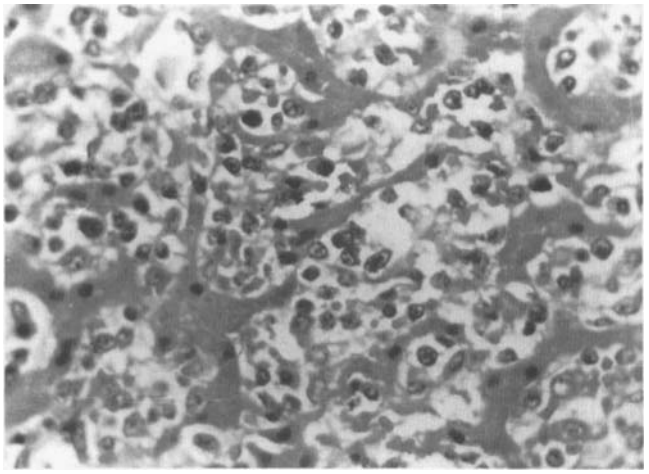

Fig. 1. Liver shows sinusoidal dilatation and packing of sinusoids by malignant T cells (H&E × 280).

This 15-year-old female presented with weight loss (14 kg), fever, epistaxis, and abdominal lump of 4 months' duration. Her liver was palpable 7 cm below the right costal margin, and the spleen was palpable 28 cm below the left costal margin. Two to three lymph nodes (1 cm each) were found enlarged in the axillary and inguinal regions. Investigations revealed hemoglobin of 5.8 g/dl, and a platelet count of 30,000/μl. The total leukocyte count was 4,200/μl with 21% immature lymphoid cells. The atypical cells were large with round-to-oval nuclei, many with prominent nucleoli, fine chromatin, and moderate amounts of cytoplasm. Many cells showed nuclear indentations. Antemortem bone-marrow aspirate was cellular and revealed 50% immature lymphoid cells of nulceated nonerythroid cells.

At necropsy, the spleen weighed 2.8 kg and was diffusely enlarged. Microscopically, the sinusoids of the red pulp were dilated and packed with malignant cells. The white pulp was atrophic. The malignant cells were medium-sized, and discretely placed with a moderate amount of cytoplasm. Most nuclei were round-to-oval with prominent nucleoli and fine chromatin. However, cells with nuclear indentation were also seen. The liver weighed 3.1 kg, and on cut section revealed a diffuse enlargement. Microscopically, marked sinusoidal dilatation and packing by similar atypical lymphoid cells were seen (Fig. 1). Postmortem bone marrow showed near total replacement by malignant cells. The lymph nodes (axillary, paraaortic, inguinal, and carinal) revealed only sinus histiocytosis with benign erythrophagocytizing histiocytes in the sinuses. Immunoperoxidase staining was done on the sections of the liver and spleen, using T (CD 45 RO), B (CD 20), and macrophage (alpha antichymotrypsin) monoclonal antibodies. The T-cell marker was strongly positive. B-cell and macrophage markers were negative. Electron microscopy was done, which further corroborated the lymphoid origin of the cells. The diagnosis was of hepatosplenic T-cell lymphoma with sinusoidal localization of malignant cells, involving the bone marrow and peripheral blood.

The revised European-American classification of lymphoid neoplasms stressed a new entity called hepatosplenic γδ T-cell lymphoma [1]. This entity was recognized by Kadin et al. in 1981 [2]. Further reports came in 1990 when Falini and Pileri studied 9 such cases [3]. They designated these cases as peripheral T-cell lymphoma associated with hemophagocytic syndrome due to the exuberant admixture of benign erythrophagocytizing histiocytes with malignant T-cells. Again in 1990, Farcet and Gaulad studied 2 such cases of hepatosplenic T-cell lymphoma with sinusoidal localization of malignant cells which expressed the T-cell receptor [4]. No erythrophagocytosis was seen in these 2 cases. The feature worth stressing in all cases is the sinusoidal localization of the malignant T-cells. The prognosis is poor.

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Cold Agglutinin Hemolysis Responding to Fludarabine Therapy

To the Editor: Cold agglutinin hemolysis is a hematological disorder characterized by immune (cold antibody)-mediated hemolytic anemia. Typically, these autoantibodies are most active at temperatures below 37°C. Either acute or chronic forms of the disorder may occur. The defect in the regulation of the immune response underlying the production of cold agglutinins remains unknown. The acute form of the disease is usually self-limited and may occur following infection with mycoplasma pneumoniae. A chronic form may be found in persons with an underlying lymphoproliferative disorder. In other individuals, no evidence of an underlying disease can be found, and these cases are termed idiopathic. Patients with a mild form of the disease may achieve control of their symptoms by avoiding cold exposure. Therapy with alkylating agents, such as chlorambucil or cyclophosphamide, is necessary for more severe forms of the disease. Splenectomy and corticosteroids are not usually effective. Spontaneous remissions and exacerbations do sometimes occur.

