GENERALIZED ASPERGILLOSIS IN AN INFANT
18 DAYS OF AGE

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Although species of Aspergillus are widespread in nature, this fungus is an uncommon cause of disease in man. The organism is frequently encountered as a contaminant of laboratory cultures and is able to thrive on foodstuffs, soil, and a host of seemingly barren media. The genus Aspergillus belongs to the class of Fungi Imperfecti (asexual reproduction) and is of the filamentous type. Of the more than 350 species identified, only two are thought to possess pathogenic potentialities in humans, namely A. fumigatus and A. niger.

Aspergillus fumigatus was the only organism cultured from or seen in widespread lesions found at post-mortem examination in an infant who died at the age of 18 days and is the subject of this report.

CASE REPORT

History and Physical Findings

W.H., an 18-day-old, white, male infant was born in the Sloane Hospital on April 30, 1959. The mother, aged 22 years, was in good health and this, her first pregnancy, was relatively uneventful. At 4-months gestation she had minor dental surgery performed. This was followed by an episode of pharyngitis and sinusitis that promptly responded to a short course of chlortetracycline therapy. The father was in good health except for recurrent external otitis.

The delivery was uneventful and the infant's birth weight was 3,270 grams. The placenta appeared grossly normal. Respirations were spontaneous and the infant's cry lustrous. The infant's stomach was aspirated as it is done routinely following all Sloane Hospital deliveries. Physical examination in the delivery room was within normal limits. The infant was later put to the breast and fed well.

On the second day of life a widespread, non-specific, maculopapular rash appeared. The rash was not considered to be of an infectious nature and no treatment was given.

From the third day of life the infant was noted to become quite cyanotic with crying. Otherwise his general condition was good. He was nursing well, and repeated physical examinations were within normal limits. The skin lesions remained dry, although a few papules showed slight crusting.

Laboratory Findings

At 5 days of age, because of intermittent cyanosis, the following laboratory data were obtained: Hemoglobin, 16.7 gm/100 ml; leukocytes, 16,400/mm³ with 42% neutrophils, 4% eosinophils, 31% lymphocytes and 22% monocytes; blood culture showed no growth; chest roentgenogram and electrocardiogram were within normal limits.

Course

The infant was discharged at the age of 7 days, his general condition unchanged. No new skin lesions had appeared, he weighed 3,110 grams and the physical examination was normal.

The infant was next seen by the family pediatrician at the age of 17 days. The mother reported that the infant was not nursing well but otherwise seemed satisfactory. Several small crusted skin papules remained. The infant was a little listless but otherwise did not appear ill.

Because of the presence of an enlarged liver and a failure to gain weight, arrangements were made for hospital admission when a bed was available. An emergency admission was not considered necessary. Chloramphenicol, orally, and a topical antibiotic ointment were prescribed. However, the following morning at home the infant was found unresponsive. He was pronounced dead on arrival at 10:45 A.M.
in the Emergency Department of the Babies Hospital.

**Necropsy Findings**

Necropsy was performed May 17, 1959, 68 hours after the infant's arrival at the hospital.

**Gross Examinations** The body was that of a well developed, well nourished, 18-day-old, white, male infant weighing 3,070 grams. There were five, circumscribed, slightly encrusted papules 3 by 4 mm in diameter, two situated in the scalp and three on the body. One of the scalp lesions had progressed to a pustule from which greenish-yellow purulent material could be expressed, and one lesion on the thigh was a multiloculated vesicle full of serosanguinous fluid. On the dorsum of the tongue there was a shallow ulcer measuring 10 by 3 mm with a flat serpiginous border and a slightly depressed, greyish-yellow, granular and indurated base.

The peritoneal cavity contained no free fluid. The serous surfaces were smooth, except for the superior and anterior surfaces of the liver which were bound to the diaphragm by firm fibrinous adhesions. The liver was enlarged, extending 6 cm below the right costal margin.

The pleural cavities contained no free fluid, but firm fibrinous adhesions bound the apices and diaphragmatic surfaces of both lungs to the parietal pleura. The pericardium was normal.

