Generalized Cryptococcosis without Central Nervous System Involvement in an Infant with Malabsorption Syndrome

Behçet Tınaztepe, M.D.*/ Keriman Tınaztepe, M.D.**

Cryptococcosis, which is also known as torulosis and European blastomycosis, is a mycotic disease of man and animals caused by cryptococcus neoformans. Littman and Zimmerman reported 300 cases in 1956,[1] but later a search through the world literature in 1968 [2] revealed more than double that number in patients of all ages.

Although cryptococcal infections are seen with increasing frequency, the true incidence of the disease is unknown, [2-5] and it is still rarely seen in children. Emanuel et al, reviewing the literature in 1961, found only 23 cases, Siewers and Cramblett[6] found 42 cases in 1964 which, with their own four, totalled 46. In most of these instances the central nervous system was involved. This approximate number of cases in the pediatric age group may not be representative of the incidence of the disease, since diagnosis still presents practical difficulties. Even so, we can conclude that the disease is relatively uncommon in the pediatric age group.

Infections caused by the cryptococcus have been known to occur in all organs of the body, but show a predilection for the central nervous system in patients of all ages.[1-3-7] However, generalized cryptococcosis

---

From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

* Associate Professor of Pathology, and Consultant in Pediatric Pathology.

** Associate Professor of Pediatrics, and Pediatric Pathologist.

without involvement of the nervous system does occur, and the first report of such a case in an adult was made in 1951.[8] Out of 46 cases of generalized or localized cryptococcal infection described in reports written in English[3-4] only 9 have shown no involvement of the nervous system. The fungus is widespread in nature and studies of the disease it causes have been published from nearly all regions of the world. [1-4-7] Cryptococcosis in Turkish children has only been reported twice to date;[9], [10] the present study was written because the generalized form of the disease without involvement of the nervous system has never been published from this country, and because of the unique feature of our case - namely, its association with malabsorption syndrome and A avitaminosis.

Case Report

A. Ç. (41008-66) a four-month-old boy, was admitted to Hacettepe Children's Hospital with chief complaints of fever, coughing, vomiting, diarrhea, enlargement of the abdomen, and poor vision. He was the first child of healthy parents without consanguinity, and of high income status, the mother being 21 years old and the father 25. There were no complications during the pregnancy or at delivery, which took place at Samsun City Hospital, nor did the baby show any cyanosis, jaundice or respiratory difficulty at birth. He weighed 4.400 gr at birth, and was breastfed for about two months. Later on various formulae (such as SMA, Lamed and Paro) were given.

The parents stated that the patient had diarrhea for one and a half months prior to hospitalization, which was described by the mother to be of a yellowish color, with frothy mucus but no blood, and to occur four or five times daily. He was taken to a local physician several times, but without success. In the previous 10 days he had had fever of around 38°C, and had been coughing, but there were no convulsions.

A week prior to admission to Hacettepe Hospital, the patient was taken to Samsun City Hospital where enteritis, protein caloric malnutrition and hypopotasemia were diagnosed. Intravenous fluids, vitamins and antidiarrheic drugs were given. During hospitalization the child was noted to have hepatomegaly (four cm below the right costal margin), perforated keratitis and paralytic ileus; the latter was successfully treated within two days. The hospital informed us that additional findings were: weight 4,500 gr, poor general condition, skin eruptions on the face, on the back and around the genitalia, rales on both lung fields, and rapid pulse rate. Physical examination on admission to Hacettepe revealed: weigth 4,000 gr. lenght 56 cm, fever 38.2°C, respiration 32-38 and pulse 114 per minute,

head, chest and abdomen circumferences 41, 37 and 39 cm respectively, patent anterior fontanel measuring 2 x 2 cm, and normal muscular tonus. The patient was restless and crying. Neurological examination was within normal limits. The other significant findings were similar to those seen in the previous hospital.

