

A Case Report of Meningeal Mucormycosis with Autopsy Findings

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The term "Mucormycosis" means the infection by members of the order Mucorales, which includes such genera as *Absidia*, *Rhizopus* and others. These are Eumycetes (true fungi) of the class Phicomycetes characterized by nonseptate hyphae, and the organisms involved in human and animals are species of *Mucor* and *Rhizopus*¹⁾. The first pathogenesis of Mucorales came from Lichteim's experimental studies in rabbits²⁾. Since then, occasional reports of human infection by these fungi have rarely appeared in the literature. Along with the excessive use of antibiotics candidiasis, aspergillosis, cryptococcosis and actinomycosis have become not so rare human infection nowadays, but mucormycosis is still uncommon through the world. The human infection by the order Mucorales involves the paranasal sinuses, orbit, central nervous system, lung and gastrointestinal tract³⁾. In Europe and America it is considered that this fungus infection involving the central nervous system is often the fatal complication of diabetes mellitus. We have recently observed a case with this fungus infection involving the meninges, however, the direct cause of death was not mucormycosis but postoperative epidural hematoma.

CLINICAL COURSE

First admission (March 15, 1956):

Mr. S.S., aged 14, was admitted to the otolaryngological clinic of Yamaguchi Medical School Hospital because of three-year history of nasal obstruction, approximately two-month history of painless persistent swelling of the left cheek area and lacrimation from the left eye; without any notable nasal discharge.

The patient had developed lacrimation from the left eye since this January, and then he noticed some swelling of the left cheek area, not associated with any pain,

tenderness, local heat or any restriction of facial muscular movement.

Approximately one month prior to admission, left nasal obstruction and cheek swelling became markedly, but no nasal bleeding was noted.

During the last three years period, the patient had been treated on several occasion by otolaryngologists with some nose drops and nasal washing. There was no history of pulmonary tuberculosis, cardiac disease or severe fits of headache pronounced.

Physical examination revealed an apparently healthy boy with some swelling at the infraorbital region. There was a relatively firm induration in the left cheek area. Rhinoscopy revealed mild septal deviation to the right and moderate swelling of the left inferior concha; however, no other notable abnormality in the nostrils. The choana, pharynx and larynx were normal. The remaining physical examination was within normal limits.

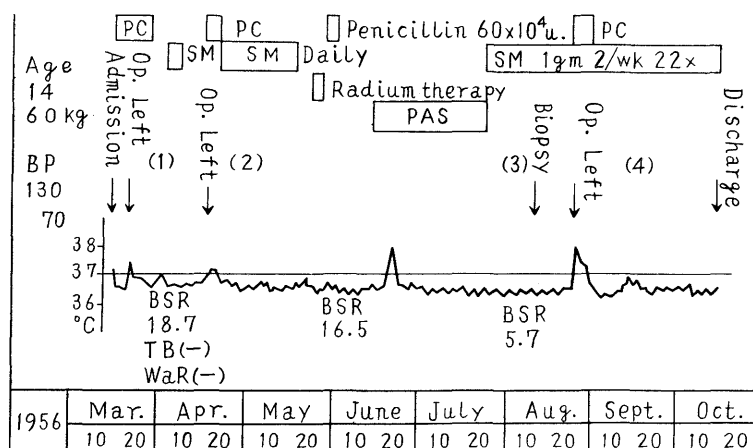
The temperature was 37.2°C, the pulse 70, and the respirations 20. The blood pressure was 140 systolic, 70 diastolic.

The peripheral blood examination showed no abnormality (RBC 455×10^4 , WBC 7200, Hb 81%). Serologic test for syphilis was negative. Ophthalmologist observed that double vision might be caused by compression with some tumor in the left orbit.

X-ray examination of the paranasal sinuses demonstrated diffuse cloudiness at the left paranasal sinuses area, but no visible deterioration of bony structure.

A tentative diagnosis of a left maxillary tumor was made. On the 7th hospital day, Denkel type operation of the left maxillary sinus was performed being observed the thickened mucosa in the sinus and no visible tumor-like mass in.

Table 1. First Hospital Course



- (1) Watsuji-Denker type Op. of the left maxillary sinus.
- (2) Removal of the mass in the left orbital floor region.
- (3) Biopsy specimen of the maxillary mucosa suggested proliferative tuberculosis.
- (4) Abrasion of the mass in the left maxillary sinus.

