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SUCCESSFUL TREATMENT OF RHINOCEREBRAL MUCORMYCOSIS: REPORT ON A PEDIATRIC PATIENT*

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Rhinocerebral mucormycosis (phycomycosis) is a fulminating and often rapidly fatal infection of the nose, paranasal sinuses and brain. Phycomycetes, a group of fungi widely distributed in nature, may be found in the nasal, throat and stool cultures. They become pathogenic when host resistance is disturbed. Diabetes mellitus, especially when associated with acidosis, is the most common predisposing factor[1]. Other predisposing conditions are blood dyscrasias[2], gastroenteritis[3], malignant diseases[4], hepatitis[5], cirrhosis[6], burns[7], tuberculosis[8,9], congenital heart disease, pneumonia[10], chronic nephritis[11] and acute nephritis[12]. It is essential to recognize the disease (by demonstrating the fungi in the tissues involved through biopsy) before irreversible changes occur. We believe that the following pediatric case is worth reporting since there are only a few published surviving cases, and this is the only successfully treated patient reported in Turkey. The therapy consisted of control of diabetes mellitus, use of amphotericin B, local drainage and débridement.

Case Report

A thirteen-year-old female was admitted to Hacettepe Children's Hospital on September 20, 1974 because of weakness, weight loss, polydipsia and polyuria. She was conscious during physical examination, cooperative but extremely cachectic. Her tonsils were hyperemic. She had submandibular and bilateral axillary lymphadenopathy 0.5 cm in diameter. The remaining systemic findings were within normal limits.

Laboratory studies on admission. Hb was 13.2 gm/dl, WBC 14200/mm^3 with 60% polymorphonuclear leukocytes, 36% lymphocytes and 4% bands. The hematocrit was 48%, ESR 72 mm/hr. Urinalysis showed density of 1023, (+ +) glucose and no acetone. Blood sugar was 140 mg/dl. Other values of blood studies were within

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normal limits. Electrocardiographic and radiographic studies showed no abnormalities. Electroencephalography showed disregularity of bioelectric activity in the right midtemporal region.

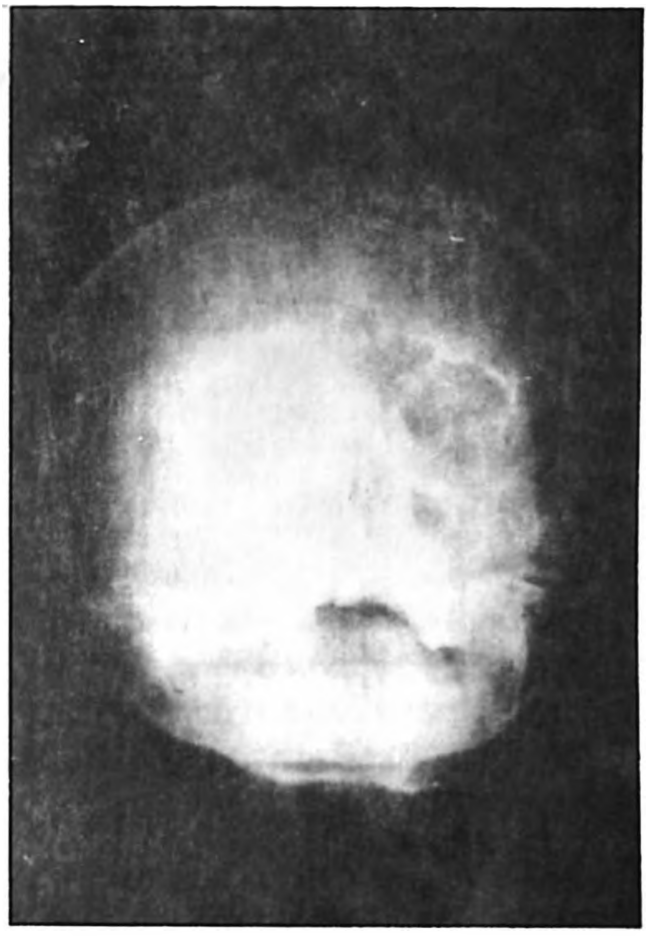
Clinical course and treatment. On the day after admission she became semicomatose and her blood pressure fell to 50/0 mmHg. Repeated urinalysis revealed (+ + +) glucose and (+ +) acetone. The serum glucose value rose to 1200 mg/dl and other findings were CO_2: 90 mEq/l, Na: 125 mEq/l, K: 2.2 mEq/l. The diagnosis was diabetic acidosis. Insulin, high-dose penicillin crystalline and gentamycin were administered parenterally. She regained consciousness on the third day. A subsequent reexamination showed edema and hypoesthesia of the left hand and depression of the motor functions of the left L 4,5 nerves. On the 25th day after admission, she complained of pain in the ears, nasal obstruction with a dark-colored bloody discharge, and hardness on the cheek. The lesions which had started as hard nodules on the cheek began to soften (Figure 1). X-rays revealed clouding of the paranasal sinuses and mucosal thickening of the right maxillary sinus (Figure 2). Her necrotic nasal septum was removed following examination by an ear, nose and throat specialist.