Laboratory Examination: Hemoglobin was 10-11.5 gm/100 ml, white cell count was 15,000-20,000 per mm^3 with a differential of 54 per cent neutrophils and 46 per cent lymphocytes, and platelets were adequate in the blood smear. CO_2: 22 mEq/L, K: 4.2 mEq/L, Cl: 101 mEq/L. Urinalysis was unremarkable. Throat culture showed no growth, and stool culture showed a growth of A. Aerogenes. PPD was negative. Eye examination revealed a perforated corneal ulcer with prolapsus of the lens due to keratitis secondary to malnutrition. The patient received intravenous fluids, antibiotics and a variety of vitamins, including vitamin A. No food was allowed in the first 24 hours and later milk plus food made with milk and rice water was given.

In spite of therapy the patient died six days after hospitalization.

Post-Mortem Examination: Autopsy was performed the day after death. Pertinent gross findings were: marked decrease of subcutaneous fat, eruptions of the skin, perforated keratitis, areas of consolidation of the lungs with emphysema, hepatomegaly of 330 gm (normal weight for this age is 261 gm,) the liver was soft with yellowish discoloration; otherwise the organs were generally underweight (kidneys 23 gm (N: 61 gm), thymus 2 gr (N: 22.1 gm). pancreas 1 gr (N: 9.24 gr), adrenals 2 gr (N: 4.97 gm) and heart 18 gm (N: 37 gm); a few small stones were present in the renal pelvis (chemical analysis of these was not made). No gross lesions were seen in the gastro-intestinal tract or the central nervous system.

The main microscopic findings were: generalized and extensive cryptococcus infection involving the lungs, liver, (Figures 1 and 2), spleen, (Figure 3), kidneys, (Figure 4), adrenals, pancreas, lymph nodes, the mucosa of the esophagus, stomach and the small and large intestines. Similar microscopic lesions were seen in all organs. Cyst-like cavities were found filled with thick capsulated fungi, but there was generally no inflammatory cell reaction around them. Various size groups of cryptococci were seen in hemotoxylin and eosin stained sections, and could easily be recognized with PAS and toluidin blue (pH 3.5). These special stains demonstrated the presence of acid mucopolysaccarides in the capsule of the cryptococci. The PAS stain showed pink-colored capsules, and toluidin blue stain showed metachromasis as expected. Radiating spikes of cap-

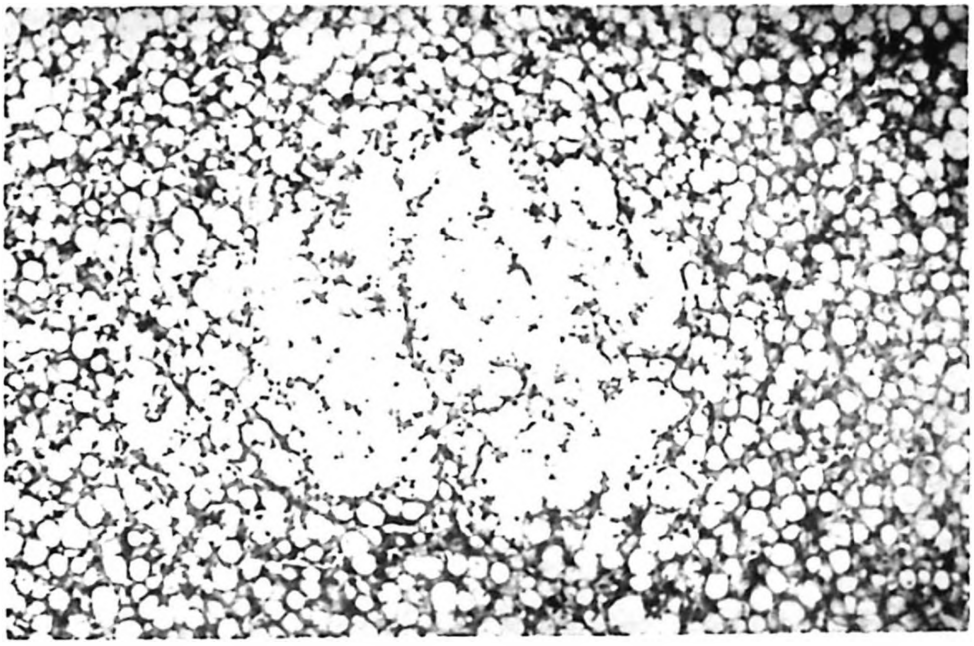

Fig. I Hematoxylin and eosin stain. x90. Section showing groups of cryptococci and fatty metamorphosis of the liver.