Table 2. Blood spectrum (5-14-1956)

Ht	42.7 ml/dl	Urea N	7.5 mg/dl
Hb	14.6 g/dl	CCFT	0
MCC	34.4 %	Albumin	3.8 g/dl
Serum Protein	6.9 g/dl	Globulin	3.1 g/dl
Blood sugar	79 mg/dl	Cholinesterase	1.0 pH
A/G ratio	1.23	Cholesterol	190 mg/dl
Icteric Index	3	Phenol turbidity test	21.8
NPN	20 mg/dl		

On the 28th hospital day, operation for removal of the mass in the left orbital floor region was tried and failed to detect any tumor-like mass in the orbit.

Through the course, Penicillin, Streptomycin, PAS were administered and radium irradiation therapy was done for nearly three months. (Table 1.)

Swelling of the infraorbital and zygomatic region did not reduced, and some induration existed continuously.

After the abrasion of the granulation grown in the left maxillary sinus, the swelling of cheek and zygomatic region was subsided slightly. Then the patient was discharged in October 1956.

Second admission (May, 27, 1956, three years later):

The patient, aged 17, progressed in fairly good local condition for about last three years.

Three months prior to this admission, the swelling of the left zygomatic and palpebral regions developed, which usually increased its size when he worked hard and/or bent his head forward down for a while.

However, the patient did not pronounced nasal discharge, hyposmia, spontaneous pain or disturbance of sleep.

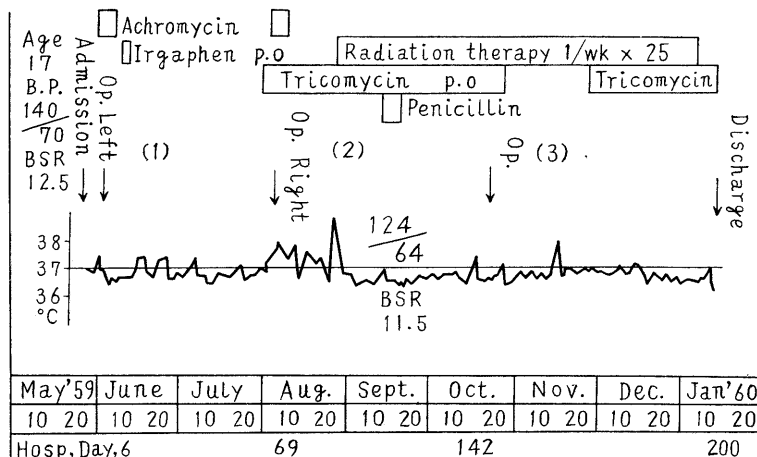
Physical examination revealed a well developed and moderately nourished, apparently healthy 17 year-old man with painless swelling and induration at the left palpebral-zygomatic region. Body temperature was 36.8°C, the puls 70, the respirations 16. Blood pressure was 140 systolic and 70 diastolic. Rhinoscopic examination showed no visible abnormality in the nostril, except for the absence of left inferior concha which was removed at the previous operation.

The examination of the blood revealed red blood cell 536×10^4 , a hematocrit of 44.5 percent, and a white cell count of 9,125 with 4.5 percent band form, 66.5 percent of lymphocytes and 2 percent of monocyte. (Table 3 and 4.)

Culture of sputum for tuberculosis bacillus was negative. Tuberculin skin test was negative. Blood sedimentation rate was 12.5 mm in average.

X-ray examination of the nose and paranasal sinuses revealed homogenous massive cloudiness in the left maxillary sinus, with defected bony wall of the lateral

Table 3. Second Hospital Course



- (1) Re-operation of the left maxillary sinus & removal of tumor in the left cheek.
- (2) Radical sinus operation on the right side & removal of tumor in the right cheek.
- (3) Dissection of the labiogingival mucosa for biopsy.

