HISTOPLASMOSIS IN INFANCY *

Report of a Case

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Histoplasmosis is a rare mycotic infectious disease. Six cases are usually cited in recent texts. A review of the recent literature indicates that 3 additional cases can be added — 1 by Hansmann and Schenken,[1] 1 by Phelps and Mallory,[2] and 1 by Müller.[3] The following case which came to our attention makes the 10th case of human histoplasmosis reported to date.

Report of Case

Clinical History: A female infant was delivered by cesarean section in Detroit. Shortly after birth the infant was removed to Missouri for a time. After returning to Detroit she developed a chronic respiratory condition characterized by intermittent paroxysms of coughing which was diagnosed as pertussis. The child developed a left otitis media followed by a persistent serosanguineous discharge. The respiratory symptoms persisted for 9 weeks, at which time the mother became alarmed because of the child's pallor and the enlarging abdomen. The infant was hospitalized and the anemia was interpreted as secondary to some infection. A roentgenogram of the thorax showed indefinite peribronchial infiltration near the hilum of each lung.

The infant was removed to another institution where she was hospitalized for 57 days. Here she ran a continuous febrile course and the paroxysms of coughing continued. The abdominal enlargement increased and was found to be due to a hepatosplenomegaly.

Blood studies showed a constant low erythrocyte count averaging 2,000,000 per cmm., and hemoglobin values which averaged slightly less than 50 per cent. There was a constant leukopenia, the leukocyte count averaging 1500 cells per cmm. The differential counts showed the neutrophilic leukocytes to average between 45 and 55 per cent, lymphocytes 40 and 60 per cent, and monocytes 2 and 12 per cent. Numerous normoblasts were present. This blood picture persisted in spite of repeated small transfusions of blood and therapy with liver extract and pentnucleotide.

On the basis of a clinical diagnosis of splenic anemia, splenectomy was performed. Because of the poor physical state of the patient no additional exploration was attempted.

Subsequent to the splenectomy there was definite improvement in the blood picture: the erythrocyte count rose steadily to 3,500,000, the hemoglobin rose to 60 per cent, and the leukocyte count rose to 5500. However, the fever, weakness and abdominal enlargement persisted.

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The child died at the age of 8 months, 3 weeks after the splenectomy and about 4 months after the onset of symptoms. At no time was jaundice noted. Slight edema of the lower extremities was present at intervals. During the last 10 days of life some stiffness of the neck without rigidity was present, but the Kernig test was negative. The spinal fluid was under slightly increased pressure and contained 1 lymphocyte per cmm.

Comment

The exact nature of the disease was not recognized until several months after the death of the child when the pathological condition present was identified by a histological examination of the spleen. Permission for an autopsy was refused.

The spleen removed at operation weighed 159 gm. The organic form was preserved and the capsule was thin. On section the pulp was rather firm in consistence and a grayish pink in color. The malpighian corpuscles were not prominent.

The most striking pathological feature seen on microscopic examination was the tremendous proliferation of reticuloendothelial cells (Fig. 1). The pulp was crowded with great numbers of large cells of the macrophage type, many of which contained clusters of round or slightly oval bodies (Figs. 2 and 3). These bodies were made up of a thick, clear, non-chromatic capsule surrounding a finely granular cytoplasm. The chromatin was ordinarily aggregated at one pole of the cell and was often arranged as a crescent or occasionally as a compact dot located near the capsule of the cell. A blepharoblast was not demonstrable in these parasites, a feature differentiating this organism from the Leishman-Donovan body. The number of parasites within individual macrophages varied from a few to as many as 25. Frequently they occurred in clusters, suggesting a mulberry arrangement with no remnant of the macrophage to be seen. The splenic blood sinusoids contained a large number of macrophages, some of which had phagocytozed variable numbers of parasites. Most of the red blood corpuscles in the splenic pulp were hemolyzed, and phagocytosis of blood pigment was prominent. Some macrophages contained both parasites and blood pigment.

Subsequent to the discovery of the parasites in sections of the spleen two blood films which had been prepared during the last week of illness were reexamined. In these blood smears the parasites were found phagocytozed in large mononuclear cells (Fig. 4) and occasionally in neutrophilic polymorphonuclear leukocytes.