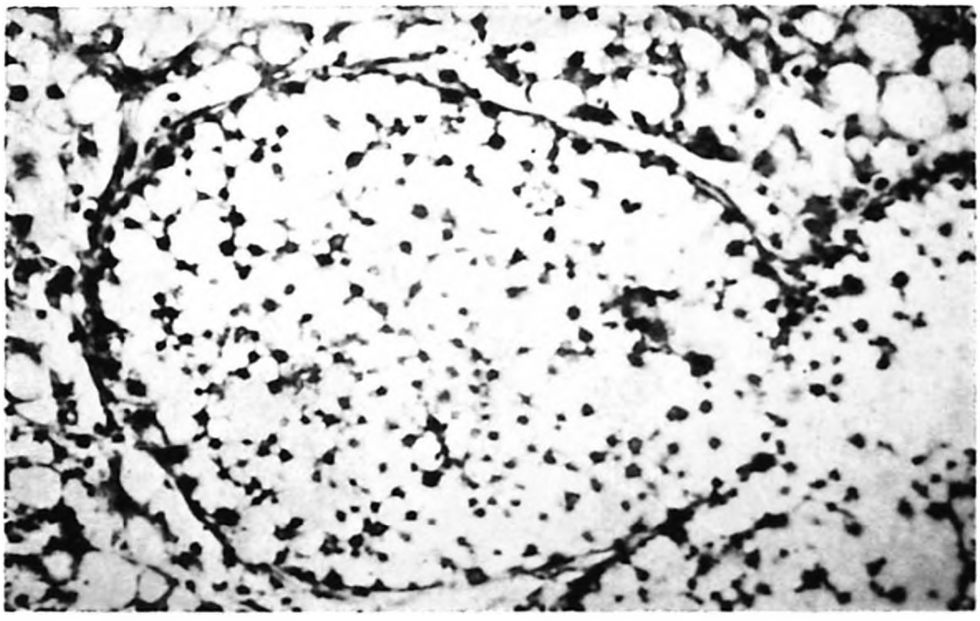

Fig. II: Toluidin Blue, p. H. 3.5 X 300. Showing a similar area of the liver as Fig. 1

sular shrinkage due to fixation were also seen. As no other known fungi have such characteristics in tissue section, the diagnosis of cryptococcosis was made.

Since it is known that cryptococci have a tendency to invade the central nervous system we re-examined the brain. The entire menenges were

