

Reticulum Cell Sarcoma Terminating in Acute Leukemia

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THE PURPOSE of this report is to summarize six cases with documented reticulum cell sarcoma whose course terminated in a syndrome resembling acute leukemia. Ewald, in 1923, presented the concept that the reticuloendothelial elements of the bone marrow could give rise to all the elements found in the peripheral blood.¹ Berman reviewed the classification of the lymphomas in 1953 and noted the infrequent association of reticulum cell sarcoma and leukemic manifestations.² Richter,³ in 1956 in a review of 192 cases of monocytic leukemia at the Armed Forces Institute of Pathology, noted, in retrospect, that four cases which he considered "myeloid leukemia" were associated with tumors "apparently of reticulum cell type." He stated that situations such as these "may be expected to give important information on the origin of the cells." Beutler, in 1954, recorded a case of "acute myelogenous leukemia" in a patient with reticulum cell lymphoma and suggested that the ionizing radiation which the patient had received over a three year period of time was the possible causal agent.⁴ Bouroncle, Wiseman and Doan recently reported 26 cases of leukemic reticuloendotheliosis whose common denominator was the finding in the bone marrow and/or peripheral blood of a "large number of primitive atypical free reticulum cells and endothelial cells." Some of their patients appear to have the same clinical courses and histologic findings as the patients described in the present report.⁵

The present report deals with a study of six cases in which there was a definite progression from a localized reticulum cell sarcoma to a leukemic process. These cases are presented to describe a variant in the natural history of reticulum cell sarcoma, to emphasize that radiation therapy is not a necessary prerequisite for such a complication, and to comment on the variety of leukemic cells which have been encountered with reticulum cell sarcoma.

MATERIAL AND RESULTS

During the past 7 years, 122 patients with the histologic diagnosis of reticulum cell sarcoma or lymphoblastic lymphosarcoma have been studied at the Francis Delafield Hospital. During this period of time, 113 have died and nine are now living. The present study concerns the 113 deceased patients. Of these, 107 patients are considered to have had the usual course of reticulum cell sarcoma.^{6,7} The life expectancy of these patients, as

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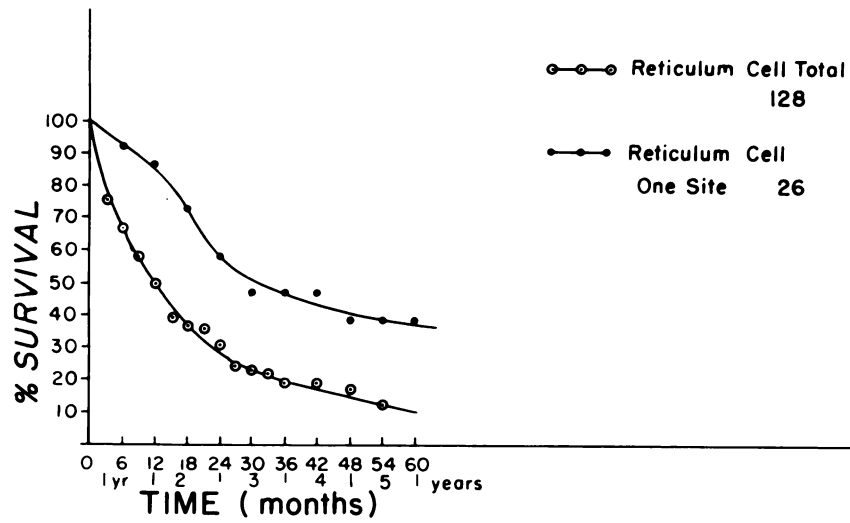


Fig. 1.—Survival in reticulum cell sarcoma confined to one site compared with survival in all cases of reticulum cell sarcoma. (Courtesy Dr. A. Gelhorn.⁷)

