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Malassezia furfur Meningitis Associated with Total Parenteral Nutrition Subdural Effusion

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ABSTRACT

We present a case of *Malassezia furfur* meningitis arising in a very low birth weight infant with chronic lung disease, necrotizing enterocolitis, and intraventricular hemorrhage. *M. furfur* meningitis was probably acquired late following successful treatment for earlier systemic central line-associated *M. furfur* infection. *M. furfur* meningitis has only once been previously reported. Unlike the previous case where meningitis was secondary to widespread blood-borne dissemination, infection was limited to the leptomeninges and arose in association with extravasation of total parenteral nutrition (TPN) and intralipid fluid into subarachnoid space via peripheral scalp catheter.

intralipid, lipid emulsions, *Malassezia furfur*, meningitis, parenteral nutrition, subdural effusion

INTRODUCTION

Systemic infection caused by *Malassezia furfur* was initially reported, by Redline and Dahms [1], in a group of preterm infants who were receiving total parenteral nutrition utilizing lipid-based preparations. Subsequent studies have confirmed prematurity, prolonged neonatal intensive care unit stay, and intravenous lipid administration as the most common risk factors for infection with this organism [2–5]. Prompt central venous catheter removal and discontinuation of the intralipid preparation is essential for cure, and antifungal therapy is recommended for those with disseminated disease [3]. A suppurative vasculitis may lead to metastatic foci in disseminated disease, most commonly involving the heart and lungs; endocarditis with embolic complications has been noted. Central nervous system involvement has been described in one patient but was limited to microscopic disease occurring in the setting of overwhelming disseminated blood-borne disease. We report a case of *M. furfur* meningitis that occurred after successful treatment and clearance of a previous systemic central catheter-related *M. furfur* infection and likely arose from venous fluid transudation from a contaminated peripheral scalp catheter. Nervous system-related complications of indwelling catheters and potential modes of entry of hyperalimentation fluid into the subarachnoid space are discussed

CASE REPORT

The patient was born at 23-wk gestation by urgent cesarean section, weighing 567 g. His clinical course was complicated by chronic lung disease, necrotizing enterocolitis, and grade III intraventricular hemorrhage. On day 24 of life, the infant developed hypotension associated with thrombocytopenia, and elevated C-reactive protein. Blood cultures did not reveal a pathogen initially and

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amphotericin was empirically added to his antimicrobial regimen. At this time, a subcapsular hepatic lesion was noted on abdominal ultrasound which was thought to result from birth trauma. *Malassezia furfur* was isolated from blood culture obtained 11 days into the course of therapy on day 35 of life. A central line was subsequently removed on day 39 of life and *M. furfur* was isolated from the tip of the catheter. Blood cultures drawn 2 and 3 days after catheter removal were negative. Echocardiogram revealed a small atrial septal defect but no vegetations or other abnormalities. A total of 26 days of amphotericin was given during which time the infant steadily improved. Blood culture obtained 2 wk following discontinuation of amphotericin was negative for *M. furfur*. Follow-up abdominal ultrasound also demonstrated decrease in size of the hepatic lesion.

Acute deterioration occurred on the 50th day of life when intestinal perforation occurred during a barium enema examination for suspected intestinal obstruction. The patient was transferred emergently to the surgical service at our institution where he underwent a diverting ostomy procedure. The infant required intensive support for the next 3–4 days but steadily improved over the subsequent 2 wk. At that time, antimicrobial therapy was discontinued and the infant's course was stable. The infant's steroid regimen of hydrocortisone, which had been initiated during the 2nd week of life, was decreased to physiologic doses with a plan to wean over the ensuing weeks. The infant was nutritionally supported over the last 4 wk of life with daily intravenous hyperalimentation infusions including intralipid. The infusions were initially through a central peripherally inserted catheter (PIC) line but switched to a peripheral scalp vein over the left temporal area when the central line clotted off 11 days prior to the demise of the patient. The scalp catheter was advanced 13 cm and placement was checked radiographically with the tip located over the left cheek and some contrast noted overlying the scalp and neck region at that time. The TPN daily infusions near the time of the patient's terminal event included 10% dextrose and 15 cc of 20% intralipid.