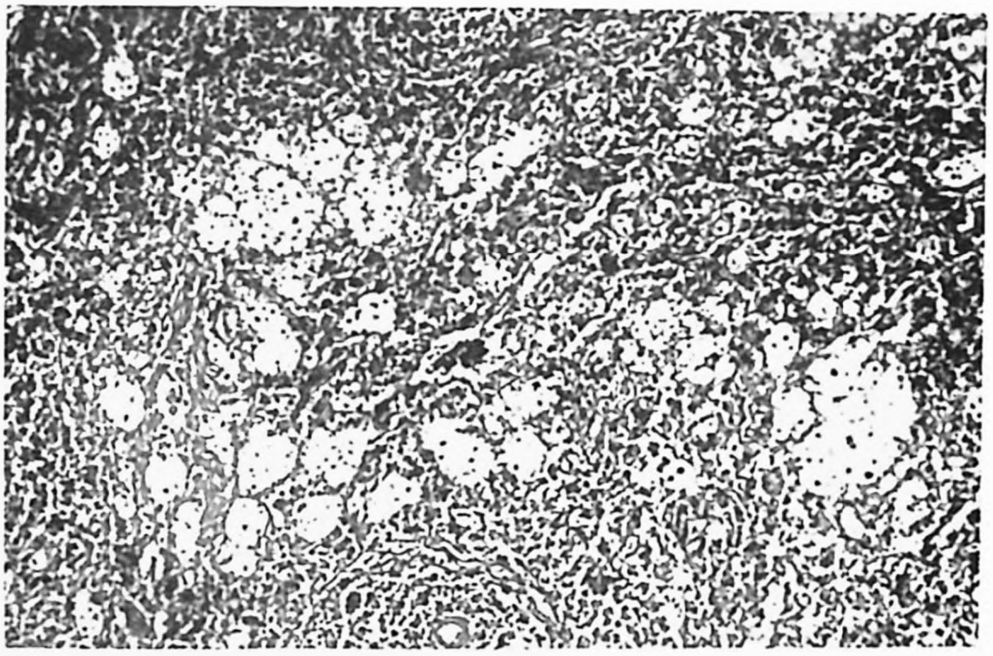

Fig. III : Hematoxylin and eosin stain x 90. Section showing small and large groups of cryptococci in the spleen.

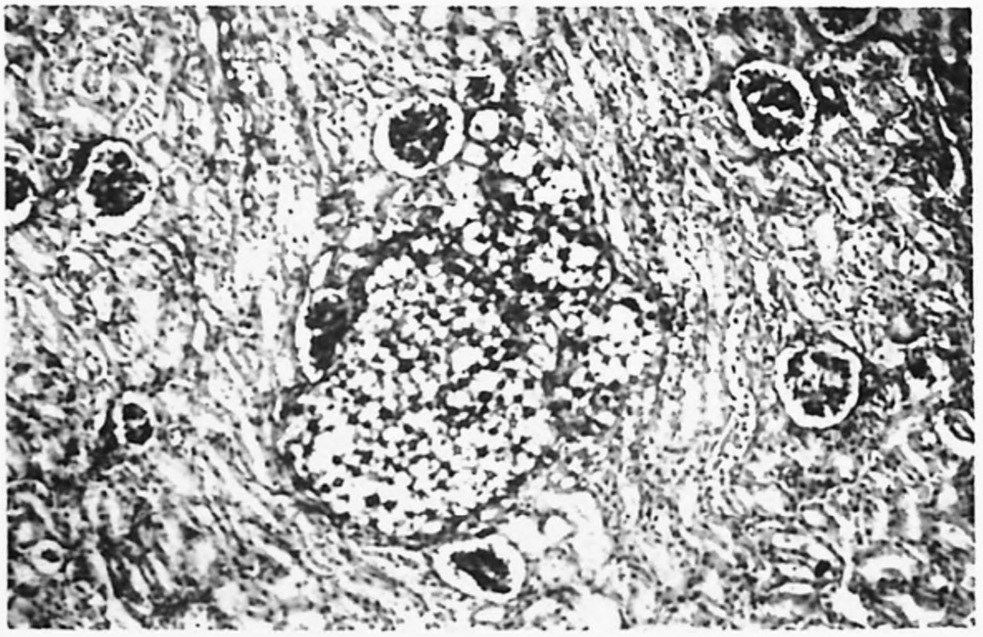

Fig. IV : Hematoxylin and eosin stain x 90. Section showing cryptococci in the kidney.

stripped examined both by frozen section and by paraffin sections, as were many additional samples of brain tissue, in order to find fungi, but no organism was found. Other microscopic findings were diffuse fatty metamorphosis and hemosiderosis, but without fibrosis of the liver.

In spite of a day's delay before post-mortem examination, the mucosa of the small intestine was well preserved. The villi were broad and club-shaped, there was a decreased number of goblet cells, the tunica propria contained many plasma cells, and there were lymphocytes and a few neutrophils, all of which are seen in malabsorption syndrome. (Figure 5)

