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Fever, Jaundice, and Histiocytic Erythrophagocytosis: Fulminant Infection or Malignancy?

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Some of the problems which we see on the infectious disease consultation service can be quite frustrating. This is one such case. A middle-aged man presented to our medical service with fever and dyspnea. His fulminant downhill course was characterized by anemia, jaundice, hypercalcemia, pulmonary abnormalities, and a lack of responsiveness to conventional antimicrobial therapy. At autopsy, malignant-appearing histiocytes were present in several organs including spleen, lymph nodes, and lung. Histopathological examination of tissues obtained at autopsy confirmed the presence of phagocytized erythrocytes within such histiocytes. This case aptly illustrates the hazy dividing line which sometimes exists between infectious and/or malignant processes which are, at present, still of undetermined etiology.

CASE PRESENTATION

A 59-year-old white man was admitted to the medical service of the West Haven Veterans Administration Medical Center with a one-week history of dyspnea, fever, chills, and periorbital edema. He was a painter who had recently returned to work after a year of unemployment. Following several days of painting in an old, dusty, school building, he noted the sudden onset of extreme fatigue, nonproductive cough, and progressive dyspnea. Fever, chills, insomnia, and anorexia followed. His wife noted puffiness around his eyes; he was taken to the emergency room for evaluation. At that time he did not complain of wheezing, chest pain, hemoptysis, headache, abdominal pain, diarrhea, night sweats, or weight loss. There was no history of allergies, tuberculosis exposure, or sick family members. Neither his friends nor co-workers were ill. The patient had travelled to Rhode Island within three months prior to his illness. One parakeet and two cats were at home; all were long-term, healthy pets.

Past medical history was remarkable for rib fractures following a fall in 1978 and a tonsillectomy as a child. He had stopped smoking cigarettes 26 years prior to admission, but smoked an occasional cigar. Three months before his illness he had his last drink, although prior to this he had been a heavy alcohol user.

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Physical examination revealed an oriented, alert, thin, white man in mild respiratory distress. His temperature was 101.4°F, blood pressure 120/85, pulse 110/minute, and respirations 24/minute. His skin was warm and dry without rash or embolic lesions. He had bilateral periorbital edema with mild conjunctival suffusion. Sclerae were anicteric. Oropharyngeal and ear exams were unremarkable. His neck was supple and without jugular venous distention. Lymphadenopathy was not detected. Chest exam revealed bibasilar rales which cleared with coughing. He had a rapid heart rate with normal heart sounds; a Grade II/VI systolic ejection murmur was heard at the lower left sternal border without radiation. A gallop was not detected. The abdomen was soft and non-tender with normal bowel sounds. The liver was slightly enlarged with a total span of 14 centimeters; the edge was not palpable. No splenomegaly or masses were detected. Rectal exam was normal except for stool which was trace-positive for occult blood. He had neither peripheral edema, cyanosis, nor clubbing. Splinter hemorrhages were not noted. His neurologic exam was normal and there were no focal findings. The white blood cell count (WBC) was 7,400 cells/μl with a predominance of segmented forms. No bands were present. Hematocrit was 45.7 percent and platelet count was 109,000/μl. Mean corpuscular volume was 87 μm^3. Prothrombin time and partial thromboplastin time were normal. Sedimentation rate (ESR) was 30 mm/hour (normal < 20). Electrolytes were remarkable for a serum sodium of 130 meq/L; the anion gap was within normal limits. Arterial blood gases on room air showed a pH of 7.48, pO_2 of 78 mm Hg and a pCO_2 of 17 mm Hg. Other serum chemistries obtained on admission included: albumin 3.2 g/dl, calcium 9.4 mg/dl, bilirubin 1.8 mg/dl (direct fraction 0.7 mg/dl), alkaline phosphatase 141 IU/L (normal 35–100), LDH 675 IU/L (normal 110–220), SGOT 44 IU/L (normal 0–41), SGPT 54 IU/L (normal 0–45). Serum amylase and lipase were both normal. Urinalysis showed 1+ bile, 4+ urobilinogen, and 2–3 WBCs per HPF; no casts were noted. Chest X-ray showed a right pleural-based density with an associated pleural effusion and a possible left pleural effusion as well.

