Fulminating Disseminated Aspergillosis Complicating Peritoneal Dialysis in Eclampsia

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Disseminated aspergillosis was not reported before the advent of antibiotics. In a review of the world literature Tan et al found 22 cases occurring since 1939, and described a further one. Almost all these cases, and others reported subsequently, had received antibiotics or steroids, or both, and most had an underlying debilitating illness; one patient had Cushing's syndrome.

The present case is unusual in that the portal of entry seems to have been a peritoneal infection resulting from peritoneal dialysis.

Patient Summary
A primigravida, age 22, had a normal antenatal course, until Nov 8, 1965 (36th week), when her blood pressure (BP) was 130/80 mm Hg and the urine contained a trace of protein. The major clinical events, together with antibiotic, steroid, and dialysis treatment are summarized in Fig 1. On Nov 20 (38th week) at 4:30 pm nausea, vomiting, and intermittent epigastric pain developed. The pain persisted and at 7 pm she was admitted to hospital. When examined she had epigastric tenderness; the uterine size was consistent with the gestation period, and showed no abnormality. The fetal heart rate was normal. The BP was 120/75 mm Hg and the neurological examination was negative.

At 7:07 pm she had a generalized convulsion. Oxygen was given by face mask and 180 mg phenobarbital by intramuscular injection. A provisional diagnosis of an epileptic seizure precipitated by pregnancy was made. She was transferred to the labor room and because of continued restlessness and epigastric pain, 50 mg meperidine hydrochloride was given by intravenous injection. The pain eased but at 8:10 pm a second seizure occurred. Her BP was now 170/100 mm Hg. Urine (200 ml) obtained by catheter contained large amounts of protein. A diagnosis of eclampsia was now made in view of the elevated BP and albuminuria. At 8:15 pm, 5.3 ml tribromoethanol (Avertin) was given rectally, this being an appropriate dose for her weight (58.5 kg [131 lb]). At 9:30 pm when the patient was well sedated, labor was induced by artificial rupture of the membranes. The BP rose to 150/100 mm Hg at 10:50 pm and because of the possibility of another convulsion a second dose of 5.3 ml tribromoethanol was prepared. Meanwhile a third convulsion occurred and the tribromoethanol was then given. Because of the unusual occurrence of fits after tribromoethanol it was thought desirable to accelerate delivery by a cesarean section. Approximately one hour later (11 pm) a lower uterine segment cesarean section was performed. Since the patient was already heavily sedated with tribromoethanol, only the addition of succinylcholine chloride and oxygen were required for anesthesia. A live male child, weight 2.54 kg (5 lb 9½ oz) was delivered and responded slowly to resuscitation. The placenta was circumvallate but otherwise normal, and there was no retroplacental clot.

During the immediate postoperative period her BP remained at about 100/
Fig 1.—Main clinical events during course of illness with temperature, blood pressure changes, and therapy.

Fig 2.—Serial changes in urea, transaminases, white blood cell counts, and platelets.
Aspergillosis/Ross et al 185

Intramuscularly 6 hourly, was used in the hope of limiting extension of the damage. Within the next hour, the BP rose to 100/40 mm Hg and then more slowly to 130/70 mm Hg at 11:30 AM. Eight hours after operation 50 ml of urine was obtained by catheter. This showed protein 300 mg/100 ml but no bilirubin; red blood cells, granular casts, white blood cells were seen on microscopy.

A forced diuresis was attempted with 40 gm of mannitol given intravenously. This was unsuccessful and it appeared that acute tubular necrosis had developed. Oliguria persisted for the rest of the patient's illness, only 20 to 60 ml of urine being obtained by catheter every 48 hours.

Laboratory results 12 hours after operation were as follows: plasma urea, 66 mg/100 ml; creatinine, 3.4 mg/100 ml; chloride, 103 mEq/liter; sodium, 138 mEq/liter; potassium, 7.1 mEq/liter; carbon dioxide, 12 mEq/liter; bilirubin, 1.1 mg/100 ml; white blood cell count, 18,600/mm³; platelets, 64,000/cu mm; the Thrombotest was 25%; fibrinogen, 585 mg/100 ml; fibrinogen titer, one sixteenth, lyzed by the method of Kozelka and Hanbury's Ltd.; hemoglobin, 9.5 gm/liter; sodium metabisulfite, 0.05 gm/liter. Dialaflex solution, 6.36% [Allen & Hanbury's Ltd.] is a mixture of sodium, 140.4 mEq/liter calcium, 3.6 mEq/liter; magnesium, 1.5 mEq/liter; total chloride, 108.8 mEq/liter; lactate, 44.6 mEq/liter; dextrose, 13.6 gm/liter; sodium metabisulfite, 0.05 gm/liter.
abdominal pain. Twitching continued but seizures seemed to be controlled by paraldehyde and diphenylhydantoin sodium.