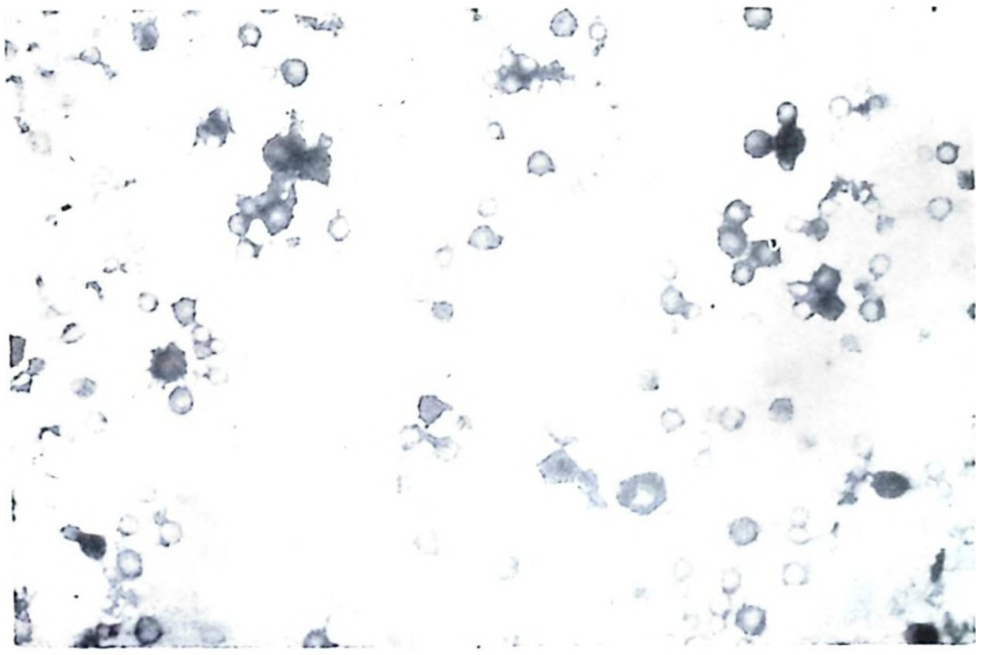

Fig. V: Toluidin Blue stain p.H. 3.5 x 750. Tissue section of cryptococci showing radiating spikes of capsular material.

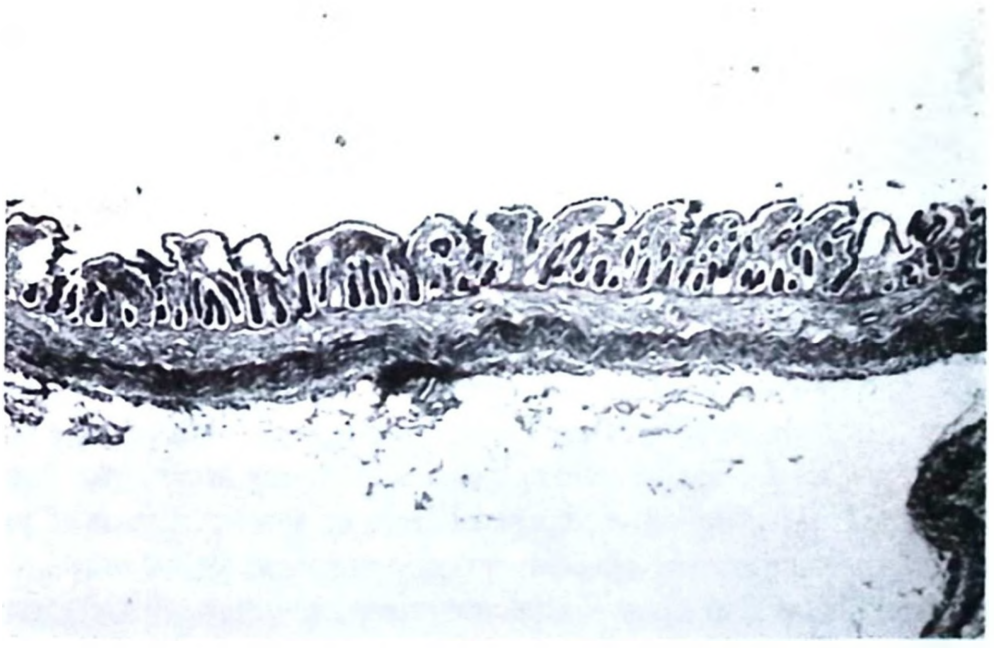

Fig. VI: Hematoxylin and eosin stain x 75. Section showing Broad, short and club shaped villi of the small intestine empty looking areas in the villi correspond to groups of cryptococci which are not visible at this magnification.