DR. VINCENT T. ANDRIOLE *(Professor of Medicine, Chief, Infectious Disease Section):* How quickly did his symptoms develop?

DR. DONALD HEIMAN *(Infectious Disease Fellow):* Over a period of one week. The first diagnostic test performed was a ventilation-perfusion lung scan looking for a possible pulmonary infarction, which was suggested by the admission chest X-ray. This study did not demonstrate pulmonary emboli. The patient was started on erythromycin, one gram intravenously every six hours, for possible *Mycoplasma pneumoniae* infection or Legionnaires' disease. Cold agglutinins at this time were negative. Approximately 24 hours after erythromycin therapy was begun, the patient developed right upper quadrant pain and tenderness associated with hiccoughs. Parenteral ampicillin and gentamicin were administered because of the suspicion of a subdiaphragmatic hepatobiliary process such as cholangitis. Further investigation included an abdominal ultrasound examination which showed sludge in the gall bladder and mild hepatosplenomegaly with normal intrahepatic ducts. A right-sided thoracentesis produced serous fluid with a pH of 7.4, glucose 146 mg/dl, LDH 227 IU/L (serum LDH 660 IU/L), protein 2.9 gm/dl (serum protein 5.6 gm/dl), 300 WBC/μl (8 percent PMNs, 80 percent lymphocytes, 12 percent monocytes), and 300 RBC/μl. Gram's stain of pleural fluid was negative. A PPD (tuberculin) skin test placed on admission was nonreactive, as were control antigens, suggesting cutaneous anergy.

During the first week of hospitalization the patient remained febrile with daily

fevers in excess of 103°F. During this time his hematocrit dropped from 45.7 percent to 33 percent. His platelet count also dropped from 109,000 to 50,000/μl while his WBC remained stable. On the sixth hospital day a hemorrhagic macular lesion was noted on his left tympanic membrane. Dr. Bia, would you like to give us your thoughts at this juncture?

DR. FRANK BIA *(Assistant Professor of Medicine and Laboratory Medicine):* At this point we attempted to reassess what was happening to this patient. Here was a man with a wide alveolar-arterial oxygen gradient being treated with erythromycin for atypical pneumonia or Legionnaire's disease who did not seem to be getting better. A new hemorrhage was noted on the left tympanic membrane along with some granularity of its anterior surface, suggesting early bullous myringitis. I felt that along with his initial presentation these findings were compatible with *Mycoplasma pneumoniae*-associated disease. Another consideration at the time was his falling hematocrit, without a clinically obvious source of bleeding. His history of travel to Rhode Island three months prior to his illness and the splenomegaly detected by ultrasound examination raised the possibility of babesiosis. Review of his peripheral smear did not demonstrate parasitemia; however, there was a large number of nucleated red blood cells seen (as many as 47 per 100 nucleated cells). A hemolytic process therefore seemed likely, considering his elevated serum LDH and slightly increased indirect bilirubin. However, the red blood cell morphology was normal. Fragmentation of red blood cells was not apparent. A second test for cold agglutinins was done and was again negative.

A PHYSICIAN: What is the incidence of negative cold agglutinins in confirmed cases of mycoplasma-associated pneumonia?

DR. BIA: Fifty percent, in most series, but positivity correlates with the severity of the illness; the more severe cases have higher rates of positivity.

A PHYSICIAN: Considering the patient's occupation as a painter and his recent return to work, was a toxic exposure entertained in the differential diagnosis?