Table 4. Peripheral Blood Examinations

Date	5-28-'59	8-26	10-14	11-9	11-30	12-14	12-28
RBC	536 × 10 ⁴	369	554	497	505	633	537
Ht	44.5%	41.5	46.7	42.0	42.8	45.8	46.0
MCV	83.1	81.0	84.3	84.5	84.7	72.3	85.5
THROMB.	128	81.0	100	96.0	94.0	97.0	69.0
WBC	9125	7425	6150	5250	10800	6700	4700
N. band	4.5%	3.0	1.0	3.0	4.0	2.0	3.5
N. segment	66.5%	54.0	55.0	52.0	67.0	84.0	53.0
Eosinoph.	1.5%	2.0	7.0	8.0	3.0	1.0	5.0
Basophil	1.0%	1.0	0	1.0	1.0	0.5	0
Lymphocyt.	24.5%	39.0	32.0	32.0	32.0	8.5	28.0
Monocyte	2.0%	1.0	5.0	4.0	3.0	3.5	10.5

aspect of the left maxilla. Chest X-ray examination was within normal limits. On the 6th hospital day, re-operation of the left maxillary sinus combined with removal of mass in the left zygomatic region was performed. Histopathological study of the specimen taken from the left maxillary sinus suggested granuloma fungoides of the paranasal sinus. Postoperative course was uneventful, except for no marked subsidence of the swelling of the left cheek. (Table 3, 4 and 5.)

During this hospital course, the swelling of the right cheek occurred and developed gradually. His general condition remained nearly good.

Table 5. Systemic blood examination

		5-28-'59*	8-26-'59**
Hemoglobin	(g/dl)	14.6	12.2
Serum protein	(g/dl)	8.8	7.9
Blood sugar	(mg/dl)	162	7.0
A/G ratio		0.83	0.98
Icteric Index		8	7.5
CCFT		1	0
Albumin	(g/dl)	4.0	3.9
Globulin	(g/dl)	4.8	4.0
Cholinestrase	PH	0.84	0.95
Alkaline Phos	(mg/dl)	3.3	2.3
Cholesterol		140	145
Phenol turb.	(mg/dl)	12.4	17.2
NPN	(mg/dl)	26	24
Urea N		11	9

* The blood spectrum indicates slight depletion which is better than before. Hepatic dysfunction remains very slightly because latent jaundice is persistent.

** The blood spectrum bears L pattern indicating slight or moderate depletion. There is a questionable rise in icteric index. Hepatic function is nearly intact or may be impaired slightly.

Table 6. Bacteriological Examination (Culture)

	6-18-'59	6-29	9-29	10-1	10-19
Kinds of Metrials	Polypous tissue in the nose	Nasal discharge	"	"	Pharyngeal tissue
Aspergillus	-	-	-	-	-
Candida		+	-	-	+
Staphylococcus aureus			+	++	

Culture of the nasal discharge and tissue of the nose for fungus was repeated. The candida were grown once from the nasal discharge and once from the pharyngeal tissue; Aspergillus negative. (Table 6)

On the 69th hospital day, the right radical sinus operation combined with removal of the mass in the right cheek was performed. The very thickened, partly edematous, mucous membrane and the tumor of the right cheek were removed.

The Tricomycin was prescribed continuously and X-ray radiation therapy over both cheeks was given nearly twice a week, 22 times, for about 4 months (totally 2455 r.).

Although postoperative managements were enthusiastic, the swelling of the left zygomatic and orbital region did not subside and persisted until January 11, 1960 when he was discharged.

Final admission (August 8, 1962):

Three months prior to the admission, the patient developed vomiting on each meal, becoming more frequent. One month prior to admission, he began to have some difficulty in walking and the incontinentia. Day after day, these symptoms became more worse.

He again admitted to our hospital in August, 1962.

Physical examination revealed slight exophthalmus of the left eye, disturbance in gait, and slight hyperactivity of knee reflexes without any pathological jerks.

On the 2nd hospital day, he had an attack of cramp associated with unconsciousness for about ten minutes.

A lumbar puncture revealed the opalescent fluid under initial pressure equivalent to 380 mm H₂O and a final pressure to 180 mm H₂O after withdrawal of 8 cc of fluid.

Quecknstedt's test was negative.

The fluid gave a +++ Pandy test and contained 270 small round cells. X-ray film of the skull showed no abnormality such as space occupying lesion or tumor. The electroencephalogram showed abnormal slow waves but gave no evidence for brain tumor.

On the 21st hospital day, lumbar puncture was done again confirming the previous findings and results.