Discussion

All of the reported cases of histoplasmosis have terminated fatally; in only 2 cases was the nature of the disease recognized before death so that cultural studies could be made. We are indebted to DeMonbreun [4] for his classical study of the infective agent isolated from the case reported by Dodd and Tompkins.[5]

As yet, mycologists do not agree as to the exact classification of this yeast-like fungus. If we accept the observations of Moore,[6] which are supported by Dodge,[7] the fungus recovered from the case reported by Dodd and Tompkins and that from Hansmann and Schenken's case belongs to the genus *Histoplasma* (*Posadasia*) of the family *Coccidioideaceae*. Two species of the genus Histoplasma are recognized, *Histoplasma capsulatum* and *Histoplasma pyriforme*. DeMonbreun and the Italian workers, Redaelli and Cifarri,[8] do not believe that the Histoplasma fungus produces asci and the latter two workers prefer to group Histoplasma with Cryptococcus.

The epidemiology and pathogenesis of histoplasmosis await further study. The occurrence of respiratory disturbances in 6 of the reported cases suggests that the portal of entry into the human host is most likely through the respiratory system. This finds additional support from the early clinical picture in our case. The infant exhibited early and persistent respiratory symptoms in the nature of intermittent paroxysms of coughing which simulated pertussis. In the case reported by Dodd and Tompkins similar respiratory symptoms were present. On the other hand, the prominent intestinal disturbances in Müller's case and the dominance of granulomatous lesions in the intestine and mesenteric lymph nodes in the case reported by Crumrine and Kessel,[9] suggest that the portal of entry may at times be through the intestinal mucosa. The association of intestinal ulcers in 2 of Darling's cases,[10] and also in Müller's case, tends to support this view. Again, it is possible that the portal of entry may rarely be through the skin. In the case reported by Hansmann and Schenken there was a protracted, chronic papulopustular dermatitis from which Histoplasmata were recovered.

Irregular fever, weakness, anemia, leukopenia and splenomegaly are the features usually described in the clinical course of the disease.

Pathologically the most prominent feature is the marked reticuloendothelial proliferation, especially in the spleen, lymph nodes, liver and bone marrow. Large numbers of macrophages are formed which engulf the parasites. There is a tendency for pseudotubercles to be produced in the lungs, and in 3 of the reported cases superficial ulcers of the intestine were observed.

Case reports of histoplasmosis indicate that the parasite may be found in the epithelial cells of the intestine and the bronchi, and even in the cortical cells of the adrenal gland. In the adrenal, caseous lesions simulating tuberculosis may be produced (Hansmann and Schenken [1]).

The accumulated data, however, indicate that the classical features of the disease are subject to considerable variation. Thus anemia was not a feature of Hansmann and Schenken's case, and leukocytosis was present in the cases reported by Phelps and Mallory, Hansmann and Schenken, and particularly in that reported by Dodd and Tompkins. Splenomegaly was absent in 2 cases, those of Hansmann and Schenken, and Crumrine and Kessel. The one feature common to all was the presence of the characteristic clusters of phagocytozed yeast-like fungi in reticuloendothelial cells of various organs.

Redaelli [11] worked with laboratory animals which had been inoculated with cultures of the organisms recovered from the case reported by Hansmann and Schenken. His experimental studies demonstrate an extreme degree of proliferation of reticuloendothelial cells in the lymph nodes, spleen and bone marrow, and an active phagocytosis of the organism by macrophages. In the early course of the experimental cases phagocytic activity was pronounced. However, sooner or later there appeared to be a collapse of this phagocytic power, and in those animals that survived infection with the saprophytic form of the fungus there remained continued impairment of phagocytic function as determined by the Congo red test.

Summary

A fatal case of infantile histoplasmosis is reported. Apparently this is the 10th case of human histoplasmosis to be recorded, and the 2nd case observed in an infant.

The clinical manifestations were chronic paroxysmal cough,

anemia, leukopenia, continuous fever, weakness and hepatosplenomegaly.

Of the organs, only the surgically removed spleen was available for study. This showed a marked proliferation of reticuloendothelial cells, many of which contained the fungus.

Phagocytic cells laden with parasites were found in blood smears from the circulating blood.

The Histoplasma is a fungus, the pathogenic form of which resembles yeast. The saprophytic form is a myceliate spore-bearing fungus whose exact taxonomic position is still in question.

Knowledge regarding the epidemiology and pathogenesis of histoplasmosis is incomplete.