DR. BIA: An occupational medicine consultation was performed by Dr. Mark Cullen who carefully reviewed the patient's exposure history. The family even brought in the patient's paint cans, but it was felt that exposure to these paints should not have contributed to his illness. This patient could have been working around various oil-based paints, solvents, and lead. For example, lead exposure may have occurred during the sanding of old door frames. Lead toxicity can account for encephalopathy and rapid hemolysis but should have been associated with more gastrointestinal symptoms. Nor would lead explain his fever and respiratory symptoms. Ethylene glycol monobutyl ether is a solvent used as a paint thinner, but exposure to this agent would not explain his entire clinical picture either.

DR. ELISHA ATKINS *(Professor of Medicine):* As far as I know, none of the agents he would have been exposed to as a painter cause fever, and I would agree that a reaction to a toxin is not an adequate explanation for his illness.

DR. ANDRIOLE: This case is somewhat reminiscent of a patient we previously took care of who rapidly developed hemolytic anemia associated with lymphadenopathy. Pathologically, he had angioimmunoblastic lymphadenopathy. Diseases such as this need to be considered, although the patient under discussion did not manifest lymphadenopathy.

DR. HEIMAN: By the seventh hospital day all of the patient's cultures remained

negative. The ampicillin and gentamicin were discontinued and the erythromycin was continued, as *Mycoplasma pneumoniae* was still considered a likely etiologic agent. His bilirubin at this time was 2.7 mg/dl (direct fraction 1.6 mg/dl). LDH was 521 IU/L and Coomb's test was negative. A lumbar puncture was performed after the patient experienced a transient episode of mental confusion. The spinal fluid was clear and contained no cells. Glucose was 100 mg/dl (serum glucose 150 mg/dl), protein was 80 mg/dl, and the test for cryptococcal antigen was negative. No organisms were seen on Gram's stain. Bacterial, mycobacterial, and fungal cultures were performed and ultimately revealed no organisms. On the eighth hospital day, a chest X-ray showed increasing bilateral pleural effusions and a right upper lobe infiltrate which, in retrospect, was probably present on admission but was now more prominent. Gentamicin and chloramphenicol were empirically added to his therapy since his condition was deteriorating and he remained febrile. Bilateral thoracenteses were done. The only remarkable change in the character of the fluid compared to the prior tap was its hemorrhagic nature, now containing 440,000 red blood cells and an elevated white blood cell count (1,400 with 60 percent PMNs). The fluid obtained from the left hemithorax was similar to that obtained from the right pleural cavity. A KOH preparation of the fluid from the right side was remarkable for the presence of what appeared to be budding yeast. At this time the microbiology lab reported that two colonies of a similar-appearing organism had been isolated from the initial culture of thoracentesis fluid. Its yeast phase resembled cigars.

DR. BIA: This was a very unexpected turn of events. The organism that these yeast forms most closely resembled was *Sporothrix schenckii.* How he could have acquired disseminated sporotrichosis was unclear to us from his history.

DR. ANDRIOLE: Disseminated sporotrichosis is extremely unusual and almost always requires a severely immunocompromised patient. Involvement of the central nervous system is almost unheard of, and pulmonary sporotrichosis is equally reportable. To explain hepatosplenomegaly and hemolytic anemia with sporotrichosis is very difficult. *Cladosporium* toxin ingestion or inhalation, however, can do this [1].

DR. BIA: Suppose we had not interpreted the morphology correctly. What type of fungal diseases might this patient develop while painting an old schoolhouse?

DR. ANDRIOLE: Histoplasmosis and cryptococcosis need to be considered. Both of these diseases are caused by a yeast, but they are clearly not cigar-shaped. Both organisms have been found in pigeon droppings in Connecticut. Blastomycosis would be less likely, since splenomegaly is not as common a finding as it is in histoplasmosis.

DR. BIA: On review of the smears, what we were looking at were broken hyphal elements, not yeast.

DR. ANDRIOLE: That eliminates cryptococcosis, since the organism is not dimorphic. However, *Blastomyces, Histoplasma,* and *Coccidioides* species are dimorphic and bear consideration. *Coccidioides* can probably be ruled out if his travel history does not include a recent trip to Las Vegas or the southwestern part of the United States.