Sections of the pancreas showed slight aciner dilatation due to epithelial atrophy without inspissated material in the lumina, but no fibrosis or inflammatory cell infiltration. Sections of the skin showed a moderate degree of hyperkeratosis and slight thinning of the epidermis. Sections of the thymus showed only atrophy, with no evidence of thymic dysplasia. Sections of the eye, including the eye-lid, showed hyperkeratosis on the epidermal site, proliferation of the conjunctival epithelium, and cystically dilated glands with focal squamous metaplasia. The cornea showed thinning of the epithelium with slight keratinisation, with an area of perforated ulcer, but inflammatory cell reaction was minimal, and no fungi were detectable.

Discussion

In spite of the fact that organisms have been cultured from normal skin, the lung, the gastro-intestinal tract, fruit juices, soil, pigeon excreta, wood and milk,[2-4 6 7 11] cryptococcosis is relatively uncommon. This is because the fungus becomes invasive as a result of the body's lowered resistance. In patients with cryptococcal infections, as in secondary mycosis, there is usually an associated disease or side-effects from modern therapy. It is not our purpose to repeat individually what has already been published, but to give a brief review of these conditions.[2 11 13] They are: lymphomas, leukemias, diabetes millitus, hemolytic anemia, pregnancy, endocarditis, tuberculosis, sarcoidosis, moniliasis, histoplasmosis, hepatic [14 15] and renal diseases.[16 17] The role of malnutrition has rarely been a very important factor, and was recently published for the first time.[12] In the present study the patient had both clinical and pathological evidence of malnutrition, plus intestinal findings of malabsorption syndrome with A avitaminosis, which may occur as a primary deficiency due to an inadequate diet. However, because the tissue reserves are of such magnitude that it would take two to three years' deprivation to exhaust them, simple deficiency would be extremely unlikely. More commonly, A avitaminosis occurs in the form of deficiency conditions affecting fat absorption such as biliary tract disease, pancreatic disease, sprure and severe intestinal disease[18]. In the present case exogenous deficiency is unikely, and there was no related pathological evidence of liver or cystic fibrosis of pancreas. There are many causes of malabsorption syndrome in infancy and childhood[19] some of which show wide and atrophic villi of the mucosa of the small intestine as seen in our case. The intestinal villi normally autolys at death which make the pathological interpretation difficult. In the presented case even though post-mortem examination was done 24 hours after death well preservation of the intestinal villi and surface epithelium

might be of significance. This suggests a lack of enzyme production leading to the delay of the autolysis. A similar suggestion has already been extended.[20] On the other hand in our case above-mentioned histopathologic changes of the exocrine pancreas and the small size of the organ might also be responsible for the enzyme deficiency.

Reviewing the literature we were unable to find any similar case of cryptococcal infection associated with malabsorption syndrome. In previously reported cases of cryptococcal infection 88 per cent of the patients had associated malignant diseases of the reticuloendothelial system,[21] which has led to the suggestion that immunological response may be disturbed. Although no immuno-globulin determination was performed in the present case, no morphological evidence of disturbed immunity[22] in the thymus and the lymphoid system was shown.

The development of bacterial infections in cases of A avitaminosis is common, and can always be explained on the basis of mechanical effects, consequent to epithelial changes.[23] However, Littmann and Zimmerman[1] cited experimental evidence that splenic lesion with cryptococci occurs only if the organism is inoculated into vitamin A deficient animals. This experiment, and our case, suggest that severe vitamin A deficiency may play a role in the pathogenesis of the disease, not only mechanically due to protection of the integrity of the surface epithelium, where the cryptococci might be naturally present, but also it may have a direct role in the dissemination of the fungi throughout the body. It could be suggested that in cases of generalized cryptococcosis associated with malnutrition, the detection of vitamin A deficiency may prove valuable in the understanding of an altered host-paresite relationship. This consideration undoubtedly requires more pathological and experimental study.

Summary

The case of a four-month-old infant showing generalized cryptococcosis associated with malabsorption syndrome and A avitaminosis without central nervous system involvement is presented. The diagnosis was made at post-mortem examination by demonstration of the typical morphologic characteristic and staining qualities of the fungi in the tissue sections. The clinical picture and additional histopathologic findings were consistent with those of malabsorption syndrome and A avitaminosis. No similar associations were encountered in the cases reported in the literature on cryptococcosis.

