FUNGI of the genus Aspergillus are ubiquitous in nature but rarely behave in a pathogenic fashion. Numerous case reports have appeared in the literature, describing principally the lesions of pulmonary and upper respiratory tract infection with these organisms. Several excellent recent reviews of the subject are available. 1, 2 Generalized Aspergillosis is quite uncommon, but is often seen following prolonged steroid or antibiotic therapy. It is also frequently associated with generalized debilitating disease, often neoplastic in nature. 3, 5

At least three cases of Aspergillus endocarditis have been described 3-7 but, to our knowledge, never in the pediatric age group. The following case is reported because of the very unusual clinical and pathological manifestations of the disease, the bizarre possible portal of entry of the organism, and the possible enhancing effect of long-term antibiotic therapy on the growth of the fungus.

CASE REPORT

The mother of this patient was a 33-year-old, white, Rh-negative female who had one previous uncomplicated Rh-positive pregnancy, and no history of prior blood transfusions. This pregnancy was unremarkable until the third trimester, at which time her anti-D titer rose from zero to 1:256 in albumin. At an estimated 37 weeks of gestation, labor was induced by pitocin administered intravenously and culminated 8 hours later in the delivery of a 2,160-gm pale, minimally hydropic female infant. Respirations were labored, and marked hepatosplenomegaly was noted. Because of the urgency of the situation, an immediate exchange transfusion with O Rh negative blood (cross matched against maternal serum prior to delivery) was carried out under clean, but nonsterile conditions via the umbilical vein. At the time of the catheterization, the venous pressure was well above 15 cm H₂O, and a blood sample therein obtained was typed O Rh positive, Coombs 4+, with a hemoglobin concentration of 4.5 gm/100 ml. Two closely spaced exchange transfusions were performed, elevating the hemoglobin to 15.5 gm/100 ml. Blood cultures taken at the time of the exchange transfusion were negative for bacterial growth. However, because of the initial nonsterile procedure, the infant received chloramphenicol and penicillin for 5 and 6 days respectively.

The total hospital stay was 51 days (Fig. 1), during most of which time the infant's course was marked by debilitation, poor feeding, the need for supportive intravenous fluids and frequent small blood transfusions to maintain an adequate hematocrit value of 30 to 40%. At no time was there a disappearance of the icterus, which was initially obvious at 12 hours of age. The level of total bilirubin fluctuated between 10 and 23 mg/100 ml, of which two-thirds was direct reacting.

Numerous cultures of blood, spinal fluid, and urine failed to reveal any bacterial growth until the thirty-first hospital day, at which time Escherchia coli was cultured from both blood and catheterized urine. It is interesting to note that the temperature course did not show an elevation until the twenty-seventh hospital day, 4 days before...

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the first positive cultures were obtained.

Another point of interest centered around the platelet counts, which at first ranged between 40,000 and 60,000/mm$^3$. By the fourteenth hospital day the platelet counts were normal and remained so until the thirtieth hospital day, when thrombocytopenic levels reoccurred and persisted along with the appearance of burr cells and fragmented erythrocytes on smear—all coincident with the onset of fever, Esch. coli septicemia, and bacilluria.

The gram-negative infection was treated with tetracycline for 13 days, at the end of which time a blood culture revealed the presence of coagulase-positive Staphylococci. The tetracycline therapy was discontinued and replaced by chloramphenicol and penicillin. Midway during the course of the tetracycline therapy, the infant received a 7-day trial of prednisone in the hope that it would decrease the apparently accelerated hemolytic process.

During the 10 days prior to death, the patient's course was marked by persistent hepatosplenomegaly, twitching as well as overt convulsions, a loud systolic murmur along the left sternal border, rales, ascites, and melana. Additional laboratory data revealed persistent elevation in serum glutamic oxaloacetic transaminase (SGOT), hyperchloremic acidosis, albuminuria without azotemia, pyuria, and cerebrospinal fluid pleocytosis with negative bacterial cultures and stains. Toxoplasma antibody studies and urine specimens for cytomegalic inclusion bodies also were negative. Bone age films were consistent with a developmental age of 30 weeks as compared with a 37-week gestational age. One additional point of interest viewed retrospectively was a blood culture obtained 10 days prior to

**Fig. 1.** Graph showing various clinical parameters of patient's hospital course.
death and reported as "no growth, with mold contamination."