DR. HEIMAN: Amphotericin B therapy was begun at this point and a bone marrow biopsy was performed. Pleural fluid was reported by the pathology laboratory to show neither malignant cells nor any fungal elements.

On the tenth hospital day, the patient seemed to stabilize and his fever had resolved. His bilirubin was still rising (5.8 mg/dl, direct fraction 3.8 mg/dl), although his liver enzymes were unchanged. Serum calcium was noted to be elevated at 11.2

mg/dl despite a low serum albumin of 2.3 mg/dl. Chest X-rays showed an increasing density in the right apical region.

DR. BIA: The relationship between granulomatous disease and hypercalcemia is being studied extensively here at Yale and has been reported previously in association with both tuberculosis and coccidioidomycosis [2,3]. As in sarcoidosis, the hypercalcemia may be a hyperabsorptive process associated with elevated levels of circulating 1 α, 25-dihydroxyvitamin D. However, other factors such as prostaglandins and osteotropic substances associated with malignancy may also be involved [4].

A PHYSICIAN: Was bronchoscopy and biopsy of the right lobe considered?

DR. BIA: The pulmonary service was asked to evaluate the patient and arrangements were made for bronchoscopy. His platelet count had dropped to 20,000 to 30,000 but transfusions of platelets successfully maintained a level greater than 50,000.

DR. HEIMAN: Sputum Gram's stains and acid-fast stains were repeated at this time, though sputum was sparse. The Gram's stains showed a very large number of pulmonary macrophages, which appeared highly active in that pseudopods were prominent. No organisms were seen on either stain.

The bone marrow biopsy done a few days earlier showed megaloblastoid changes in a hyperplastic marrow with a leftward shift of the myeloid series. Megakaryocytes were present in normal numbers. The question of a myelodysplastic or a lymphoproliferative process was raised. Acid-fast stains, silver stains for fungi and Brown-Brenn stains for bacteria were performed on bone marrow and were negative. His blood cultures were persistently negative, so gentamicin and chloramphenicol therapy was discontinued; he remained on parenteral erythromycin and Amphotericin B.

On the thirteenth hospital day he became hypotensive during his Amphotericin B infusion (50 mg). He remained afebrile, but became dependent upon the vasopressor, dopamine. Tobramycin therapy was initiated because of concerns over possible gram-negative sepsis.

The fungus which had been isolated from the initial pleural fluid sample was identified as a *Hyalodendron* species, which usually represents laboratory contamination. All other samples of pleural fluid were sterile. The amphotericin was discontinued after the patient had received a total dose of 320 mg. He remained dependent upon dopamine and on the seventeenth hospital day developed respiratory failure which led to respiratory arrest. Resuscitation efforts were unsuccessful and an autopsy was ultimately performed, eight hours after the patient's death.

DR. GEORGE THORNTON *(Clinical Professor of Medicine, Chief of Medicine, Waterbury Hospital):* What were your diagnostic considerations at the time of his death?

DR. HEIMAN: We felt strongly that the patient had an infectious process, possibly of viral origin, since all of our cultures and diagnostic tests did not lead us to a bacterial, mycoplasma, or fungal etiology. We also felt that a neoplastic process was possible, but the fulminant nature of his illness and his relatively rapid demise made this unlikely as the sole explanation for his death. However, an infectious process occurring in the presence of an underlying malignancy and an immunocompromised state seemed plausible.