Figure 1

Hard nodules on the cheek.

Figure 2

X-ray showing clouding of paranasal sinuses and mucosal thickening of the right maxillary sinus.



Pathological examination. Biopsy of the nasal septum produced a 4×3×0.3 cm dark purplish bone which was fixed and later decalcified. Decalcified sections revealed almost completely necrotic bone with abundant inflammatory cell infiltration, mostly polymorphonuclear leucocytes. Large and nonseptate hematoxophilic fungi were readily observed (Figure 3). Additional smear and cell blocks prepared from the aspiration material of one of the nodules on the cheek also indicated fungi with inflammatory cells (Figure 4), but the culture showed no growth.

Treatment with amphotericin B 0.25 mg/kg/24 hr was started. Forty-five days later, a Caldwell-Luc operation and ethmoidectomy were performed. During the operation a mucosal polypoid thickening at the base of the orbit and a bone defect at the medial border of the sinus were noted. Sections obtained from these tissues showed no fungi. The operation was uneventful and the patient was discharged in good condition on January 8, 1975.

Follow-up studies. A month after her discharge, the patient's general condition was good and there was no sign of infection. Her diabetes was under control. No signs or symptoms of residual peripheric neuropathy were detected. The patient was followed up regularly in the out-patient department for three years and was asymptomatic and in satisfactory general condition.

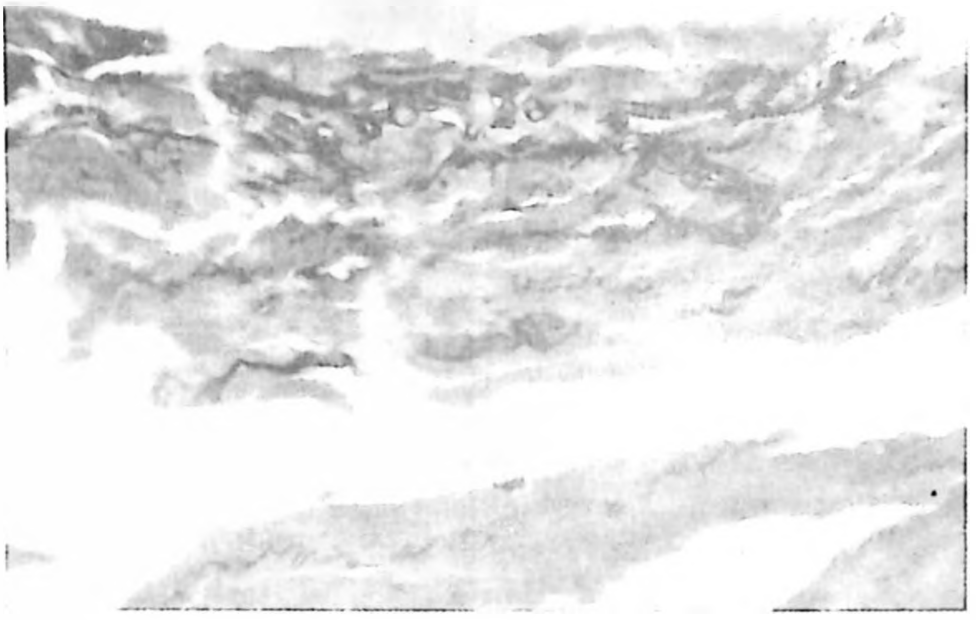


Figure 3

Section of nasal septum showing hematoxophilic, large, nonseptate fungi (H + E stain, high power).