On the fifty-first hospital day the patient had numerous convulsive movements, became apneic, and abruptly died.

Final clinical diagnoses were erythroblastosis fetalis due to anti-D, septicemia (Esch. coli), meningitis, anemia (probably hemolytic) and thrombocytopenia, and possible hepatitis.

**AUTOPSY FINDINGS**

The body was that of a thin, cachectic, white female with moderate icterus. There was 210 ml of slightly cloudy, sterile ascitic fluid. There was no evidence of peritonitis. The heart weighed 32 gm and showed moderate biventricular hypertrophy (right ventricle 0.3 cm, left ventricle 0.4 cm in width). There were adherent mural vegetative lesions which involved both ventricles. These were firm, smooth-surfaced, bulbous, and pale yellow-red. Four such lesions were located at the apex and inferior portion of the right ventricle (Fig. 2). Each of these measured 0.4 cm in greatest dimension. Another similar lesion, which measured 1.5 by 0.5 cm, was located at the pulmonary infundibulum, projecting into and completely occluding the pulmonary valvular orifice. In the left ventricle a 1.5-by-0.5-cm similar lesion was located on the lateral left ventricular endocardium extending to the undersurface of the lateral mitral leaflet which it elevated but did not involve (Fig. 3). These lesions replaced approximately 50% of the luminal volume of each ventricle. Microscopically, the endocardial lesions were composed of masses of large, septate, branching hyphae, with bulbous ends, mixed with large numbers of polymorphonuclear leukocytes. Occasional lymphocytes and macrophages were also present. The endocardium underlying these lesions was destroyed. Extensive myocardial abscess formation was present, within which fungi were identified (Figs. 4 & 5). Some of these abscesses were contiguous with the endocardial lesions. Scant fibrosis and lymphocytic infiltration of the myocardial lesions was noted in a few regions, but granulomatous reaction was not prominent. No fungi or significant lesions were identified in the lungs. The esophagus, stomach, and intestines were normal grossly and microscopically.

The liver weighed 195 gm and was diffusely dark green and firm externally. On gross section the lobular architecture was
The kidneys were of the normal size and shape externally. On gross section, there was intense pyramidal hyperemia. There were multiple 0.2 to 0.4 cm cortical and medullary abscesses present bilaterally, with bilateral extensive necrotizing papillitis. Microscopically, suppurative necrosis of the renal papillae and multi-focal medullary and cortical abscesses were found. All of these lesions were colonized by large numbers of Aspergilli. Many of the fungi were found within renal tubular lumens. The glomeruli were normal. There was an associated cholemic nephrosis. This was characterized by the presence of bile casts within the lumens of scattered proximal, distal, and collecting tubules. Slight tubular epithelial degenera-

The spleen weighed 36 gm. Its capsular surface was smooth and glistening and deep blue-red. A similar appearance was noted on gross section with no focal lesions present. There were no microscopic abnormalities. No fungi were identified.

The extrahepatic biliary ductal system was entirely normal and patent. The mucosal surface of the common duct was bile stained. Microscopically the liver showed marked intralobular and moderate ductal bile stasis. Diffuse bile pigmentation and ballooning degeneration of parenchymal cells was noted. Giant cells were seen occasionally, randomly placed, and presumably were formed by syncytial coalescence of liver parenchymal cells. There were no inflammatory changes present. There was no evidence of extramedullary hematopoiesis. No fungi were seen in the liver.

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tion was associated with the bile casts. Microscopic sections of the thyroid showed multiple confluent recent abscesses containing large numbers of Aspergilli, replacing approximately 75% of the gland.