Autopsy was restricted to the chest and abdomen. Examination revealed an icteric white man with mild periorbital edema and a distended abdomen containing 1,000 cc of greenish-yellow, foul-smelling ascites. The right pleural cavity contained 1,500 cc of serosanguineous fluid, and 1,000 cc of similar-appearing fluid was present in

the left pleural space. Both pleural cavities contained fibrinous adhesions, largely at the bases and at the apex of the right lung. The right lung weighed 700 g; the left lung 625 g (normal, 250–400 g). There was mild diffuse emphysema, congestion at the bases, and a nodular lesion at the right apex. Heart examination revealed a normal-sized organ with an area of recent ischemic change in a left ventricular papillary muscle. The liver weighed 2,650 g (normal, 1,200–1,800 g) and showed diffuse bile staining. The gall bladder was normal. The spleen weighed 400 g (normal <200 g). No distinct areas of red and white pulp were discernible. Both the liver and the spleen were very soft, the spleen being quite diffluent. The genitourinary system was unremarkable. There was mild enlargement of several thoracic and abdominal lymph nodes.

On histologic examination, the spleen exhibited total effacement of the normal splenic architecture (Fig. 1). Many large, bizarre-appearing, malignant cells were present. They were characterized by their large, open nuclei, with finely clumped chromatin and prominent nucleoli which are characteristic of malignant histiocytes. Multinucleated cells, some resembling Reed-Sternberg cells, were also present.

DR. ANDRIOLE: This histology is very suggestive of histiocytic medullary reticulosis, a process which would explain many aspects of this patient's clinical presentation.

DR. HEIMAN: Histopathology confirmed the diagnosis suggested by Dr. Andriole. It is most consistent with an entity referred to as histiocytic medullary reticulosis, or malignant histiocytosis, as it is now most often called. Figure 2 demonstrates focal collections of malignant histiocytes found in the right apical lung lesion. Malignant histiocytes were also found in the hepatic sinusoids along with focal bile stasis as shown in Fig. 3. In the lymph nodes, erythrophagocytosis was also demonstrated (Fig. 4) although the erythrophagocytic cells appeared benign.

DR. ANDRIOLE: For a patient to present with histiocytic medullary reticulosis and develop such a fulminant disease pattern over the course of three weeks is highly unusual. The diagnosis is usually made with a liver or lymph node biopsy and the duration of the disease is usually three to six months. Angioimmunoblastic lymphadenopathy can be a more fulminant process and that is why I suggested that diagnosis earlier. In retrospect, I wonder if those macrophages you were looking at on Gram's stain of the sputum were malignant cells.

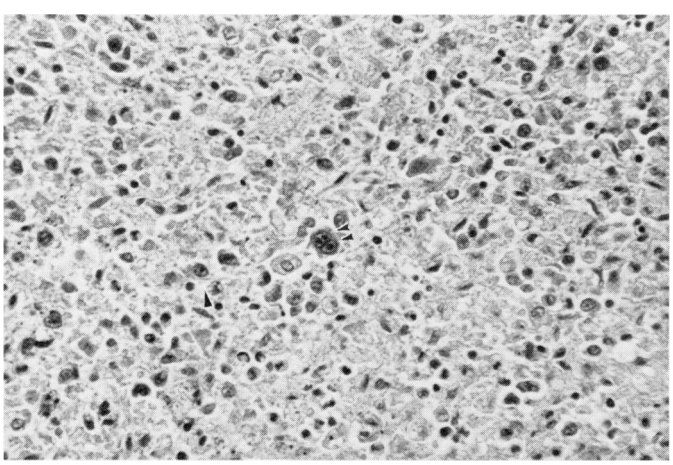

FIG. 1. Photomicrograph of spleen showing the presence of large, bizzarre-appearing cells with open nuclei and finely clumped chromatin (*arrow*). These cells are malignant histiocytes. Also note the presence of a binucleated cell resembling a Reed-Sternberg cell (*double arrow*). Hematoxylin and eosin stain, 400 ×.