On the ninth day there was a transient fall in BP which responded to additional hydrocortisone and saline given intravenously.

On the tenth day her temperature rose to 103°F (39.4°C) and cephaleoridine was substituted for ampicillin. Her blood urea was again rising and a third PD was begun at 5:30 pm. Routine culture from the abdominal wound grew no organisms but oxytetracycline was, nevertheless, added to the dialysis fluid. On the following day (11) the abdominal wound dehisced and required resuturing. This was done with the patient under cyclopropane anesthesia. At operation the bowel looked slightly red but was otherwise normal. At this time the patient was tetraplegic and on the 12th day of the puerperium a left facial paralysis was present. The peritoneal wash now contained numerous polymorphs but no bacteria were grown aerobically or anaerobically. A repeat of the lumbar puncture showed an increase in CSF pressure to 425 mm of the lumbar puncture showed an increase in CSF pressure to 425 mm

The bilirubin reading was diagnostic of A. fumigatus. The small lesions scattered throughout the hemispheres were similar micro-abscesses, containing fungal elements which in many cases had a perivascular arrangement suggesting growth along penetrating vessels. Spinal cord sections showed large "felt-works" of fungi around and invading the posterior roots. At the upper thoracic level there was destruction of the right anterior horn by fungi.

All lung sections examined showed considerable edema and congestion. Despite an extensive search using the special stains, no fungal elements were seen in either lung. Both kidneys showed intact glomeruli and acute tubular necrosis without evidence of regeneration of the tubular epithelium. The liver showed extensive periporal necrosis and fibrosis with proliferation of biliary canaliculi. There was evidence of previous hemorrhage related to the portal tracts as seen in eclampsia. The capsular surfaces showed fungal mycelia with an acute inflammatory response, but no deep invasion. The serosal surfaces of spleen, ovaries, fallopian tubes and uterus all showed overlying layers of fungal mycelium with superficial infiltration and an accompanying acute inflammatory response. Serial blocks taken from the placental bed showed no fungi. The myocardium appeared normal, except for one small area of microinfarction, which contained a single small Medusa-like formation of fungi.

A pure culture of A. fumigatus was grown from the base of the brain.

Comment

This patient's illness had two phases, both with prominent neurological features, separated by a period of improvement. The initial phase was probably atypical eclampsia and the postmortem findings of old periporal hemorrhage with necrosis and fibrosis supported the clinical evidence of eclamptic liver necrosis. Acute tubular necrosis may have been precipitated by severe hypotension in the early postpartum period. In retrospect she probably received too much sedation, particularly of tribromoethanol. This drug is valuable in controlling eclamptic seizures, and is normally rapidly
conjugated in the liver and then excreted by the kidneys. In excessive dosage it can cause liver damage and this is particularly liable to happen if there is already impaired liver function. It can also cause proteinuria and frank renal damage especially if renal function is already impaired. At the time, the need to control the convulsions was paramount, and for this reason the 5.3-mmol dose was repeated once. Dialysis played an important part in her rapid early improvement, and approximately one third of the tri-bromoethanol she had received was recovered from the dialysate. Hemodialysis was not used because of the risk of hemorrhage due to the low platelet count, and because it was considered undesirable to move this critically ill patient to the hemodialysis unit which is in another hospital.

The second phase of the patient's illness, beginning on the fifth postpartum day was puzzling. In the light of the postmortem findings, we presume now that she was developing a fulminating Aspergillus meningoencephalomyelitis. The route of entry appears to have been across the peritoneum, which was found to be extensively involved at postmortem. In most of the reported cases of disseminated aspergillosis, the route of entry was through the lungs, the nasal sinuses or the ears; in this case the postmortem findings excluded these.

The cause of the convulsions which started on the fifth postpartum day is conjectural. If infection and dissemination to the central nervous system had already occurred by that time it is curious that she was apyrexic until the ninth day. The finding of normal CSF on day 5 does not exclude a small localized cortical abscess as a cause of these convulsions, and if this is true the onset of pyrexia on day 9 probably marked the spread of a rapidly fatal meningoencephalomyelitis from a localized focus.