On day 83 of life, 3 days prior to death, the infant presented with apnea, temperature instability, and bilious residual from his nasogastric tube.

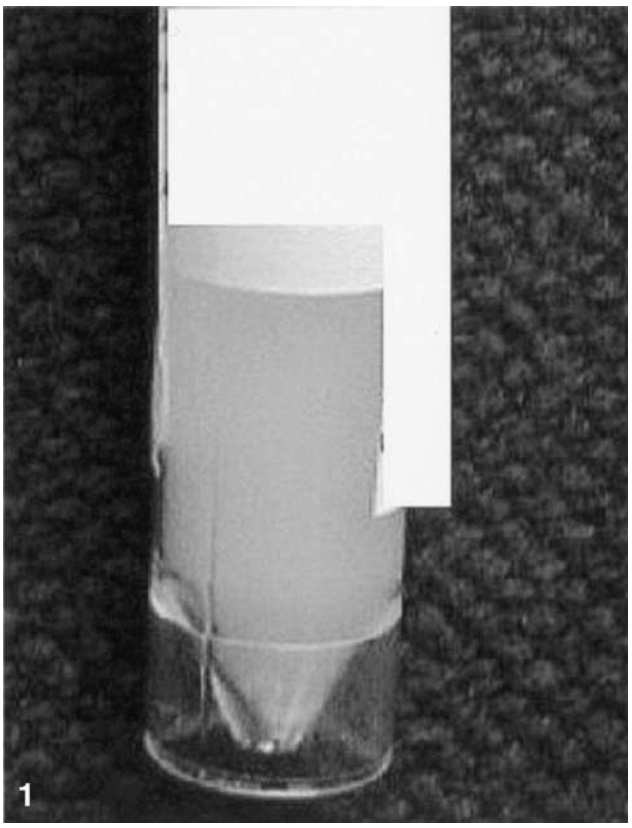

Figure 1. Gross appearance of subdural fluid.

An evaluation for sepsis was undertaken and antimicrobial therapy was initiated. A generalized seizure occurred 12 h later and the fontanel was noted to be bulging. Lumbar cerebrospinal fluid (CSF) revealed cloudy, slightly xanthochromic-appearing fluid that contained 8100 white blood cells (WBC), 98% polymorphonuclear (PMN) leukocytes, glucose 1325 mg/dl, and protein 141 mg/dl. A concomitant blood glucose was not measured but the median blood glucose noted over the week prior to, and then subsequent to, the diagnosis was 95 mg/dl. Gram-stained smear of the spinal fluid revealed fungal forms consistent morphologically with *M. furfur,* and amphotericin B was started. Blood culture obtained through the scalp catheter and brachial artery were positive for *M. furfur*. Head ultrasound was suggestive of subdural empyema. Two days later, the subdural collection was drained and noted to have a milky appearance and contained 2313 WBC with 98% PMN, 100 mg/dl of glucose, 243 mg/dl protein, and 19 mg/dl triglycerides. The milky turbid nature of the fluid remained in spite of centrifuging the sample to remove the WBCs (Fig. 1). Lumbar CSF obtained 2 h earlier

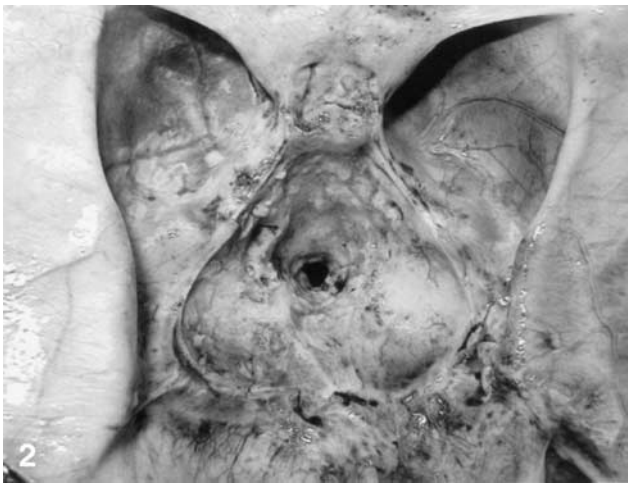

Figure 2. Dense ragged inflammatory meningeal exudates of the posterior and left-middle cranial fossa.