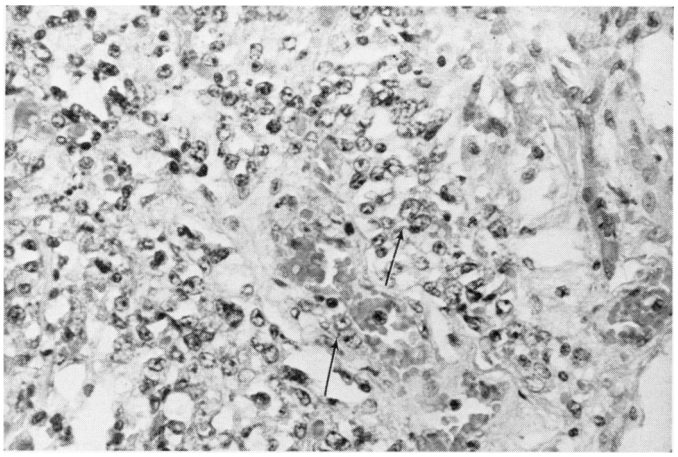

FIG. 2. Photomicrograph of right lung showing a section of upper lobe. Note the focal collections of malignant histiocytes (*arrows*). Hematoxylin and eosin, 400 ×.

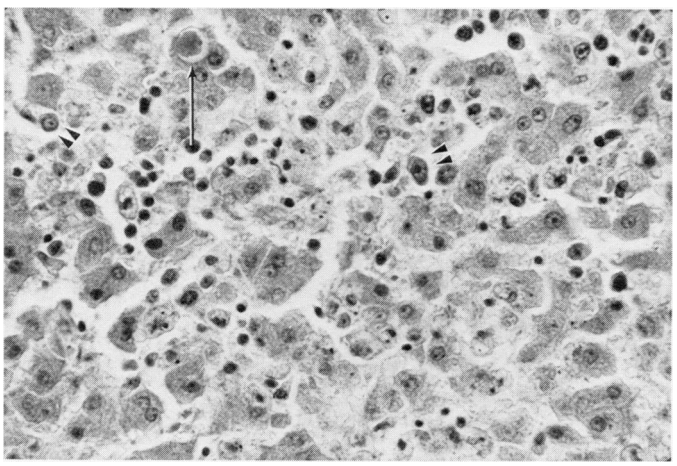

FIG. 3. Photomicrograph of liver showing both malignant histiocytes (*double arrows*) in the hepatic sinusoids and focal bile stasis (*single arrow*). Hematoxylin and eosin, 400 ×.

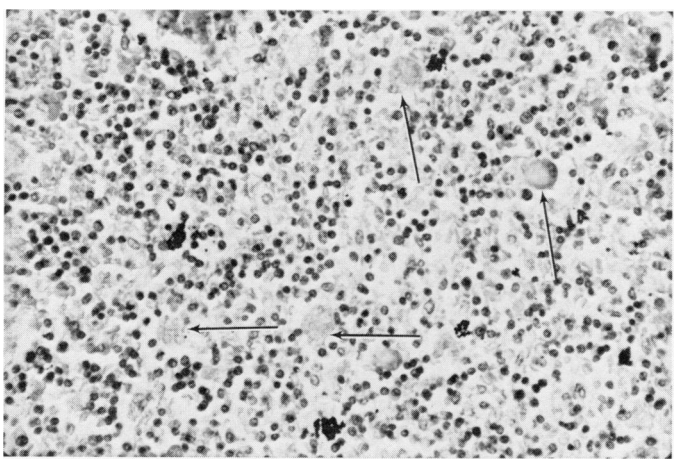

FIG. 4. Photomicrograph of lymph node showing erythrophagocytosis (*arrows*) by benign-appearing histiocytes. Hematoxylin and eosin, 400 ×.