Zimmermann attributed the dissemination of fungus in the body to a combination of three factors, all of which obtained in this case. These are a general lowering of resistance by a debilitating disease (usually a leukemia or malignant lymphoma), a local point of entry for the fungus, and the use of antibiotics causing suppression of the normal bacterial flora. Subsequent studies have supported this and emphasised the role of steroids in the suppression of inflammatory response. On the other hand, the recent description of rapidly fatal pulmonary aspergillosis in two young sisters, occurring almost simultaneously, shows that even in the absence of steroids, antibiotics or an underlying illness, Aspergillus may cause a rapidly fatal infection.

A case with interesting similarities to our own is described by Finegold et al. Their case 9 was a 33-year-old woman in whom acute renal failure developed following a septic abortion. She showed transient improvement after hemodialysis and two peritoneal dialyses but was intermittently febrile, and died after seven weeks of illness. Postmortem examination revealed disseminated aspergillosis with involvement of heart, lungs, spleen, brain, and uterus. The route of entry was not established with certainty, and the possibility that it entered during peritoneal dialysis was not discussed.

In our case it was a striking finding at postmortem that, apart from the peritoneal surfaces and a very small focus in the myocardium, the brain and spinal cord were the only areas where the Aspergillus had grown. Aspergillosis of the brain, spinal cord, or meninges may occur as a result of direct spread from adjacent structures; following intrathecal injections; in the drug addict who injects himself; or without evident portal of entry or primary focus. It may also be part of a generalized disseminated aspergillosis often involving many organs and usually with a primary focus in the lung. The lesions may vary from a slowly growing localized granuloma or abscess, to the fulminating meningoencephalomyelitis seen in our case. In a review of 23 cases of disseminated aspergillosis, Tan et al. found that the brain was involved in 15 cases and was second in frequency only to the lungs (19 cases) which were often the portal of entry and therefore involved primarily. The postmortem findings in our case suggest that, in the event of a hematogenous infection, the surfaces of the brain and spinal cord are more suitable than other organs for the proliferation of Aspergillus.

The causative organism, A fumigatus is a common air contaminant and was isolated from two out of ten plates exposed to the air, and from three of eight swabs taken from various points, in the labor suite in which the patient was nursed. Access may have been direct from the air, through the peritoneal dialysis puncture wound. However, recent investigation of our stocks of peritoneal dialysis fluid (Dialaflex) which is supplied in plastic containers has shown an incidence of leakage and organismal contamination in 2%, and in many the growth was fungal. Aspergillus fumigatus was not one of the organisms isolated from this fluid but the organism cultured at postmortem from our patient grew well at room temperature in fluid of both high (6.36 gm/100 ml) and low (1.36 gm/100 ml) glucose concentrations. When this patient was dialysed we were not aware of the hazard associated with these bags, and leakage without gross contamination could easily have been missed. We have no direct evidence for implicating the dialysis fluid in this case, although it must have provided a favorable cul-
tures medium for the organism once inoculated.

This experience demonstrates that peritoneal dialysis must now be considered an additional predisposing cause for mycotic infection, in this instance by *A. fumigatus*. We now believe that the prophylactic addition of broad-spectrum antibiotics to peritoneal dialysis fluid is wrong. First, bacterial peritonitis may still occur due to resistant organisms, and second, when peritonitis does complicate peritoneal dialysis it is usually readily controlled subsequent to diagnosis by adding the appropriate antibiotic to the peritoneal dialysis fluid. The use of a broad-spectrum antibiotic, as in this case, is no safeguard against fungal infection. We suggest that routine culture of peritoneal dialysis fluid should be done at least twice daily, and should include the use of Sabouraud's medium.

**Summary**

Rapidly fatal *Aspergillus fumigatus* meningoecephalomyelitis complicated peritoneal dialysis in a 22-year-old woman with eclamptic liver necrosis and acute renal tubular necrosis. Important factors were (1) the underlying illness, antibiotic therapy, and use of high doses of hydrocortisone, all of which encourage the growth and dissemination of fungi; and (2) the florid growth of the *Aspergillus* on all the peritoneal surfaces, bathed as they were in a strong glucose fluid.

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**Generic and Trade Names of Drugs**

- Phenobarbital—Luminal.
- Meperidine hydrochloride—Demerol.
- Hydrocortisone—Cortef, Cortil, Hycort, Cortison, Hydrocortone.
- Dicloxacilin sodium—Penbritin-S, Polycillin.
- Diphénylhydantoin sodium—Deme rol.
- Hydrochloride, Dilantin Sodium, Diphentoin.
- Hydrocortisone—Cortef, Cortil, Hycort, Cortison, Hydrocortone.
- Oxytetracycline hydrochloride—Terramycin, Hydrochloride.
- Cyclopropane—Trimethylene.

**References**