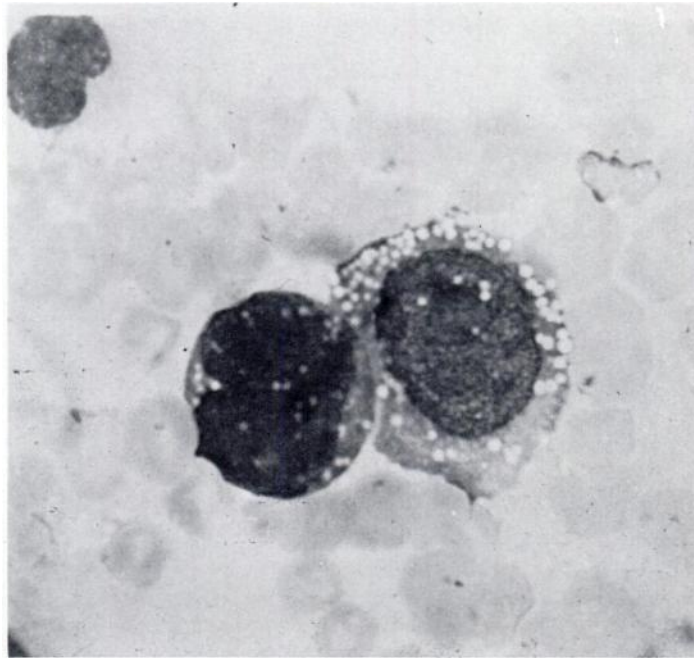


Fig. 2.—Bone marrow smear of case 1, showing two reticulum cell sarcoma cells. Wright stain, $\times 1800$.

compiled by Gelhorn⁷ from cases at the Columbia-Presbyterian Medical Center, including Francis Delafield Hospital, is noted in figure 1. The remaining six patients had a terminal course considered unusual in the natural history of reticulum cell sarcoma.

All patients had biopsy-proved reticulum cell sarcoma. Initially, treatment by radiotherapy to local areas resulted in moderate benefit. The total duration of disease from

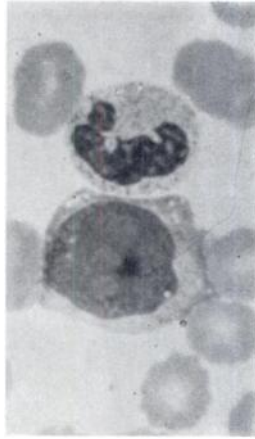


Figure 3A

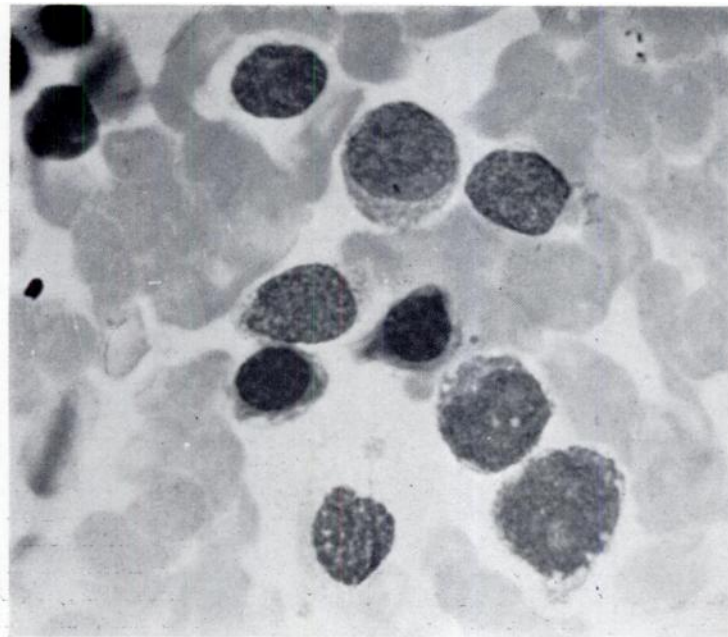


Figure 3B

Fig. 3.—A, Peripheral blood smear and B, bone marrow smear of case 2, showing reticulum cell sarcoma cells. Wright stain, $\times 1800$.

clinical onset to death was six months or less in four cases, and 20 to 30 months in two cases. In all cases, however, the acute terminal state was only of 1 to 2 months' duration, marked by the explosive onset of fever, bleeding diathesis and hepatosplenomegaly. The hematologic findings demonstrated severe anemia, markedly elevated white blood cell count (30,000 to 80,000/cu.mm.), and thrombocytopenia. The peripheral blood was marked by relative neutropenia and a high percentage of immature cells (30 to 80 per cent) which had the characteristics of immature reticulum cells in three cases (figs. 2 and 3), of myeloblasts in two cases (fig. 4), and of monocytoid granulocytes in one case (fig. 5).