Because of persistence of vomiting, the ventricular drainage was at last performed on September 4, 1962.

The next day he began to have severe dyspnea and expired on September 5, 1962.

Autopsy Findings;

A postmortem examination was performed only at the head, because the permission of autopsy of the other parts of the body was not obtained. The body was that of well developed and moderately nourished 21 year-old man. There were no external abnormalities except the head. The skin of the head was edematous especially at the right side, and a clear wound was visible at the right occipital region. The skull showed no abnormal findings, but under the skull there was large epidural hematoma which covered almost all over the right cerebral hemisphere.^{Fig. 1)} The leptomeninx at the basis of the brain was grayish white and remarkably thickened,^{Fig. 2)} and it was adherent to the dura. The leptomeninx of the inferior surface of the cerebellum and the medulla oblongata was also grayish white and slightly thickened. The spinal fluid was normal in color. The brain was 1420 gm. in weight and there was no abnormality on its surface except that the right polus temporalis seemed

slight edematous. No lesion was recognized in cut surface, but the both ventriculus lateralis, especially that of the left side, were enlarged, so the septum pellucidum was deviated to the right.^{Fig. 3)} The middle ears, paranasal sinuses and orbit were not examined.

Microscopical findings were as follows;

The basal meninges was thickened and many small foci were observed. The central portion of the foci revealed necrosis,^{Fig. 4)} around which infiltration of plasmocytes, lymphocytes and foreign body giant cells was recognized,^{Fig. 5)} and most of these abscesses were surrounded by hyaline connective tissue. Within the necrotic mass numerous broad, nonseptate hyphae were observed.^{Fig. 6)} In the leptomeninges of the inferior surface of the cerebellum and medulla oblongata, infiltration of plasmocytes and lymphocytes was seen, but no hyphae was observed. In spite of repeated examination no lesion was found in the section from the brain.

The hyphae, which were observed in necrotic mass, were pleomorphic, broad and aseptate, measuring from 10 to 60 micron in length and 4.5 to 12.6 micron in width. These hyphae have few lateral branches but sometimes short and broad branching was recognized. The tubular structure of the hyphae was clearly visible in periodic acid Schiff preparation.^{Fig. 7) Fig. 8)}

Comments;

Mucor and Rhizopus are considered to be of world-wide occurrence and have a widespread natural distribution. The hyphae of the genus Mucor and the genus Rhizopus appear similar in tissue, so the true identification rests upon cultural characteristics. However, it has been customary to make the diagnosis of "Mucormycosis" on the basis of finding the broad nonseptate hyphae in tissue section⁴⁾. Although the culture for the fungi was not performed at autopsy, the diagnosis "Mucormycosis" in this case was made on the basis of the morphological findings of the hyphae in the tissue.

Mucormycosis involving the central nervous system is often regarded to be secondary to the infection of the paranasal sinuses, nasal cavity or orbit. The infection, arising in the paranasal sinuses and/or orbit, often spreads to the brain via the internal carotid arteries and cavernous sinuses. So in most cerebral mucormycosis the inferior surface of the frontal lobe and the meninges around the optic chiasm area are firstly infected. It is likely that in this case the primary focus was the paranasal sinuses and spread to the meninges continuously involving the orbit, since there was clinical evidence of preceding sinus and orbital involvement. In many case reports on cerebral mucormycosis the brain substance is often involved and the fungus in the brain has the tendency to invade the vessel resulting thrombosis and subsequent infarction. In this case, however, the involvement was localized to the basal meninges and no lesion was recognized in the brain substance.

It is reported that majority of cerebral mucormycosis is associated with uncontrolled diabetes and a few cases with uremia, tuberculosis, leukemia or malignant diseases, but there was no evidence of diabetes clinically in this case. According to M. E. Smith et al hyperglycemia in itself may contribute to the fungal growth, since these fungi thrive on sugar. P. Neame et al pointed out that acidosis might play a dominant role as a contributing factor. Cortison and malnutrition are also reported as a contributing factor.

SUMMARY:

A case of mucormycosis involving the basal meninges is reported. The brain substance was not involved. The paranasal sinuses are suggested as a primary focus, since there was clinical evidence of severe paranasal sinusitis and the histopathological examination of the biopsy, taken from the sinus, revealed broad and nonseptate hyphae. There was no clinical evidence of diabetes and no other predisposing factors. The direct cause of death is presumably epidural hematoma occurred postoperatively.