Large granulomatous lesions were found scattered through the viscera. The lungs were severely involved; 12 to 15 of these granulomas, varying in diameter from a few millimeters to 6 centimeters, were found in each lung. The lesions were fairly well circumscribed, slightly elevated, firm, and a homogeneous tan-grey in color. The largest lesions showed central caseation. Both lung apices contained large caseous granulomas that projected posteriorly from the lung surface to extend deep into the posterior superior mediastinum. A striking feature was a firm, tumor-like mass of granulomatous tissue measuring 4 cm in vertical diameter and 0.5 cm in anteroposterior diameter; this extended across the superior mediastinum. It was situated posterior to the esophagus and trachea, infiltrating adjacent structures and forming a bridge between the two apical lung lesions. There were large nodules in the posterior portion of both lower lobes, which extended through the adjacent domes of the diaphragm. They were continuous with similar caseous granulomas on the superior aspect of the liver. When the infiltrated portions of the diaphragm were peeled away from the adherent liver, the nodules in the lower lobes appeared as large caseous granulomas with deep, central, undermined cavities. The picture was reminiscent of that sometimes seen in actinomycosis in the adult. The peripheral portions of the lungs were air-containing, and here the granulomas tended to be smaller and more superficial.

The liver was markedly enlarged and congested, extending 6 cm below the costal margin and weighing 215 grams (normal weight 120 grams). The surface was studded with multiple, circumscribed, necrotic foci, 15 lesions being counted on the superior surface and 10 on the inferior surface. Many more were scattered through the deeper portions of the parenchyma. The larger ones were umbilicated.

There were large caseous granulomas on the convex aspect of the liver resembling the lesions in the lungs. They were adherent to the diaphragm and communicated with granulomas in the lungs, as previously described. The remaining lesions in the liver differed slightly from those in the lung in that they were flat or depressed, more greyish-yellow in color and the majority showed a peripheral zone of hemorrhage.

The heart was normal in size and contour. On examination of the posterior aspect of the epicardium, linear yellow nodules, 1 by 2 mm in diameter, were found along the posterior descending branch of the coronary artery. These were interpreted as arterial thromboses. No endocardial thrombi were found.

The spleen was firm and congested and weighed 12 grams. It showed four small circumscribed granulomas, three visible on the surface and one lying deep within the parenchyma.

Both kidneys had many similar circumscribed lesions. On the cut surface most of them had the triangular configuration typical of infarcts.

The jejunum showed multiple, small, hemorrhagic erosions of the mucosa overlying the solitary lymph follicles. The remainder of the intestine appeared normal.

The remaining organs were not remarkable. Permission for examination of the brain had not been granted.
MICROSCOPIC EXAMINATION: The granulomatous lesions in the lung revealed central caseation with adjacent broad zones of necrosis. The margins of the necrotic areas were massively infiltrated with polymorphonuclear leukocytes and a few phagocytes (Fig. 1). Scattered throughout the necrotic foci and in adjacent viable parenchyma were numerous thrombosed veins and arteries with necrotic walls and perivascular collections of polymorphonuclear leukocytes. Large numbers of hyphae were seen in the necrotic foci with accumulations at the margins of the central caseous areas. They were also numerous in the perivascular tissues, and individual filaments could be seen penetrating the necrotic vascular walls and lying embedded within the thrombi. The intervening portions of lung parenchyma showed various degrees of atelectasis, polymorphonuclear leukocyte infiltration and evidence of chronic aspiration.

The liver lesions appeared as multiple granulomatous foci with necrotic centers. The walls were formed of early granulation tissue heavily infiltrated with polymorphonuclear leukocytes. Extending from the margin were finger-like projections of leukocyte accumulations, each extending a liver sinus. The sinusoids appeared swollen, and in places eroded the adjacent liver cords leaving only irregular strands of residual liver cells (Fig. 2). Numerous hyphae could be seen lying centrally along the sinusoids and also in the walls of the necrotic foci (Fig. 3). Inflamed or frankly necrotic vessels containing thrombi were numerous. The intervening portions of liver parenchyma were congested but well preserved.

The splenic granulomas were punched-out foci of pyknotic polymorphonuclear leukocytes, containing hyphae and thrombosed vessels.

The kidneys revealed segmental infarcts infiltrated with polymorphonuclear leukocytes, and containing numerous hyphae.

Scattered throughout the epicardium and the interstitial tissue of the myocardium were necrotic vessels filled with thrombi and surrounded by granulomatous foci in which hyphae were numerous.

A surprising finding was the presence of thrombosis of a thyroid artery with foci containing hyphae in the thyroid.

There was no generalized lymph node involvement. In one section of a peribronchial node a granulomatous focus perforated the
Fig. 2. Margin of liver abscess showing extension along sinuses. (Hematoxylin and eosin, $\times 67$.)

Fig. 3. Aspergillus hyphae in margin of liver abscess. (Grocott stain, $\times 210$.)
capsule and extended into a portion of the lymph node parenchyma, but the remainder of the node was free of disease. However, the focal necroses of the jejunal mucosa lay over lymph follicles, and hyphae were seen in these lesions.