DISCUSSION

DR. HEIMAN: Histiocytic medullary reticulosis was first described in 1939 by Scott and Robb-Smith as a disease characterized by fever, generalized lymphadenopathy, hepatosplenomegaly, and preterminal jaundice, in association with anemia, leukopenia, and thrombocytopenia [5]. Since the initial description of this disease, it has been widely reported, under various names. In the mid-nineteen-sixties, Rappaport introduced the term malignant histiocytosis (MH), which has become the accepted name for this disease [6]. The most extensive study of MH came from a Stanford University series published in 1975 [7]. Warnke et al. reviewed twenty-nine cases of MH and found a mean age of 31 years with a male-to-female case ratio of 2.2 to 1. Physical findings at presentation included fever in 22 of 29 patients, with development of fever in four other patients during the course of their illness. Generalized lymphadenopathy was found in four patients at presentation and in 15 additional patients later in their course. A palpable spleen was present in 21 patients. Hepatomegaly was detected in 22 patients, six of whom developed jaundice, generally during the terminal stages of their disease. Median survival was six months with a mean survival of 14 months, ranging from one month to eight years. Lampert et al. presented similar findings in their review of 12 cases of MH [8].

As Dr. Andriole mentioned, the case under discussion today is not typical of MH, because of the rapidity of this patient's deterioration. However, there is an interesting report in the *Archives of Internal Medicine* in 1965 which described two fulminant cases of histiocytic medullary reticulosis, in a father and son, with onset of symptoms occurring within two days of each other [9]. Their clinical courses were very similar to that of today's case. What is most intriguing is the temporal proximity of onset in patients who shared a common environment, suggesting exposure to a common infectious or toxic agent.

In 1977, a group from the University of Minnesota published a review of 19 cases of a histiocytic proliferative disorder characterized by benign histiocytic hyperplasia and prominent hemophagocytosis associated with an active acute viral infection [10,11]. The term virus-associated hemophagocytic syndrome (VAHS) was used to describe this clinicopathologic entity. Their patients presented with high fever, constitutional symptoms, liver function and coagulation abnormalities, as well as pancytopenia. Hepatosplenomegaly, lymphadenopathy, and pulmonary infiltrates were also present in several cases. Fourteen of the 19 patients described were overtly immunosuppressed (13 were renal transplant recipients, one had systemic lupus erythematosus, and all were on prednisone and azathioprine). Five patients were without obvious underlying disease (median age in this group was one year). Acute viral infection was documented in 15 cases (ten cytomegalovirus, two Epstein-Barr virus, one herpes simplex virus, one varicella-zoster virus, one adenovirus). In five patients viral studies were inadequate. Bone marrow examinations revealed histiocytic proliferation and hemophagocytosis by benign histiocytes. In five autopsies this process also involved the spleen, liver, and lymph nodes. For the most part, these illnesses were self-limited, with reversal of the process after immunosuppressive therapy was discontinued. Thirteen of the 19 patients recovered within one to eight weeks.

For today's case, the question of VAHS is a valid one because of the rapid progression of this patient's illness. All viral cultures were negative including blood, urine, liver, spleen, and bone marrow. Unfortunately, routine viral titers were unreportable because his serum was consistently anticomplementary in the comple-

ment fixation test. Special studies done in Dr. Warren Andiman's laboratory (virology) have shown low titers of anti-EBV viral capsid antibodies in three serum specimens (1:40, 1:20, 1:20) and no such antibody in the CSF. DNA spot hybridization was performed on liver and spleen tissue looking for evidence of EBV virus genome. None was found. At this point, we cannot rule out a viral illness; however, the presence of malignant cells argues against a viral infection and VAHS as the patient's primary illness. The final pathologic diagnosis is malignant histiocytosis.

DR. ANDRIOLE: Based on the histopathology of this disease, specifically the reticuloendothelial proliferation, I believe that malignant histiocytosis may very well be caused by an infectious agent.

DR. HEIMAN: The case report involving the father and son, which I alluded to previously, is certainly suggestive of an infectious agent as one etiology for this syndrome. There is a case report of an infant with histiocytic medullary reticulosis who had an associated acute Epstein-Barr virus infection [12]. I suppose it is conceivable that a benign proliferation of histiocytes, in response to such an agent, could transform into a malignant process depending more upon the host response than the nature of the organism itself.

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