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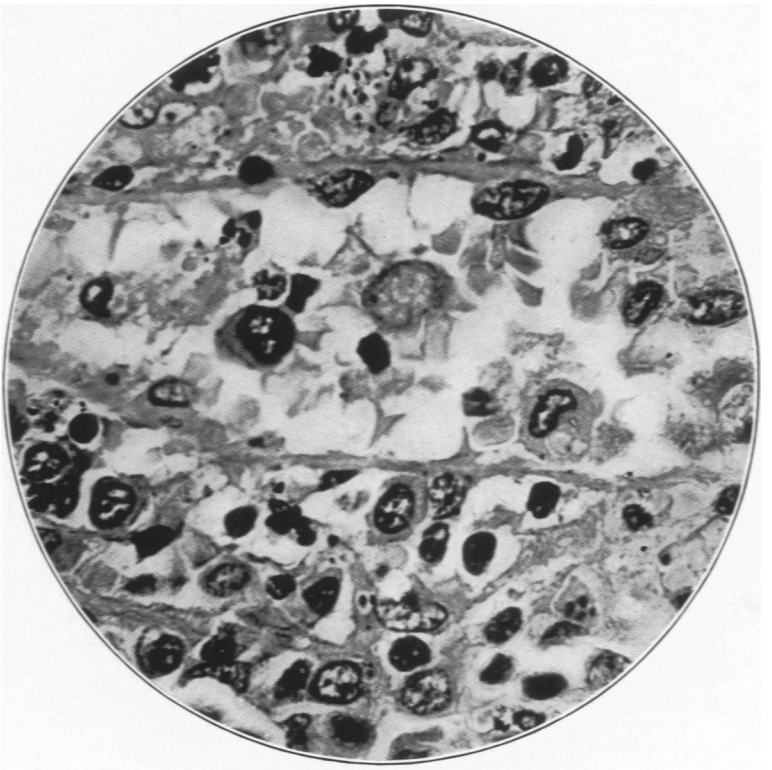
DESCRIPTION OF PLATES

PLATE 78

FIG. 1. A splenic blood sinusoid with surrounding red pulp showing reticuloendotheliosis. Numerous encapsulated blastospores in small and large clusters are seen. Macrophages are present in the sinusoid, many of which show degenerative changes. Iron hematoxylin and Masson's trichrome lichtgrün stain. × 1000.

FIG. 2. A splenic blood sinusoid containing macrophages. Clusters of *Histoplasmata capsulata* are seen in the degenerated pulp cells. Iron hematoxylin and Masson's trichrome lichtgrün stain. × 1400.



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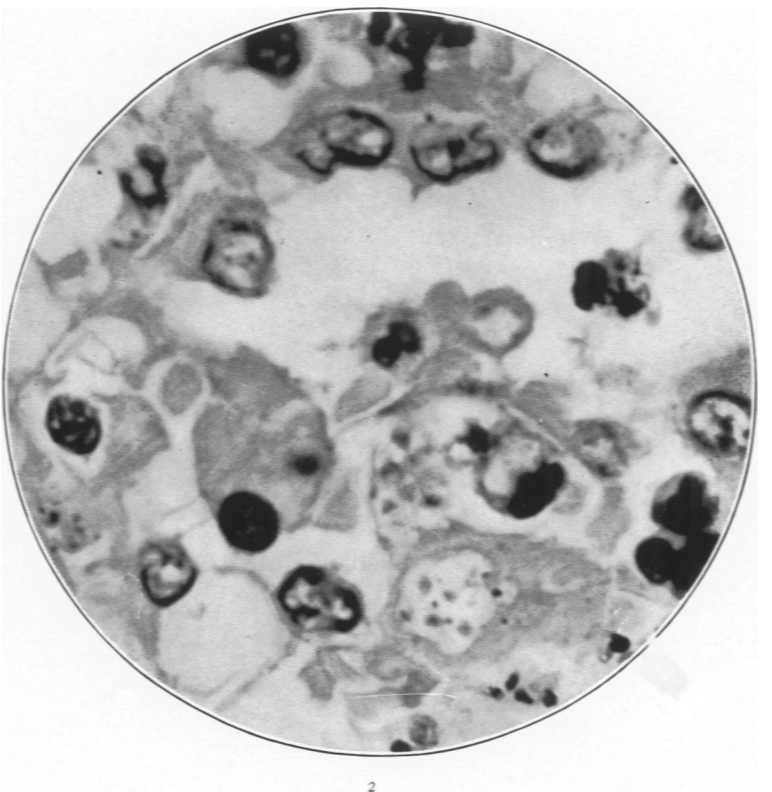