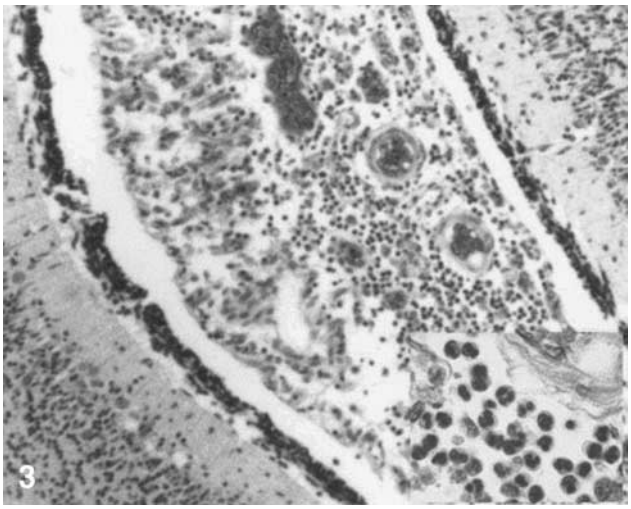

Figure 3. Low-power photomicrograph of meningeal exudates between cerebellar folia with high-power photomicrograph (insert, lower right) of neutrophilic exudate.

was described as clear and colorless, and contained 26,600 WBC, 96% PMN, 1948 mg/dl glucose, 130 mg/dl protein, and less than 10 mg/dl triglycerides. Fungal organisms were seen on gram-stained smear of the lumbar puncture (LP) but not the subdural fluid though both grew *M. furfur*. The infant's course continued to deteriorate with increasing hydrocephalus, and the parents requested that aggressive therapy be withdrawn. The infant died on day 86 of life.

AUTOPSY FINDINGS

At autopsy, the baby showed milky subarachnoid fluid and subacute fungal meningitis due to *Malassezia furfur*. The inflammatory changes most prominently involved the spinal cord, basilar leptomeninges, and left-middle cranial fossa, and were much less intense over the cerebral convexities and right-middle cranial fossa (Figs. 2–4). The location of the tip of the scalp catheter was not established, though there were no defects or lesions found in the skull to suggested direct inoculation of the leptomeninges over the brain convexities. There was no evidence of soft tissue extravasation over the scalp or neck in relationship with the scalp catheter, as had been noted radiographically when the catheter was inserted. The superior vena cava and dural venous sinuses were grossly patent and without thrombi. The common and internal jugular, facial, and emissary veins were not examined. Budding yeast with characteristic features of *M. furfur* were seen in silver-

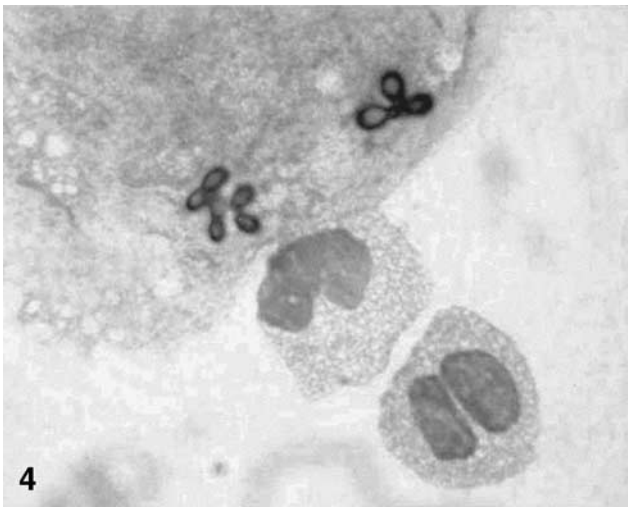

Figure 4. High-power photomicrograph of *Malassezia furfur* and neutrophilic exudates in cerebrospinal fluid (periodic acid-Schiff).