The brain weighed 330 gm. On external examination the meninges were diffusely cloudy but not hyperemic, Otherwise, the brain was well formed, and there was no evidence of pressure coning. On gross section there was no evidence of kernicterus. Multiple discrete recent and partially cavitated abscesses were found in both frontal, parietal, and temporal lobes, varying in size from 0.2 to 1.5 cm and numbering 15 in all. Microscopic section of these lesions showed multi-focal abscesses with extensive necrosis of brain substance and associated large numbers of Aspergilli, many of which were within vessels. Moderate focal acute and chronic meningitis was found overlying the cerebral abscesses. Marked, diffuse astrocytosis of the cerebral white matter and thalamus, with large numbers of Nissl plump astrocytes, was present. These latter lesions are interpreted as being compatible with neonatal anoxia. The gray matter was relatively spared of this process.

Postmortem cultures were performed 2 hours after death. Cultures of the blood, the endocarditic vegetations, and kidneys yielded a pure growth of Aspergillus fumigatus. Microscopic examination of the cultured material showed wide, septate hyphae of variable staining qualities, with extensive lateral branching. Numerous conidiophores were seen of the type characteristic of the species Fumigatus (Fig. 6). The ascitic fluid was sterile. Cultures of the meninges yielded a few colonies of Staphylococcus albus, which probably represented contamination, as no organisms were seen either on smear or on microscopic section.

COMMENT

The genus Aspergillus belongs to the class of Fungi imperfecti, which is characterized by asexual reproduction. Upward of 350 species have been defined at present, with only seven or eight human pathogenic species identified.

Aspergillus infection may be either primary or secondary. Primary Aspergillosis is an infection in patients without preexisting disease, who have been exposed to massive inocula of the organism. All other cases are secondary, in that they are found in patients with some other disease process which has altered their natural resistance to infection. Primary Aspergillosis is often an occupational disease affecting individuals having intimate contact with birds, domestic animals, and grain dusts. Its manifestations are usually upper respiratory or pulmonary in nature. The pulmonary lesions may be either localized or invasive, with the development of abscess, granuloma or confluent lobar pneumonia. Primary lesions also commonly involve the skin, external ear, nails, sinuses, vagina, and urethra. Widespread dissemination of the organism is rare in the primary form of the disease.

Most of the cases of Aspergillosis reported recently have been of the secondary type. In 1955, Zimmerman enumerated three basic factors which he felt were important in predisposing the individual to any fungal
infection: (a) debilitating disease, especially leukemia and the lymphomas, (b) a localized break in the skin or mucosal membrane providing a portal of entry for the fungus, and (c) disturbances in the saprophyte-host relationship produced by drugs such as anticancer chemotherapeutic agents, steroids, and antibiotics. The clinical manifestations of secondary Aspergillus infections depend on the portal of entry of the organisms and on the host resistance. The process again may be either localized or invasive. Pulmonary Aspergillosis is by far the commonest variety of the secondary type of infection. The pulmonary variety may vary from an acute tracheobronchitis to an indolent progressive lobar pneumonia, or it may remain a localized granulomatous process resembling tuberculosis. It is in this secondary group that the cases of endocarditis belong. Embolic and generalized disease is more common in the secondary form and may involve any organ in the body.

Aspergillosis is, for the most part, a disease of middle life, and is distinctly unusual in any form in infants and children, but a few cases have been reported. Table I shows the reported cases of generalized Aspergillosis in infancy, the types of lesions, the basic underlying disease process, and the presence or absence of antibacterial and steroid therapy. More than half of the reported cases are of the secondary type, being associated with some underlying disease. The present case fits this category, since the marked prematurity and Rh incompatibility probably acted as predisposing conditions. The prematurity is substantiated by the birth weight of 2,160 gm and bone age radiographs compatible with gestation of only 30 weeks. Several of the generalized Aspergillus infections in newborn infants appear to have been associated with prematurity, which perhaps reflects the increased susceptibility on the part of premature infants to infections of many types. After a review of the literature we believe that this case probably represents the first case of Aspergillus endocarditis reported in the pediatric age group.