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Fig. 1) Large epidural hematoma



Fig. 2) The basal leptomeninges is remarkably thickened.



Fig. 3) Enlarged ventriculus lateralis

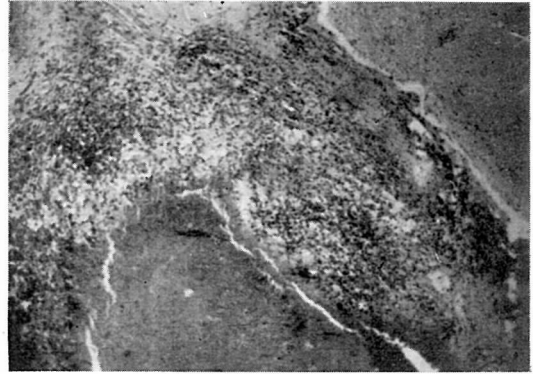


Fig. 4) Central portion of the foci reveals necrosis and peripheral zone shows cell infiltration. H. E. $\times 100$

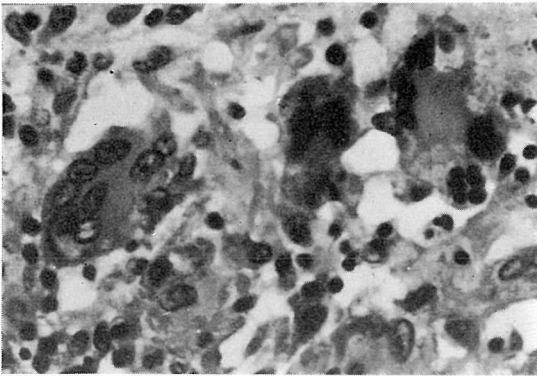


Fig. 5) Cell infiltration H. E. $\times 400$

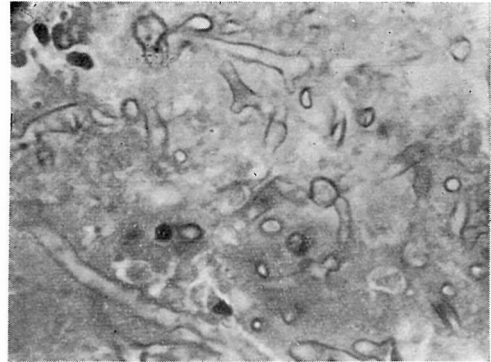


Fig. 6) Hyphae in the necrotic mass H. E. $\times 400$

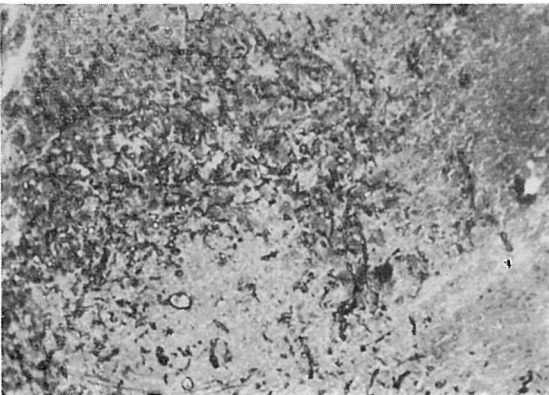


Fig. 7) Many hyphae are clearly visible in periodic acid Schiff preparation. P. A. S. $\times 100$

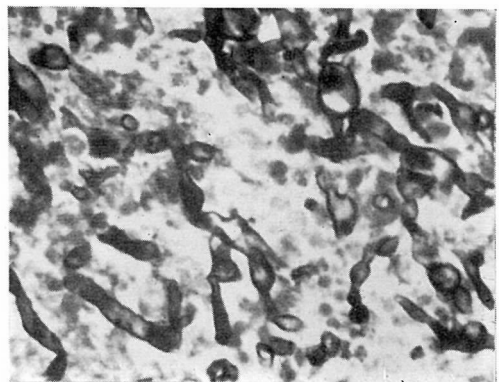


Fig. 8) Pleomorphic, broad, nonseptate hyphae P. A. S. $\times 400$