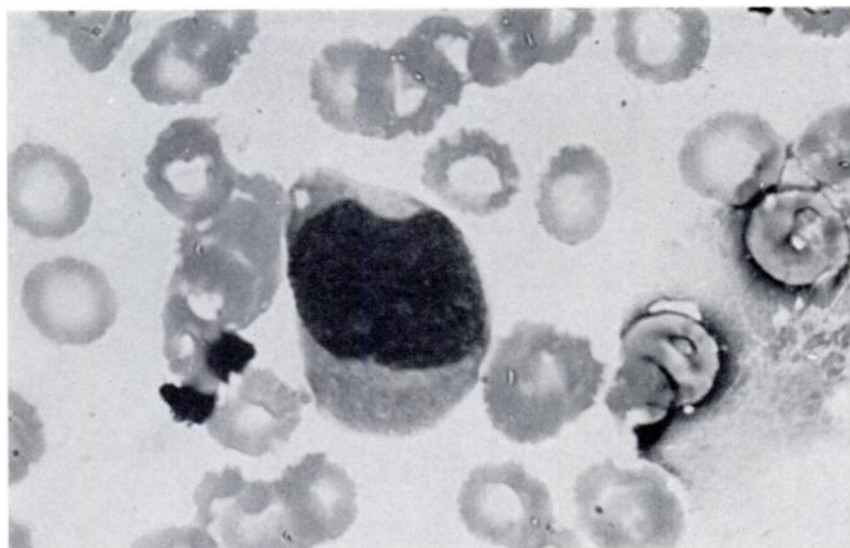


Fig. 4.—Peripheral blood smear of case 4, showing a myeloblast. Wright stain, $\times 1800$.

The bone marrow aspirations during the acute hematologic state or at postmortem contained similar cells in large numbers. Treatment in all cases with either 6-mercaptopurine, synthetic adrenal steroids, or both, failed to provide lasting subjective or objective benefit, and the appearance of the explosive hematologic picture presaged a rapid downhill course and death.

CASE REPORTS*

Case 1.—This 33 year old white female noted a mass at the angle of the right mandible in January 1956. A biopsy revealed reticulum cell sarcoma. The hematologic picture at that time was entirely normal. Treatment consisted of 3600 r to the mass with partial remission. The patient remained asymptomatic for one year, when axillary lymphadenopathy and a breast infiltration appeared. A repeat biopsy again demonstrated reticulum cell sarcoma. The hemoglobin was 12 Gm. per cent; the white blood cell count and differential were normal. Radiotherapy (2000 r) again produced improvement. Two weeks prior to admission, nausea and vomiting appeared. On admission, 5-23-57, jaundice, lymphadenopathy, pleural effusion and hepatosplenomegaly were noted. The hemoglobin was 12.1 Gm. per cent and white blood cell count 12,150/cu.mm. with a differential showing 77 per cent neutrophils (2-5-20-50); 9 per cent lymphocytes, 8 per cent monocytes, 6 per cent reticulum cells and platelet count 154,000/cu.mm. Two weeks later, the white blood cell count rise rapidly to a high of 31,800/cu.mm. and the platelet count fell to 90,000/cu.mm. The differential revealed 57 per cent neutrophils (1-2-5-27-22), 8 per cent lymphocytes, 1 per cent monocytes and 34 per cent reticulum cells (fig. 2). A marrow aspiration showed reticulum cells throughout the entire specimen. Treatment with 6-mercaptopurine and prednisone was followed by a further fall in platelets and a fall of white blood cell count to 1250/cu.mm. and some improvement in the differential count. However, jaundice progressed and death occurred on 6-30-57 with massive gastrointestinal hemorrhage. No autopsy was permitted.

Case 2.—A 32 year old white male visited his private physician (11-20-54) complaining of shortness of breath of six months' duration. Examination by his doctor demonstrated

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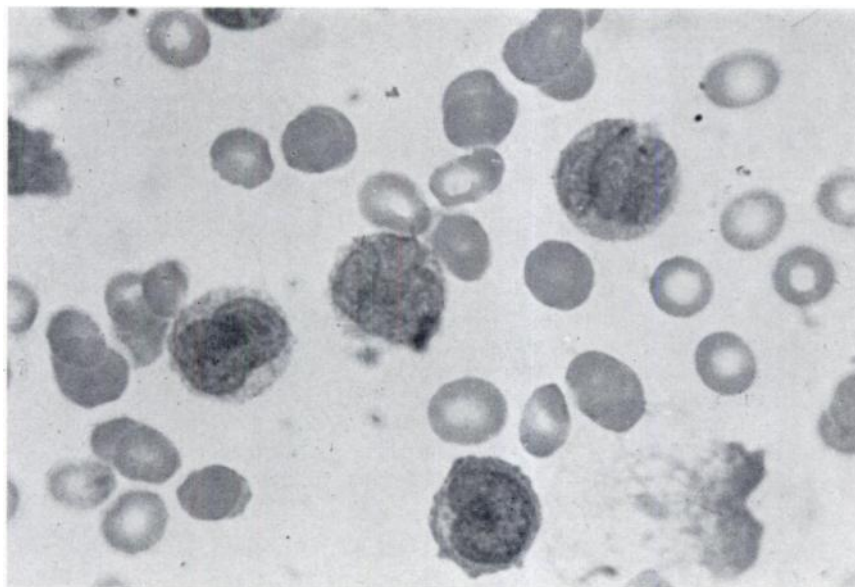


