Two patients manifested the typical clinical and pathological features of malignant histiocytosis. Objective remissions of 3 months and 2 months, respectively, were induced by combination chemotherapy with vincristine and prednisone. The patients eventually died from complications of this rapidly progressive and uniformly fatal illness without significant prolongation of survival time. Combined chemotherapy may be useful for induction of remission in this disorder, and suitable maintenance programs should be developed.

Malignant histiocytosis is a rapidly progressive and usually fatal disease characterized by an invasive proliferation of morphologically atypical histiocytes in multiple organs (1). The disease was first described as a separate clinical entity by Scott and Robb-Smith (2), who labeled it “histiocytic medullary reticulosis.” Its low prevalence has made difficult the study of effectiveness of single drug chemotherapy in a large series of patients. In general, the experience with single drug therapy, except for high-dose prednisone therapy in three patients (3-5), has been disappointing. Failure to palliate symptoms or prolong survival has been reported with vincristine (6), prednisone (3, 7-9), Cytoxan® (3, 9, 10), nitrogen mustard (11), and antibiotics with or without transfusions (12-15). Two cases of malignant histiocytosis in which temporary but definite remissions were induced with vincristine-prednisone combined therapy are presented.

Case Reports

CASE 1

A 45-year-old white male dairy farmer was first admitted to the University of Chicago Hospitals on 27 February 1968 with a 7-week history of episodic sweating, recurrent fever, loss of weight from 97.7 kg to 80 kg, and progressive development of generalized lymphadenopathy most prominent in the cervical region. A diagnosis of malignant histiocytosis had been made on our review of a cervical lymph node biopsy (Figure 1) performed by his private physician.

Pertinent physical findings included tachycardia (120/min) without fever, bilateral tonsillar enlargement without exudate, generalized 1- to 2-cm tender lymphadenopathy, and hepatosplenomegaly (liver edge 3 cm below the right costal margin and spleen felt 5 cm below the left costal margin).

Hemoglobin was 8.1 g/100 ml; hematocrit, 23%; WBC, 6,750/mm³; platelet count, 183,000/mm³; reticulocyte count, 2.0%. Peripheral blood smear showed 11% histiocytes. Liver enzyme tests and sulfobromophthalein (BSP) retention were normal. Prothrombin time was 16.5 sec (control, 12.8 sec). Total serum protein was 9.5 g/100 ml. Serum protein electrophoresis showed a gamma globulin fraction of 4.6 g/100 ml. Chest roentgenogram showed bilateral hilar adenopathy and a large right paratracheal node. A radiologic bone survey was normal. A bone marrow aspiration was normal except for the presence of 15% histiocytes, many of which demonstrated nuclear immaturity and phagocytosed platelets in the cytoplasm.

Initial therapy consisted of 60 mg/day of prednisone, orally, and 2 mg/week of vincristine, intravenously. During the first week there was symptomatic improvement as well as softening and some reduction in lymphadenopathy. A reticulocytosis of 14.4% was noted on the eighth day. After discharge from the hospital on 8 March 1968 the patient was treated by the referring physician with weekly vincristine (2 mg, intravenously, per week) and gradually tapered oral prednisone dose until readmission on 1 July 1968. The patient remained asymptomatic on this regimen until mid-June 1968.
By 5 April 1968 the prednisone dose was 40 mg every other day and the patient was in clinical remission as judged by his weight gain (7 kg), ability to work almost full time on his farm, a normal physical examination except for minimal residual lymphadenopathy, hemoglobin of 12.3 g/100 ml, and absence of histiocytes in the peripheral blood smear.

When the patient was first noted to have recurrence of hepatomegaly on May 16, prednisone dosage was increased from 15 mg to 20 mg every other day. Four weeks later he began to note anorexia and intermittent fever. On July 1 he was acutely ill and required readmission to the hospital because of fever (temperature, 40.5 C), epigastric pain, nausea, vomiting, dark urine, and black stools. The liver edge was 8 cm and the spleen edge 4 cm below the respective costal margins. Prominent diffuse lymphadenopathy had reappeared. The white count was 1,150/mm³, hematocrit was 38%, and the platelet count was reduced for the first time to 21,000/mm³. Peripheral blood smear once again contained histiocytes (Figure 2A). His clinical status deteriorated rapidly as intestinal bleeding continued. He became progressively jaundiced and azotemic and died after a massive gastrointestinal hemorrhage on the fourth hospital day.