The origin of the Aspergillus infection in this case is not certain. With the nonsterile exchange transfusion performed at birth, and the subsequent clinical picture compatible with sepsis, it is possible that the fungal organisms were introduced through the umbilical vein. Bacterial infection may also have been introduced in the same manner but may have been masked by the first course of antibiotic therapy. Then, fungal overgrowth may have occurred subsequently. The potentiating effect of antibiotic and steroid therapy on the in vitro

TABLE I
REPORTED CASES OF GENERALIZED ASPERGILLOSIS IN INFANCY AND CHILDHOOD

<table>
<thead>
<tr>
<th>Source</th>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Type of Lesion</th>
<th>Underlying Disease(s)</th>
<th>Antibacterial Therapy</th>
<th>Adrenocorticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cawley</td>
<td>1</td>
<td>7½</td>
<td>M</td>
<td>Pulmonary with widespread dissemination</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tobler et al.</td>
<td>15</td>
<td>6</td>
<td>M</td>
<td>Pulmonary with widespread dissemination</td>
<td>Prematurity; ascariasis; hemolytic anemia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Akkoynolu et al.</td>
<td>18</td>
<td>20 da</td>
<td>M</td>
<td>Pulmonary; central nervous system</td>
<td>None</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Allan et al.</td>
<td>17</td>
<td>18 da</td>
<td>M</td>
<td>Pulmonary with widespread dissemination</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Zimmerman</td>
<td>13 da</td>
<td>13 da</td>
<td>M</td>
<td>Pulmonary with widespread dissemination</td>
<td>Staphylococcal pneumonia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Luke et al.</td>
<td>7 wk</td>
<td>F</td>
<td>Endocarditis with widespread dissemination</td>
<td>Prematurity; erythroblastosis fetalis</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
growth of Aspergillus has been reported.\textsuperscript{18} Esch. coli was grown from blood and urine on one occasion midway through the patient's hospital course. The coincident febrile temperature response makes it unlikely that this was a contaminant. It is noteworthy that burr cells and fragmented erythrocytes were found in the peripheral blood at this time. Of considerable interest is the fact that a blood culture drawn one week prior to death was reported as showing mold contamination.

The enormous size of the endocardial lesions suggests that they probably had been present for a matter of weeks. The extensive suppurrative myocarditis, thyroiditis, and bilateral pyelonephritis and necrotizing papillitis are evidence of widespread blood stream dissemination. The cerebral lesions, because of their size and chronic inflammatory component, are estimated at between 1 and 2 weeks of age.

Ancillary postmortem findings in this case pertain to the liver and brain. Extreme intralobular biliary stasis was noted microscopically in the liver, with a ballooning degeneration of parenchymal cells, and occasional giant cell formation. There was no appreciable inflammatory reaction. The giant cells were apparently formed from syncytial coalescence of degenerating liver cord cells. This process may represent the pre-exudative state of neonatal hepatitis, a hepatic manifestation of sepsis, or may reflect drug-induced parenchymal injury. Diffuse, extensive astrocytosis was noted in the cerebral white matter, and numerous Nissl plump astrocytes were present. This finding is compatible, as to its age and distribution, with the severe anemic anoxia suffered at birth. These interesting hepatic and cerebral lesions adequately explain most of the bizarre hepatic and central nervous system manifestations noted clinically.

As for therapy of Aspergillus infection, iodides have in general been disappointing.\textsuperscript{2} Desensitization has been advocated for the allergic variety. The use of hydroxystilbamidine has not met with much success. Griseofulvin has likewise added little.\textsuperscript{2} Mycostatin has been found effective in the treatment of bronchial disease.\textsuperscript{19} In a case reported by Peer,\textsuperscript{50} Amphotericin B appears to have been lifesaving, despite severe toxic reaction. It is our hope that with the increasing concomitant incidence of antibiotic therapy and fungal disease, a heightened awareness of the presence of fungal disease will eventuate in more accurate antemortem diagnosis and therapy.

**SUMMARY**

To our knowledge, this is the first reported case of Aspergillus endocarditis with widespread dissemination in infancy. The possible entry of the organism through the umbilical vein at birth during exchange transfusions, and the relatively silent clinical course in view of the spectacular postmortem findings, are noteworthy.

**REFERENCES**


Acknowledgment

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