The tongue lesion was a circumscribed granuloma with mucosal ulceration and a large number of hyphae on the surface. A section of a pustule revealed a similar punched-out granuloma with a vesicular surface erosion and heavily infiltrated with hyphae (Fig. 4).

The hyphae were faintly basophilic in the routine hematoxylin-eosin sections and fairly distinct, especially when the filaments were cut longitudinally. The fungi did not take the periodic acid-Schiff stain well. They were somewhat more distinct when stained with methylene blue. With these three stains the septa and the fine cytoplasmic granules in the central portions of the cells were well seen. The Grocott modification for fungi of Gomori’s methenamine-silver nitrate stain proved invaluable, especially when applied to frozen sections of formalin-fixed material. With this stain septa were not seen, but the number of hyphae appeared far greater than with other stains. The hyphae had the morphology typical of Aspergillus—long, irregular, septate filaments with abundant angled branching, approximating an erythrocyte in diameter. When cut in cross section, they usually appeared as oval, ring-like, often swollen, cell membranes. Entire tree-like mycelia could be seen frequently, but no conidiophores were found in tissue sections.

Aspergillus fumigatus was cultured from liver, spleen and bowel, which had been frozen and preserved at time of necropsy. Routine bacterial cultures showed no growth.

Source of the Infection

A search for the source of the infection was unsuccessful. At the time of delivery the mother was in good health and no abnormality was noted. At the follow-up visit 1-month postpartum, vaginal examination and fungal cultures were negative and a roentgenogram of the chest was normal. The father was examined at the same time and appeared in good health. Examination of his ears was negative and cultures for fungi showed no growth. The household contained no birds.
Investigation of the hospital environment (delivery room, nursery and personnel) uncovered no leads as to a possible source of Aspergillus.

Among the infants who were in the nursery during the same period, there was only one with a comparable clinical course. This infant was born on April 28, 2 days before W.H. She was the fourth child of a 22-year-old Negress who had recurrent pyelonephritis and a personality disorder leading to suicidal attempts. Bilateral tubal ligation was performed. Her infant had a birth weight of 3,135 grams and appeared entirely normal for the first week. On the eighth day, a buccal lesion suggesting thrush was found, cultures were taken, and oral administration of mycostatin begun. The cultures grew out moderate numbers of Staphylococcus aureus hemolyticus, coagulase positive. The smears also showed many yeast organisms, not Candida albicans, which were not further investigated. She was discharged with her mother on the eleventh day.

The infant was seen at the age of 14 days because of constipation which was treated with a glycerine suppository.

She was again seen on April 28, at 4 weeks of age, because of cough and fever for 3 days. At this time, she had a moderate nasal discharge and many small white patches on the oral mucosa. She was given mycostatin solution, and a diagnosis of upper respiratory infection was made.

On May 2, she suddenly developed respiratory distress and died. No further details could be obtained. The death certificate, signed by the Medical Examiner, gives bronchopneumonia as the cause of death. There is no record of post-mortem examination.

Efforts to recall the mother for further examination and mycologic studies were for some time unsuccessful. Eight months post-partum, smears and cultures from the nose, throat, ears and vagina were negative for Aspergillus. The clinical course of the infant and the presence of fungi other than Candida albicans are therefore suggestive of disease comparable to the case presented, but proof is lacking.

DISCUSSION

The disease aspergillosis in man is usually classified as either a primary or secondary form, although a precise distinction is often not possible. As stressed by Cawley in his comprehensive review of aspergillosis, the term primary should be confined to patients exposed to a massive inoculum of the organism and who have no other discernible disease. All other cases are secondary.

The important reservoirs of the fungus include milled grain, hay, animal danders and birds. The last mentioned are particularly susceptible to infection with this organism, and a severe respiratory disease due to Aspergillus fumigatus is frequent among domesticated fowl and captive birds. Primary aspergillosis is included among the occupational diseases, and the majority of the case reports have involved individuals intimately in contact with grain dust or birds.

The majority of the recently reported cases of aspergillosis have been of the secondary type. Zimmerman elaborated on this aspect of the disease and enumerated three basic factors that he considered important in lowering human resistance to fungus infection; a) debilitating illness, particularly the lymphomas and leukemia; b) a local break in the skin or mucous membrane serving as a portal of entry for the fungus; 3) disturbances in the relationship between host and organism produced by such drugs as antibiotics, steroids and bone marrow depressants. Under such circumstances Aspergillus and Candida are the most frequent fungal pathogens.