Fig. 5.—Peripheral blood of case 6, showing monocytoïd granulocytes.

supraclavicular nodes, a retrosternal mass and a left pleural effusion. A supraclavicular node biopsy revealed reticulum cell sarcoma, and neoplastic cells were found in the pleural fluid. Treatment with hydrocortisone and ACTH produced no benefit and the patient was transferred to Francis Delafield Hospital on 1-22-55. The major physical findings were: hemorrhagic mass in the oropharynx, cervical lymphadenopathy, and signs of superior vena cava obstruction, bilateral pleural effusions and hepatomegaly. Hemoglobin was 15 Gm. per cent; the white blood cell count was 46,900/cu.mm. with a differential of 37 per cent neutrophils (3-6-15-13), 14 per cent lymphocytes, and 49 per cent very immature cells having the characteristics of reticulum cells, and the platelet count was 150,000/cu.mm. Bone marrow aspiration revealed 56 per cent immature cells, characteristic of immature reticulum cells (fig. 3A and B). Radiotherapy treatment, 2000 r. to the mediastinum coupled with large doses of adrenal steroids produced a drop in the white blood cell count to 12,250/cu.mm. and a change in the differential to 84 per cent neutrophils (1-2-3-25-53), 7 per cent lymphocytes, 1 per cent monocytes and a decrease in immature cells to 8 per cent. The hemoglobin level was maintained but the platelet count fell to 100,000/cu.mm. Bone marrow aspiration revealed no change. The patient's course was marked by return of the white blood cell count to 20,750/cu.mm. and return of the differential to admission values, with a continuing fall in platelet count. Addition of 6-mercaptopurine to the therapeutic regimen produced no objective benefit. The patient developed an axillary vein thrombosis, epistaxis and melena. Terminally, a sharp rise in temperature with a pleural friction rub occurred, followed by rapid death (12-25-55). Autopsy revealed reticulum cells infiltrating all organs and the bone marrow, with particularly severe involvement of the mediastinum, pericardium, and epicardium. Hemorrhage was present in the lungs, thyroid, renal pelvis and the gastrointestinal tract. Moniliasis of the lungs was also present.

Case 3.—An 81 year old white male was admitted on 5-20-55 with the chief complaint of edema of both lower extremities. Six months prior to admission, supraclavicular and axillary lymphadenopathy was noted, accompanied by increasing anorexia and weakness. The major physical findings were: pallor, generalized glandular enlargement, signs of congestive heart failure and hepatomegaly. Axillary node biopsy revealed reticulum cell

sarcoma. Complete blood cell count showed a hemoglobin of 6.9 Gm. per cent; white blood cells count of 29,750/cu.mm. with 17 per cent neutrophils (0-0-1-2-14); 5 per cent lymphocytes; 1 per cent monocytes and 77 per cent immature cells resembling reticulum cells, and platelet count of 60,000/cu.mm. A bone marrow aspiration demonstrated 50 per cent large mononuclear cells resembling reticulum cells. Treatment with whole blood and Thio-TEPA resulted in a decrease of glandular enlargement and hepatomegaly, a mild rise of hemoglobin but a fall of the platelet count to 16,000/cu.mm. One month later, the peripheral blood and bone marrow were again similar to those seen on admission. 6-Mercaptopurine was begun and continued for two months. Repeated blood transfusions were given. These measures produced no change in the hematologic picture. Hepatomegaly increased and splenomegaly appeared. He was able to be discharged, however, for the next three months. He was readmitted on 5-20-55 with increasing weakness and diarrhea of one week's duration. There was no change in the physical findings. Complete blood count revealed a hemoglobin of 8.5 Gm. per cent; white blood cell count of 49,000/cu.mm. with 6 per cent neutrophils (1-5) and 94 per cent immature cells of the same type as previously described and a platelet count of 40,000/cu.mm. Prednisone had no effect on the course. The patient developed high fever, became semicomatose and died on 6-5-55. A blood culture taken on the day of death was positive for *Staphylococcus aureus, hemolyticus*. No autopsy was permitted.