At autopsy generalized lymph node enlargement and enlargement of spleen and liver were observed. The spleen weighed 980 g and the liver, 3,360 g. The bone marrow of the ribs, sternum, and vertebrae was soft and pale red. Microscopic examination of the lymph nodes showed that the normal architecture was obliterated and replaced by a proliferation of cells similar to those seen in the lymph node removed for diagnosis (Figure 1). The white pulp of the spleen was replaced by masses of neoplastic histiocytes which extended into the red pulp. These cells were also observed throughout the red pulp either singly or in small focal collections. The splenic cords showed pronounced widening due to sequestration of red blood cells, and the lining cells of the splenic sinuses showed hyperplasia and prominent nuclei. Erythrophagocytosis, both by normal and neoplastic histiocytes, was evident, particularly in the sinuses. The portal triads of the liver contained large numbers of neoplastic histiocytes. Small collections of these cells were also seen within the hepatic sinusoids.

The bone marrow was diffusely infiltrated by abnormal cells similar to those seen in the peripheral blood (Figure 2A), resulting in reduction of the normal marrow elements.

The remaining significant autopsy findings were scleral and cutaneous icterus, multiple petechial hemorrhages of skin and mucous membranes, 2,400 ml of "coffee ground" fluid within the gastrointestinal tract, and recent hemorrhage into the retroperitoneal soft tissues and psoas muscles.

CASE 2

An acutely ill 18-year-old single white woman was admitted to this hospital on 5 September 1968 with a 5-week history of recurrent fever and chills, a 10-lb weight loss, and nonproductive cough. A diagnosis of malignant histiocytosis had been made on our review of the peripheral blood smear, bone marrow aspirate, and lymph node biopsy (Figure 3) obtained at another hospital.

Physical findings included a temperature of 39.3 C with a pulse rate of 104/min; respirations of 20/min; liver edge palpable 6 cm below the right costal margin; palpable spleen tip on deep inspiration; and several small, rubbery axillary, inguinal, and submandibular nodes. She weighed 45 kg.

Blood counts before initiation of treatment were hematocrit, 32%; hemoglobin, 8.7 g/100 ml; WBC, 6,000/mm³; platelet count, 268,000/mm³; and reticulocyte count, 2.2%. Peripheral smear showed 5% histiocytes. Serum iron was 30 µg/100 ml with a total iron-binding capacity of 195 µg/100 ml. The serum alkaline phosphatase (81 I.U.), lactate dehydrogenase (70 I.U.), and prothrombin time (16.7 sec with a 13.0-sec control) were abnormal. The albumin to globulin ratio was 2.88:3.60, with a moderate increase in the alpha₁ globulin fraction.

Therapy was begun on September 20 with 0.5 mg vincristine intravenously per week and 40 mg of oral prednisone daily. The fever subsided, and the patient felt better the next day. The lymphadenopathy was noticeably decreased 3 days later. She was discharged on September 26 and seen weekly in the clinic during the following 3 months.

During the first 6 weeks of this period the vincristine dose was gradually increased to 1.0 mg/week, and the prednisone dose was tapered to 20 mg/day. She felt...
well, gained 10 kg in weight, had no residual abnormalities on physical examination, and resumed her normal activities. On November 14 the hematocrit was 37%; hemoglobin, 12.6; and WBC, 16,700. The vincristine injection was omitted on this date because of progressive sensory neuropathy. In the following week she experienced fever and abdominal pain, and a tender liver was once again palpable 6 cm below the right costal margin. The vincristine was reinstated at 0.5 mg/week.

Despite continuation of the combined treatment with prednisone and vincristine, malignant histiocytes reappeared in the peripheral blood in mid-December (Figure 2B). The histiocytes disappeared after the patient was started on Cytoxan® (100 mg/day, orally), but she soon developed other evidence of progressive disease. Incapacitating dyspnea on exertion, massive cervical lymphadenopathy, and a large left pleural effusion necessitated readmission on 2 January 1969. Malignant cells were found in the pleural fluid, and pleural biopsy showed nests of malignant histiocytes. Despite a tracheostomy on January 16 required to bypass a large subglottal mass, there was only temporary relief from dyspnea. Bronchoscopy on January 27 showed numerous tumor nodules encroaching on the bronchi at all levels and in all areas of the bronchial tree. Over the next 10 days her breathing became more labored, fever recurred in spite of antibiotics and increasing the prednisone dose to 100 mg/day, numerous subcutaneous nodules with violaceous discoloration of the overlying skin appeared on her body, and there was a progressive fall in platelet count to 34,000/mm³ by February 5. After massive gastrointestinal bleeding on February 7, she became hypotensive and died early the next day. Permission for an autopsy was denied.

Discussion

Malignant histiocytosis, frequently called histiocytic medullary reticulosis or sometimes histiocytic leukemia, is a rare disease with a rapidly fatal outcome. The malignant cells resemble those seen in malignant lymphoma, histiocytic type (1) (so-called reticulum cell sarcoma). In contrast to this tumor, malignant histiocytosis usually presents as a generalized disease at the outset, with early involvement of liver, spleen, multiple lymph nodes, and bone marrow and with systemic symptoms such as fever, anorexia, weight loss, and weakness. In some instances circulating histiocytes are evident relatively early in the course of the disease; in other instances histiocytes appear in the peripheral blood only terminally, or not at all. It is important to appreciate that this disease is a distinct entity and is different from differentiated progressive histiocytosis (so-called histiocytosis X, Schüller-Christian disease, or Letterer-Siwe disease) (1).