stained sections of the basilar leptomeninges. Multiple stains for fungus of other tissues including lung, liver, and spleen showed no evidence of fungal dissemination beyond the leptomeninges. There were a variety of other changes due to complications of prematurity including: brain intraventricular hemorrhage with microcephaly, widespread white matter astrogliosis, and hydrocephalus ex-vacuo; chronic peritonitis from remote perforated necrotizing enterocolitis; bronchopulmonary dysplasia; chronic cholestatic liver disease with portal fibrosis and bile duct proliferation consistent with TPN-associated liver injury;

8-mm cardiac atrial septal defect without endocarditis; atrophy of thymus, lymphoid tissues, and adrenal glands consistent with chronic steroid effects; and transfusion-associated splenic siderosis.

DISCUSSION

The first case of *M. furfur*-induced sepsis in a patient receiving lipid therapy was reported by Redline and Dahms in 1981 [1]. The predominant pathologic changes associated with *M. furfur* sepsis involve the heart (vegetations) and lung (emboli, vasculitis, and alveolitis) [3]. Reports of *M. furfur* infection of the central nervous system are limited to a single report. In this report, Shek et al. [6] in 1989 described more widespread disseminated *M. furfur* infections to other organs besides the lungs and heart, including kidney, pancreas, colon, adrenal gland, liver, spleen, brain, and leptomeninges. The one infant with meningoencephalitis had vessels of the subarachnoid space occluded with septic thrombi and yeast, and multiple foci of encephalitis involving white and gray matter indicating blood-borne dissemination. This pattern of dissemination to the central nervous system (CNS) was not observed in our case. Rather, the physiochemical profiles of the CSF with milky appearance, elevated glucose and triglycerides, and absence of *M. furfur* in other locations indicates that seeding of the leptomeninges most likely resulted from transudation or direct, or indirect, inoculation of hyperalimentation fluid into the subarachnoid space. We suspect that the CNS infection represents a second primary infection rather than recrudescence of a smoldering inadequately treated initial infection for several reasons including: 1) negative blood culture results 2 wk after completing the 26-day course of antifungal treatment; 2) stable course for several weeks without clinical manifestations after treatment for the initial *M. furfur* infection; 3) absence of persistent *M. furfur* infection outside the CNS; 4) temporal evidence of parenteral fluid and intralipid effusion into the CSF associated with *M. furfur* meningitis.

Pericardial and pleural effusions are the most common effusions complicating central catheter malposition and TPN therapy. Less frequently reported [7] are subdural and subarachnoid effusions, and a variety of other central nervous system complications of this form of therapy, including paraplegia, myoclonus, focal tonic seizures, spinal cord necrosis, and neurogenic bladder dysfunction. Most CNS complications were related to malposition of saphenous or femoral vein percutaneous catheters into the lumbar spinal venous plexus [7–12]. Intracranial effusion is rare but has been reported as a complication of facial vein catheterization with thrombosis of the internal jugular vein and retrograde extension across bridging veins of the dural sinuses [13,14]. Radiographic studies in our case showed a temporal scalp catheter with the tip overlying the cheek, indicating that the effusion may have developed in a similar manner. However, we did not demonstrate jugular vein thrombosis that would predispose to retrograde flow into the dural sinuses. Alternative routes of entry of scalp intravenous solutions into the CSF exist. The venous system of the scalp and dura is quite variable with extensive intercommunication with other scalp veins and with emissary veins that connect with the intracranial dural sinuses [15]. These emissary veins include a parietal emissary vein that traverses the parietal foramen and connects the superior sagittal sinus with scalp veins, and the venous plexus of the foramen ovale linking the cavernous sinus to the pterygoid plexus via the foramen ovale. The pterygoid plexus also has a number of connections including a deep facial vein that connects with the facial vein. Glucose and intralipid alimentation fluids could have passed through one of these collateral connections before passing though a ruptured bridging dural vein.