Case 4.—A 16 year old Negro male was admitted on 7-11-58 with the chief complaint of generalized lymphadenopathy of two months duration. Physical findings were: temperature of 100.2 F., generalized lymphadenopathy and hepatosplenomegaly. A lymph node biopsy revealed reticulum cell sarcoma. A complete blood count revealed hemoglobin 14.2 Gm. per cent; a white blood cell count of 4,450/cu.mm. with 32 per cent neutrophils, 67 per cent lymphocytes, and 1 per cent monocytes; and platelet count 133,000/cu.mm. A bone marrow aspiration on admission revealed a mild increase in "normal reticulum" cells. Initial therapy with chlorambucil was followed by a leukopenia of 2,000/cu.mm. and a thrombocytopenia at 70,000, and the drug was discontinued. Three weeks following admission, the white blood cell count rose rapidly to 54,000/cu.mm. with 3 per cent neutrophils, 15 per cent lymphocytes, and 82 per cent very immature cells considered to be "blasts" (fig. 4). Hemoglobin was 14.2 Gm. per cent and the platelet count, 28,000/cu.mm. Bone marrow aspiration at the onset of this phase revealed decreased cellularity with 12 per cent blast forms and 50 per cent large immature cells resembling reticulum cells. Prednisone therapy was begun with rapid fall in the total white blood cell count to a level as low as 600/cu.mm. but anemia and further thrombocytopenia (6,000) developed. Marrow aspiration revealed increased cellularity in comparison with the previous marrow smear; cells of the lymphoid series were present in increasing numbers and immature cells were less common. The clinical course was marked by signs of peritonitis, accompanied by spiking fever and severe diarrhea. One month after admission, severe, recurrent epistaxes became a problem, jaundice appeared and death occurred on 9-2-58. Autopsy revealed diffuse lymph node infiltration by very immature cells of the myeloid series. These cells had infiltrated the lymphoid follicles of the intestine and the mucosa of the cecum leading to perforation of the cecum and subacute peritonitis. Hepatosplenomegaly and acute necrotizing enterocolitis were also noted. No lymph node pathology similar to the original biopsy, on which the diagnosis of reticulum cell sarcoma had been made, could be found, although review of the original biopsy material was considered characteristic for reticulum cell sarcoma.

Case 5.—A 75 year old white male noted the insidious onset of a painful mass in the right preauricular area in November 1956. A complete blood count at this time was entirely normal. A needle biopsy revealed reticulum cell sarcoma in the parotid gland. A good remission was produced by 2500 r to this area. He was asymptomatic until 2½ weeks prior to admission (2-8-57) when sore throat and mouth, accompanied by weight loss and anorexia, began. This was followed by melena and gingival bleeding. On admis-

sion, the physical findings were: generalized petechiae, ulceration of the uvula, 3 x 3 cm. mass over the right mandible, splenomegaly and a midabdominal mass. Complete blood count on admission revealed a hemoglobin of 10.8 Gm. per cent, white blood cell count of 14,650/cu.mm., with 24 per cent neutrophils (2-5-5-12), 8 per cent lymphocytes and 68 per cent very immature cells thought to be myeloblasts. Prothrombin time was prolonged and stool guaiac, 4+. A culture of the uvular ulcer grew *Candida albicans*. Three days later the white blood cell count rose to 31,300/cu.mm. Treatment with high doses of prednisolone resulted in a drop of the white blood cell count to 1200/cu.mm. and a change in the differential to 44 per cent neutrophils (16-28), 8 per cent lymphocytes, 8 per cent monocytes and 40 per cent immature cells. Anemia became profound, and severe bleeding ensued with platelet count as low as 46,000/cu.mm. The course terminated in a severe generalized headache, sharp rise in temperature without localizing neurologic signs and rapid death on 3-10-57. No autopsy was permitted.