REFERENCES

1. Littman, M. L. and Zimmerman, L. E.: Cryptococcosis, Torulosis or European Blastomycosis. 1st ed. New York and London, Grune and Stratton, Inc., 1956.
2. Littman, M. L. and Walter, J. E.: Cryptococcosis: Current Status. Am. J. Med. 45: 922, 1968.
3. Twinning McMath, W. F. and Hussain, K. K.: Cryptococcal Meningo-Encephalitis, Brit. Med. J. 2: 91, 1961.
4. Emanuel, B., Ching, E., Lieberman, A. D. and Goldin, M.: Cryptococcus, Meningitis in a child Successfully Treated with Amphoterecin B, with a review of the literature J. Pediat. 59: 577, 1961.
5. Tumulyt, P. A. and Sheldon, W. H.: Clinicopathologic Conferance, John Hopk. Med. J. 124: 44, 1969.
6. Siewers, C. M. F. and Cramblett, H. G.: Cryptococcosis (Torulosis) in Children. Pediat. 34: 393, 1964.
7. Wilson J. W. and Plunkett, O. A.: The Fungus disease of Man, Berkeley and Los Angeles, University of California Press, 1965.
8. Zelman, S., O'Neil, R. H. and Plaut, A.: Disseminated Visceral Torulosis Without Nervous System Involvement with clinical appearance of Granulocytic Leukemia, Am. J. Med. 11: 658, 1951.
9. Sosyal, Ş. S., Unat, E. K. and Tahsinoğlu, M.: A case of cryptococcosis, Arch. franç. Pediat. 11: 246, 1954.
10. Unat, E. K., Pars, B. and Kosyak, J. P.: A case of cryptococcosis of the colon. Brit. Med. J. 2: 1501, 1960.
11. Nanda, S. P., Kass, I., Cohn, M., and Dressler, S. H.: Coexistence of Tuberculous and cryptococcal Meningitis Pediat. 20: 45, 1957.
12. Pedraza, M. A.: Mycotic Infections at autopsy-A comparative Study in two University Hospitals, Am. J. clin. Path 51: 470, 1969.
13. Berkel, I., Say, B. and Tınaztepe, B.: Pulmonary aspergillosis in a child with leukemia New. Engl. J. Med. 269: 893, 1963.
14. Sabesin, S. M., Fallon, H J. and Andriole, V. T.: Hepatic failure as a Manifestation of Cryptococcosis, Arch. INT. Med. 111: 661, 1963.
15. Koçak, N., Yenerman, M., Ergün, Y. and Özdoğan, E.: Karaciğer sirozu vakası üzerine eklenmiş bir cryptococcus infeksionu. Türk Tıp Cemiyeti Mecmuası 33: 651, 1967.
    (A case of cryptococcosis superimposed in the Cirrhosis of liver)
16. MacGillivray, J. B.: two cases of cryptoccocosis J. Clinc. Path. 19: 424, 1966.
17. Tınaztepe, B. and Tınaztepe, K.: Cerebral Mucormycosis in a child. The Turkish, J. Pediat. 8: 206, 1966.
18. Robins, S. L.: Pathology, 3rd Edition. 432 pp. W. B. Saunders co. Philadelphia, London. 1967.
19. Nelson, W. A., Vaughan V. C. and Mckay R. J.: Textbook of Pediatrics Ninth edition pp. 807 W. B. Saunders Co., Philadelphia. London. Toronto. 1969.

20. Clinicopathological Conference. A case of Swiss-type Agammagloblunemia and Achondroplasia, Brit. Med. J. 2: 1371, 1966.
21. Hutter, R.V.P. and Collin, H. S.: The occurance of opportunistic fungus infections in a cancer Hospital. Lab. Invest. 11: 1035, 1962.
22. Cottier, H., Bürki, K., Hess, N. W. and Hassig, A.: Pathological Considerations of Immunological Deficiency Disease in Man, In Immunological Deficiency in Man, National Foundation-Birth Defects series 4: 152: 168, 1968.
23. Anderson, W.A.D.: Pathology 5th Edition, 388 pp. C. V. Mosby Comp. St. Louis, 1966.