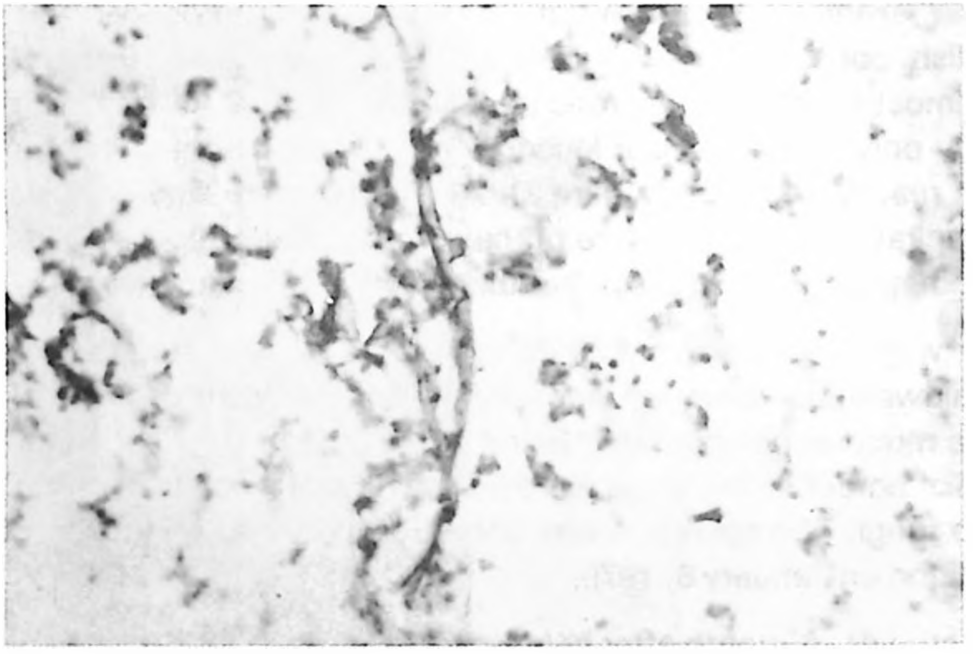


Figure 4

Cell block prepared from material aspirated from the nodule on the cheek. Same fungi as in Figure 3 with many inflammatory cells (H + E stains, medium power).

Discussion

Although the first case[13] of rhinocerebral mucormycosis was diagnosed post mortem in 1847, it was not until 1955 that a case of clinical recovery was reported[20].

In the fungus class of phycomycetes, the causative organisms involved are Mucor, Rhizopus, Absidia, Mortierella and Basidiobolus[13]. These fungi are called "bread molds" or "sugar fungi" and may be found in decaying animal and vegetable matter or in the soil. All these fungi in tissue sections have similar characteristics, including broad branching and nonseptate hyphae[14]. Exact identification is possible through culture studies. The presence of an inflammatory reaction and necrotizing changes with fungi in the tissue sections indicate its pathogenic effect[18]. Since the results of the culture studies in our case were negative, it was not possible to identify the specific type of fungus involved.

Four forms of the disease mucormycosis have been described[15]: rhinocerebral, pulmonary, alimentary and disseminated. As in the case presented, rhinocerebral mucormycosis is more frequently associated (70%) with diabetic acidosis than the other forms[1]. There have been approximately 168 reported cases of phycomycosis, of which 56 were of the rhinocerebral form. Over 25% of the total number of cases and 75% of the rhinocerebral form were associated with diabetes mellitus[16]. Studies suggest that either hyperglycemia or subsequent acidosis may disturb the metabolism of the host, allowing the fungus to proliferate[14]. The initial symptoms due to local involvement may be non specific. The patient may complain of nasal obstruction and dark bloody nasal discharge with facial pain, soft periorbital and perinasal swelling progressing to induration and discoloration, ptosis of the lid and proptosis of the eye, dilatation and immobility of the pupil, difficulty in movement, and progressive lethargy. Although the disease responds well to the type of treatment described above, the black necrotic region on the nasal septum and loss of corneal reflex with facial weakness or numbness persist. The patient may first present with proptosis, ophthalmoplegia, blindness, and sometimes involvement of other cranial nerves, especially the V. and VII. nerves. The cavernous sinus may also be affected. A review of some cases of mucormycosis in the literature revealed 48 cases of central nervous system involvement; of these, only 14 showed definite cavernous sinus involvement. Of the 48 patients with cerebral involvement, 33 were diagnosed at autopsy, evidence that the disease is highly fatal[17]. Our case exhibited several similarities to the ones reported previously in the literature; symptoms appeared after diabetic ketoacidosis, facial and orbital cellulitis was present, and there was nasal obstruction with dark bloody discharge.