There was an odd discordance in the chemical constituents of the spinal and subdural fluid that persisted on repeat testing. The normal glucose concentration and measurable triglycerides in the subdural collection, in contrast with CSF from the lumbar puncture, is consistent with preferential contamination by intralipid. Similarly, the exceptionally high glucose and absent measurable triglycerides in the lumbar CSF is consistent with preferential effusion of the glucose-containing solution into the basilar and spinal cord leptomeninges. This difference in contamination is unexplained but may reflect dynamics of the inflammatory process, changing intercommunications and site of venous obstruction or rupture, as well as differences in the timing of administration of the two intravenous alimentation solutions.

Infection of subdural hyperalimentation effusion with *Staphylococcus epidermidis* has been reported [13]. However, this is the first report of *M. furfur* CNS infection arising in association with CNS hyperalimentation effusions.

REFERENCES

1. Redline RW, Dahms BB. *Malassezia* pulmonary vasculitis in infant on long-term intralipid therapy. N Engl J Med 1981; 305:1395–1398.
2. Ascher JL, Punsalang A, Maniscalco WM, Menegus MA. Percutaneous central venous catheter colonization with *Malassezia furfur:* incidence and clinical significance. Pediatrics 1987;80:535–539.
3. Marcon MJ, Powell DA. Human infections due to *Malassezia* spp. Clin Microbiol Rev 1992;5:101–119.
4. Powell DA, Durrell DE, Marcon MJ. Growth of *Malassezia furfur* in parenteral fat emulsions. J Infect Dis 1986;153: 640–641.
5. Powell DA, Hayes J, Durrell DE, Miller M, Marcon MJ. *Malassezia furfur* skin colonization of infants hospitalized in intensive care units. J Pediatr 1987;111:217–220.
6. Shek YH, Tucker MC, Viciana AL, Manz HJ, Connor DH. *Malassezia furfur* disseminated infection in premature infants. Am J Clin Pathol 1989;92:595–603.
7. Vidwans A, Neumann DP, Hussain N, Rosenkrantz T, Sanders MR. Diagnosis and management of spinal epidural space extravasation complicating percutaneous central line placement in a premature infant: case report and review of literature. Conn Med 2000;64:79–82.
8. Bergman KA, Doedens R, vd Akker E, Wust AF. Displacement and extravascular position of a saphenous vein catheter: a serious complication. Eur J Pediatr 1999;158:868–869.
9. Chen CC, Tsao PN, Yau KI. Paraplegia complication of percutaneous central venous line malposition. Pediatr Neurol 2001;24:65–68.
10. Glasier CM, Hassell DR. Spinal canal extension or hyperalimentation catheter without neurologic sequela. Pediatr Radiol 1989;19:206–207.
11. Knobel RB, Meetze W, Cummings J. Case report: total parenteral nutrition extravasation associated with spinal cord compression and necrosis. J Perinatol 2001;21:68–71.
12. Linden DH. Rhinorrhea with total parenteral nutrition fluid complicating central venous catheterization. Can Med Assoc J 1988;138:1119–1120.
13. Stine MJ, Harris H. Subdural collection of intravenous fat emulsion in a neonate. Complication of central venous catheterization for total parenteral nutrition. Clin Pediatr 1985;1:40–41.
14. Tuthill DP, Samuel L, Morris S, Drayton M. Neonatal subdural transudation of total parenteral nutrition. J Pediatr Gastroenterol Nutr 1998;27:359–361.
15. Gabell G. Cardiovascular system: veins of the head and neck In: Bannister LH, Berry MM, Collins P, Dyson M, Dussek JE, Ferguson MWJ, eds. Grays Anatomy, 38th ed. New York: Churchill Livingstone, 1995;1576–1589.