Case 6.—This 50 year old white male noted a left supraclavicular mass in November, 1953; biopsy in March 1954 revealed reticulum cell sarcoma. A mediastinal mass was noted on chest X-ray and radiotherapy (3000 r) to both areas produced regression in both masses. Complete blood counts during the above period were entirely normal. The patient was asymptomatic and without further therapy when he was admitted in April, 1956, with melena of four weeks' duration. Physical examination revealed decreased resonance at the left lung base and splenomegaly as the major findings. Complete blood examination revealed a hemoglobin of 12 Gm. per cent, a leukopenia of 2250/cu.mm. with 33 per cent neutrophils (1-1-2-29), 28 per cent lymphocytes and 39 per cent "monocytes," and a platelet count of 114,000/cu.mm. Bone marrow aspiration showed 22 per cent multinucleated reticulum cells. Approximately five weeks after admission, the white blood cell count had risen to 50,000/cu.mm. with 20 per cent neutrophils, 10 per cent lymphocytes, 13 per cent "monocytes" and 57 per cent immature cells. Bone marrow aspiration showed 31 per cent immature reticulum cells and 20 per cent immature cells not characteristic of reticulum cells. During therapy with 100 mg. of prednisone daily, the leukocytosis increased to 80,000/cu.mm. and the percentage of immature cells to 73 per cent, identified as monocytoid granulocytes (fig. 5). Anemia and thrombocytopenia became profound. The patient's course was marked by increasing dyspnea, epistaxes, ecchymoses and marked temperature elevation on the day of death, 5-31-56. Autopsy revealed diffuse organ involvement by immature cells which at this time had the characteristics of the myeloid series, and the final diagnosis was myelogenous leukemia. No evidence of reticulum cell sarcoma could be found at postmortem, although on review the original slides were again interpreted as reticulum cell sarcoma.

DISCUSSION

This study has revealed an unusual termination in the natural history of reticulum cell sarcoma. This complication is not frequent, occurring in only about 5 per cent of our patients with reticulum cell sarcoma. The appearance of the leukemic picture is an ominous sign. None of the patients responded to supportive measures, antimetabolites or steroid therapy and all patients died within a period of two months. The explanation for the sudden change in clinical events and for the appearance of immature cells is not apparent. Radiation therapy has been implicated as a possible causal agent for these changes.^{4,6} In our six patients, however, three received no radiotherapy at any time during their illness, while one patient received local radiotherapy to the mandible only three months prior to the terminal disease. It therefore appears unlikely that radiation is the causal agent of this complication. The appearance in reticulum cell sarcoma of circulating reticulum cells, myelo-

blasts, monocytoid granulocytes or monocytes reported herein and by others²⁻⁵ may represent clinical examples illustrating Ewald's concepts.¹

SUMMARY

The records of 113 patients dying at the Francis Delafield Hospital with documented reticulum cell sarcoma revealed six cases whose course terminated in a syndrome resembling acute leukemia. Their course was characterized by weakness, pallor, petechiae, hemorrhages and hepatosplenomegaly. The blood showed anemia, leukocytosis (white blood cell count 20,000 to 80,000/cu.mm.) and thrombocytopenia (platelet count <100,000/cu.mm.). Differential count in the blood and the bone marrow revealed a high percentage of immature cells (35 to 96 per cent). These were identified as reticulum cells in three patients, as myeloblasts in two and as monocytoid granulocytes in one. In all six patients, this explosive illness terminated in systemic infection or hemorrhage within two months. Therapy with 6-mercaptopurine, adrenal steroids, or both, gave no benefit.

SUMMARIO IN INTERLINGUA

Le scrutinio del dossiers de 113 patientes morte al Hospital Francis Delafield con documentate sarcoma a cellulas reticular resultava in le identification de sex casos con cursos a termination in un syndrome simile a leucemia acute. Iste cursos esseva characterisate per debilitate, pallor, petechias, hemorrhagias, e hepatosplenomegalia. Le sanguine monstrava anemia, leucocytosis (numeration leucocytic, 20.000 a 80.000 per mm³), e thrombocytopenia (numeration plachettal minus que 100.000 per mm³). Le numeration differential in sanguine e medulla ossee revelava un alte procentage de cellulas immatur (35 a 96 pro cento). Istos esseva identificate como cellulas reticular in tres patientes, como myeloblastos in duo, e como granulocytos monocytoide in un. In omne le sex patientes, iste morbo de character explosive se terminava in un infection systemic o in hemorrhagia intra duo menses. Therapia con 6-mercaptopurina, steroideas adrenal, o un combination del duo produceva nulle beneficio.

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