Although an increasing number of cases are reported in the literature, successfully-treated cases of rhinocerebral forms remain rare. This is the fourth pediatric case of the disease seen at Hacettepe Children's Hospital and the first to be treated suc-

cessfully. Our previous cases of mucormycosis, reported in 1966 and 1971, were all diagnosed post mortem. None of them was diabetic, and in one of the three cases the course rapidly terminated in death[18,19]. The autopsy revealed necrotizing encephalitis in which the predisposing factor was uremia with acidosis due to renal disease[18]. The other two cases were associated with leukemia and lymphoma[19].

Another interesting clinical finding (no nerve biopsy was performed) in our case was the early appearance of peripheral neuropathy of the extremities and its disappearance after treatment of mucormycosis. Neuropathy commonly appears in the later phases of chronic diabetic syndrome. However, it is possible that lesions may occur in diabetics in whom neither coma nor apparent acidosis has been observed, suggesting a possible indirect effect of mucormycosis on the peripheral nerves.

Summary

A case of rhinocerebral mucormycosis associated with diabetic acidosis in a thirteen-year-old girl is presented. The diagnosis was made on the basis of sections of nasal septum and smears and cell blocks from aspirates of nodules on the cheek. The culture investigation was negative. Therapy consisted of controlling diabetes mellitus, the use of amphotericin B, local drainage and débridement. The patient was followed up for three years and remained asymptomatic. This was the first successfully-treated patient among the four pediatric cases of the disease seen at Hacettepe Children's Hospital. Interestingly, her temporary peripheral neuropathy of the extremities was suggestive of a possible indirect effect of mucormycosis on the peripheral nerves.

REFERENCES

1. DeWeeze DD, Schleuning AJ 2nd, Robinson LB. Mucormycosis of the nose and paranasal sinuses. *Laryngoscope* 75:1938, 1965.
2. Wasserman AJ, Shiels WS, Sporn IN. Cerebral mucormycosis. *South Med J* 54:403, 1961.
3. Borland DS. Mucormycosis of the central nervous system. *Am J Dis Child* 97:852, 1959.
4. Stefanini M, Allegra S. Pulmonary mucormycosis in acute histiocytic leukemia. *N Engl J Med* 256:1026, 1957.

5. McBride RA, Corson JM, Dammin GJ. Mucormycosis; two cases of disseminated disease with cultural identification of rhizopus. Review of literature. *Am J Med* 28:832, 1960.

6. Baker RD. Mucormycosis. A new disease? *JAMA* 163:805, 1957.

7. Rabin ER, Lundberg GD, Mitchell ET. Mucormycosis in severely burned patient: Report of two cases with extensive destruction of the face and nasal cavity *N Engl J Med* 264:1286,1961.

8. Faillo PS, Sube HP, Anderson NH. Mucormycosis of the paranasal sinuses and the maxillar. *Oral Surg* 12:304, 1959.

9. Hoagland RJ, Sube J, Bishop RH Jr, Holding BF Jr. Mucormycosis *Amer J Med Sci* 242:415, 1961.

10. Jackson JR, Karnauchov PN. Mucormycosis of the central nervous system. *Can Med Assoc J* 76:130, 1957.

11. Gunson HH, Bowden DH. Cerebral mucormycosis. Report of a case. *Arch Path* 60:440, 1955.

12. Kurrein F. Cerebral mucormycosis. *J Clin Path* 7:141, 1954.

13. Abramson E, Wilson D, Arky RA. Rhinocerebral phycomycosis in association with diabetic keto-acidosis. *Ann Int Med* 66:735, 1967.

14. Straatsma BR, Zimmerman LE, Gass JD. Phycomycosis. A clinicopathologic study of fifty-one cases. *Lab Invest* 11:936, 1962.

15. Castleman B, McNelly BU. Case records of Massachusetts General Hospital. *N Engl J Med* 279:1220, 1968.

16. Battlock DS, Grousz H, Bobrowsky M, Littman ML. Alternate-day Amphotericin B therapy in the treatment of rhinocerebral phycomycosis (mucormycosis). *Ann Int Med* 68:122, 1968.

17. Latouche CJ, Sutherland TW, Telling M. Rhinocerebral mucormycosis. *Lancet* 2:811, 1963.

18. Tınaztepe B, Tınaztepe K. Cerebral mucormycosis in a child. *Turk J Pediatr* 8:206, 1966.

19. Tınaztepe B, Tınaztepe K. Opportunistic deep fungus infections in children: a histopathological study. *Turk J Pediatr* 13:13, 1971.

20. Harris JS. Mucormycosis: Report of a case. *Pediatrics* 16:857, 1955.