The clinical manifestations of aspergillosis vary widely depending upon the route of entry of the organism and upon host susceptibility. Otomycosis and onychomycosis are generally considered as the commonest types of Aspergillus infection. Pulmonary aspergillosis tends to have an insidious onset and to run a chronic or subacute course simulating tuberculosis. However, an acute fulminant bronchopneumonia has been described. Pulmonary lesions may be the primary manifestation of massive inhalation of organisms, but the lungs are also commonly involved in secondary froms of aspergillosis. Case reports of lesions involving the nasal passages and paranasal sinuses,
Aspergillosis is rare in the pediatric age group, being considered primarily a disease of middle life. A few cases have been reported both in childhood and in infancy. Previously reported fatal cases of primary aspergillosis in infancy and childhood are listed in Table I; the clinical and pathologic manifestations of the disease varied widely in the cases listed.

The 11-month-old boy reported by Iyer et al. was unusual in that the lesions were confined to the central nervous system and resembled toxoplasmosis. The clinical picture was one of slowly progressive mental deterioration over a 7-month period with convulsions and evidence of pyramidal tract involvement. The authors were unable to determine the portal of entry.

In the newborn period both primary and secondary aspergillosis have been reported. Secondary aspergillosis complicating steroid and antibiotic therapy occurred in a 30-day-old infant reported by Zimmerman. Akkoyunlu et al. described the only case of primary aspergillosis in this age group. A 20-day-old infant had an acute illness of 1-week duration, manifesting as fever, diarrhea, respiratory distress and coma. The clinical diagnosis was bronchopneumonia and purulent meningitis. Necropsy revealed

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<tr>
<td>Cawley</td>
<td>7½ yr, male</td>
<td>Pulmonary aspergillosis with widely disseminated emboli foci</td>
<td>Culture: A. fumigatus</td>
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<tr>
<td>Hertzog et al.</td>
<td>5 yr, male</td>
<td>Pulmonary lesions only</td>
<td>Culture of lung: A. fumigatus</td>
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<tr>
<td></td>
<td>Sibling, 7 yr, female</td>
<td>? Pulmonary aspergillosis. Clinical picture similar to above.</td>
<td>? No cultures or necropsy</td>
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<tr>
<td>Iyer et al.</td>
<td>11 mo, male</td>
<td>CNS only, chronic granulomatous meningoencephalitis</td>
<td>Morphology of hyphae</td>
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<tr>
<td>Tobler et al.</td>
<td>6 yr, male</td>
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multiple granulomatous lesions in the lungs and meninges, from which Aspergillus was cultured. The authors thought the pulmonary lesions constituted the primary focus with embolization to the central nervous system. The infant lived on a farm, and contaminated grain dust was considered as a possible source of Aspergilli.

CONCLUSION

Generalized aspergillosis in an 18-day-old infant is evidently a rare disease. The combination of compatible pathologic lesions, massive numbers of typical hyphae and positive cultures for Aspergillus fumigatus from multiple foci confirms the diagnosis. After a review of the literature, we believe that this is the second authenticated case of lethal primary aspergillosis in a newborn infant to be reported.

The clinical history presented by this infant and the advanced stage of the pathologic lesions suggest that the initial inoculation occurred at or near the time of delivery. The extensive pulmonary lesions, with direct extension into the superior mediastinum as well as through the diaphragm into the liver, suggest that the respiratory tract was the portal of entry. The widespread embolic foci in the liver, spleen, kidneys, heart and thyroid are compatible with later dissemination through the blood stream, probably derived from thrombosed pulmonary veins. The lesions found on the tongue and in the skin more closely resemble embolic foci than sites of surface contamination.

Intrauterine infection with transplacental transmission of Aspergillus is conceivable. Burry has reported an infant with central nervous system lesions and hydrocephalus due to monilia that he believed was of intrauterine origin. The permeability of the placenta to fungi is still uncertain. The placenta appeared grossly normal and was not saved for microscopic study. Sections of the umbilicus at time of necropsy showed superficial infection which was interpreted as secondary.

The disease in this infant differed significantly from the previously reported case of primary aspergillosis in a newborn. In the latter instance the infection was acquired at a later date, probably in the home environment. The clinical course was acute and fulminant and the comparatively young granulomatous lesions were confined to the lungs and meninges.

SUMMARY

A case of fatal primary aspergillosis in an 18-day-old infant is presented. The clinical course was deceptively benign and death was sudden. Necropsy revealed extensive pulmonary lesions with widely disseminated embolic foci. Aspergillus fumigatus was cultured from the lesions.

The literature pertaining to primary aspergillosis in infancy and childhood is reviewed with special reference to the newborn period.

Acknowledgment

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