Combination chemotherapy has been used in a number of hematologic malignancies in order to attempt maximum killing of malignant cells (16). The success of the VAMP program (vincristine, amethopterin, 6-mercaptopurine, and prednisone) in treatment of acute lymphoblastic leukemia (17) led to the development of a combined chemotherapy program for advanced Hodgkin’s disease which has

Figure 2A. An immature histiocyte in peripheral blood from the patient in Case 1 (July 1968). The cytoplasm is deep blue and contains numerous small vacuoles. The nuclear chromatin is slightly coarser than that of the cell illustrated in 2B. Two light-blue nucleoli are evident. (Wright-Giemsa; original magnification, × 1,880.)

Figure 2B. An immature histiocyte from the peripheral blood of the patient in Case 2 (December 1968). The cytoplasm is deep blue, and numerous vacuoles are evident. The margin of the cell is irregular, and several pseudopod-like structures can be seen extending between adjacent red blood cells. A delicate chromatin skein-like pattern is evident. Three light-blue nucleoli are present. At the top of the nucleus a single cleft can be seen. (Wright-Giemsa; original magnification, × 1,880.)
resulted in a nearly 100% response rate (18). Similarly, in lymphocytic lymphosarcoma, 100% remissions were obtained with Cytoxan, vincristine, and prednisone (19). This last combination, reported after treatment of our patients was begun, brought about 85% remission in reticulum cell sarcoma with a mean duration of unmaintained remissions of 3 months. A comprehensive review of the chemotherapy of lymphomas, including the results of combination chemotherapy, is available (20).

Each of our patients with malignant histiocytosis survived 6 months from the onset of symptoms. This duration is not significantly different from that of cases reported previously (3-8). What is important, however, is that both of these patients treated with vincristine and prednisone experienced symptomatic and objective remissions of 3 and 2 months, respectively. Cytoxan was used in Case 2 when relapse occurred. It resulted in clearing of the histiocytes from the peripheral blood but did not significantly affect the course of the illness. The combination of vincristine and prednisone was chosen because of the reported beneficial effects of vincristine in refractory reticulum cell sarcoma (21) and because of the apparent benefit of corticoids in previously reported single cases of malignant histiocytosis (3-5). The cases presented here suggest that vincristine and prednisone, in combination, may be useful in the initial therapy of malignant histiocytosis.

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Figure 3. The normal architecture of the lymph node is obliterated. The capsule is thickened and focally infiltrated by neoplastic histiocytes. The lymphoid parenchyma is infiltrated by these cells (insert), which are intermingled with residual lymphocytes. Cohesive masses of these neoplastic cells were not evident. Plasma cells were present in moderate numbers. These latter two features aid in distinguishing malignant histiocytosis from malignant lymphoma of the histiocytic type (reticulum cell sarcoma). (Hematoxylin and eosin. Original magnifications: × 165; insert, × 1870.)
The Ideal Physician

He is first and foremost humane.
He is constantly observant.
He uses a systematic approach.
He knows and understands basic principles.
He uses reason in all his actions.
He is aware of the limitations of his own knowledge and of knowledge in general.
He respects the information that comes from the patient.
He is a perpetual student.

WILLIAM L. MORGAN, JR. and GEORGE L. ENGEL.
Introduction to the Patient,
Chapter One in The Clinical Approach to the Patient,
The Inadequate Terminology of Medicine

Better diagnostic testing, treatment of individual diseases, and total patient care will depend upon an improved interface between the physician, the hospital system, and the computer. Presently, a language gap continues to impede the satisfactory introduction of computers into clinical medicine and to delay an optimum delivery of health services. Mathematicians and engineers have discovered that programming a computer for fundamental biomedical research is one thing, but that using it for decision-solving tasks in clinical medicine is quite another matter. The disappointments to date have been largely due to the oversimplification of medical problems in order to make use of the computer’s present language capabilities. Too often mathematical solutions have been attempted on problems in the clinical area where sufficient hard data do not exist. On the other hand, physicians have not made the most of the present potential of the computer. They must become more intimately acquainted with what the computer can and cannot do. Their data must be assembled in a different format if the most is to be made of the capabilities inherent in present-day computer systems.

An important general problem of physician-computer interaction is the need for a natural language input to these machines. The difficulty, of course, is that natural language depends on context, which the computer is simply not able to handle in its present stage of development. This means that terms in medicine should become more formalized. To date, terms in medicine have grown helter-skelter and there is no real logic to medical terminology. We should get on with an arrangement of terms in a more logical fashion, but this will be difficult because there are many features of medicine as an art that cannot be formalized. We should consider whether more effective types of standardization and classification of disease processes could be developed.

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