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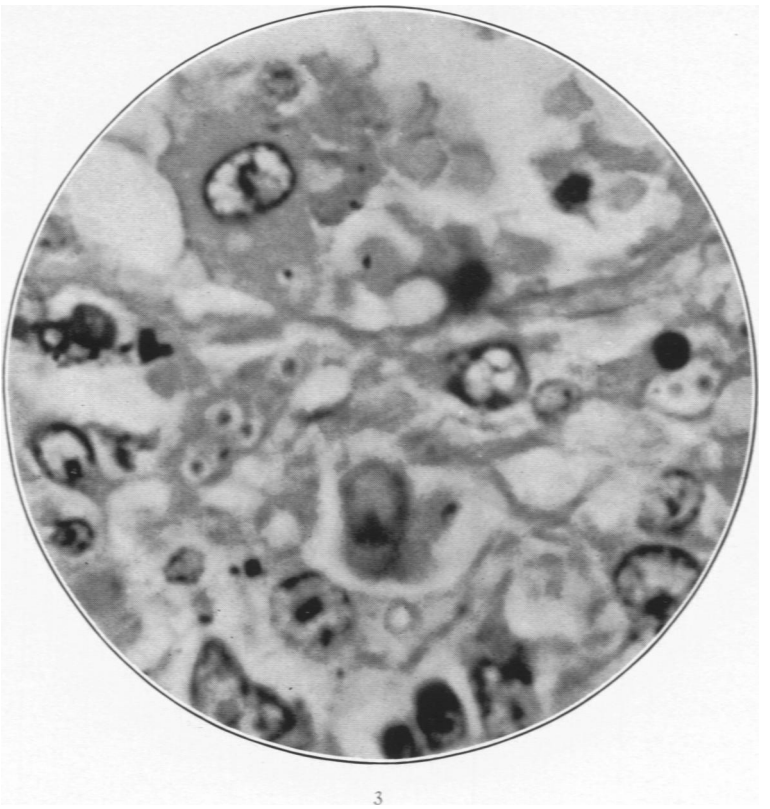
PLATE 79

FIG. 3. A degenerating macrophage in a splenic blood sinusoid is shown on the right. A cluster of *Histoplasmata capsulata* is present in a degenerated macrophage in the pulp. Iron hematoxylin and Masson's trichrome lichtgrün stain. × 1400.

FIG. 4. A macrophage in the peripheral blood showing a large cluster of *Histoplasmata capsulata* in the cytoplasm crowding and deforming the cell nucleus. The typical mulberry-like formation is seen. Wright's blood stain. × 1400.



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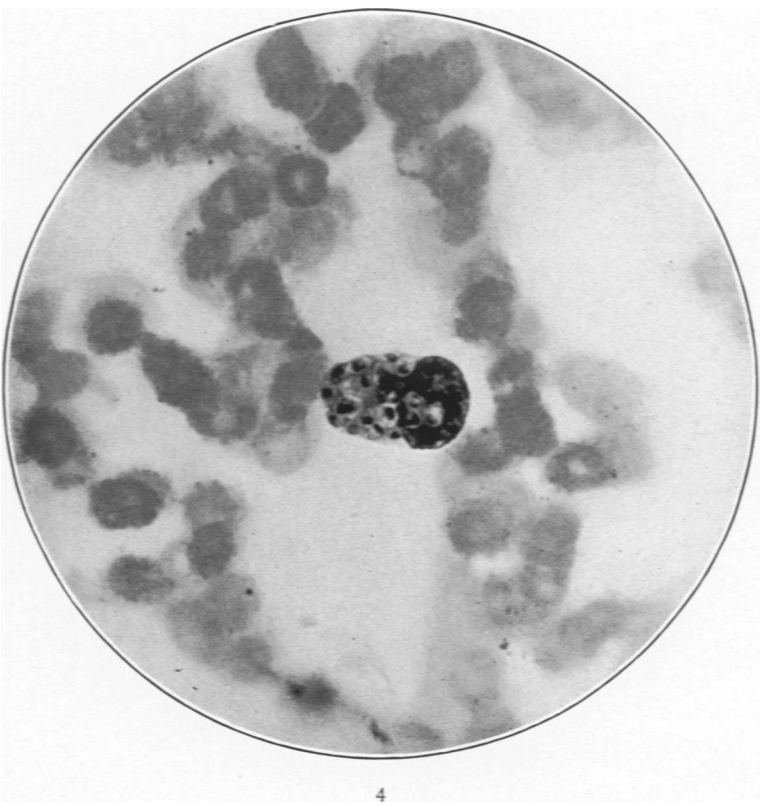

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