit</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

The severity of associated meningitis varies widely. The patient with mycotic intrasellar abscess reported by Goldhammer and associates died after surgery, as did our patient. This suggests that the surgery could have exacerbated a septic meningitic reaction. The second important aspect in our patient was the septic invasion of the cavernous portion of the carotid, with subsequent occlusion, which has not been previously reported to our knowledge. Such occlusion, however, could lead to serious occlusive vascular phenomenon and should be thought of as a possible complication in these patients.

The mode of presentation in our patient was unique in that proptosis, the most common clinical feature, was not present. Instead, this patient had an orbital apex syndrome, with visual loss, complete ophthalmoplegia, and corneal hypoesthesia. Only one other patient reported in the literature had a similar presentation, however, four cases of primary aspergillosis affecting the chiasmal region and optic nerves have been reported.

We can only speculate on how this seemingly healthy woman acquired this fungal disease, as well as on its mode of spread to the basal skull area. Sinus or chest involvement was not clinically or radiographically evident, but this does not exclude a primary central nervous system or primary orbital infection.

Clues to the correct diagnosis in our patient were sparse in the early course of the illness. The patient was afebrile in the early stages and the carotid arteriogram was described as normal, although minimal narrowing of the carotid syphon was noted on subsequent review of the films. As in other unusual diseases, only a high index of suspicion and persistent investigation could have led to the correct diagnosis.

REFERENCES