This letter describes a patient with idiopathic cold agglutinin disease who initially responded to cyclophosphamide-containing chemotherapy but subsequently became refractory to this agent. Treatment was changed to fludarabine, a purine nucleoside analog which resulted in a prolonged clinical remission. This is the first report of clinical activity of fludarabine in idiopathic cold agglutinin disease.

A 75-year-old male was referred with a 6-week history of intermittent chest pain and dyspnoea on exertion. He had had no recent fever, sweats, or weight loss. There was no history of respiratory infection. He was not on any medications, was a nonsmoker, and did not drink alcohol.

Physical findings showed the patient to be afebrile with a pulse of 70 beats per min, a respiratory rate of 15 per min, and blood pressure of 140/80. There was no palpable lymphadenopathy. Examination of the heart, lungs, and abdomen found no abnormalities. Laboratory examination in-

cluded hemoglobin of 8.9 g/dl, platelet count of 187,000/mm^3, and a white-cell count of 6,000/mm^3 with a normal differential. The reticulocyte count was 165,000/mm^3. The fluorescent antinuclear antibody test was negative. Total bilirubin was 2.25 mg/dl (normal, 0.2–1.1 mg/dl), and the LDH was 320 IU/l (normal, 122–220 IU/l). Quantitative immunoglobulins (IgG, IgA, and IgM) were normal. The cold agglutinin titer was positive at 1:256, demonstrated anti-I specificity, and was nonreactive at 37°C. A direct antiglobulin test was positive for the C3 component and negative for anti-IgG. Antibodies to mycoplasma and a chest X-ray were both negative. Examination of the bone-marrow biopsy and aspirate showed erythroid hyperplasia but was otherwise normal.

The patient was transfused with warmed packed red-blood cells, and in August 1990, began cytotixic chemotherapy with cyclophosphamide, 1,200 mg, and vincristine, 2 mg, both given intravenously, and prednisone, 80 mg per day by mouth for 5-days. Treatment was repeated every 21 days. The rate of hemolysis slowed with decreased transfusion requirement, from two units of packed red-blood cells every 2 weeks to two units every 4–6 weeks. The reticulocyte count remained elevated in the range of 90,000–160,000/m^3. In April 1991, the rate of hemolysis increased with increasing transfusion requirement. A repeat bone-marrow examination again showed erythroid hyperplasia, this time with increased iron stores. The remainder of the bone-marrow morphology was normal.

In June 1991, treatment was begun with fludarabine, 25 mg/mm^2 of body surface area daily for 5 days intravenously. This treatment was repeated every 28 days for a total of three courses. Following the third course of fludarabine therapy, hemoglobin, reticulocyte count, and bilirubin returned to normal. At the time of writing, which is 4 years following completion of therapy, the hemoglobin remains normal.

Interestingly, di Raimondo et al. [1] reported on the results of fludarabine treatment of 112 patients with CLL, 8 of whom had autoimmune hemolytic anemia before therapy was initiated. Their report did not indicate whether any of their patients had cold-reacting antibodies. Only 1 of the 8 patients achieved a remission of hemolysis after fludarabine therapy. The remaining 7 patients either had no response or experienced a worsening of their hemolysis, even though their CLL appeared to be responding to fludarabine. Five other patients developed autoimmune hemolysis after fludarabine therapy despite a continuing response of their leukemia. A recent report from Byrd et al. [2] suggested that fludarabine therapy might possibly precipitate hemolytic anemia in patients with CLL. Chlorambucil and other alkylating agents have also been reported to trigger autoimmune antibody production in patients with lymphoproliferative diseases [3,4].

Clearly, the relationship between fludarabine therapy and antibody-mediated hemolysis is complex. It is possible that a different immune perturbation underlies the production of warm antibodies in contrast to that resulting in cold antibodies, and in addition, there may be differences in the immune pathophysiology of autoantibody production between patients with an underlying lymphoproliferative malignancy and those without. Further elucidation of the biology underlying these syndromes is required. While it is possible that the favorable results induced by fludarabine in this case may have been coincidental, the time course of response to therapy suggests otherwise.

This case suggests that fludarabine can produce remission in patients with cold agglutinin-induced hemolysis, and that despite current reports of ineffectiveness or possibly even provocation of warm antibody-mediated hemolysis in the setting of CLL, consideration should be given to fludarabine's use in patients with idiopathic cold agglutinin disease who are refractory to conventional alkylating agents.

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Further Hemolytic Disease of the Newborn Caused by Anti-M

To the Editor: Hemolytic disease of the newborn due to the anti-M antibody is extremely rare [1]. In this report, an infant with hemolytic disease of the newborn due to anti-M is described.

A 21-year-old woman was admitted to the Maternity Department of Hacettepe Hospital with preterm labor. Her blood group was A Rh-positive, and she had never received a blood transfusion. Her first pregnancy was terminated at 28 weeks of gestation due to intrauterine death of the fetus. On this admission, her pregnancy was at 33 weeks of gestational age, and she gave birth to a 2,100-g premature baby by cesarean section. The baby was pale, and his hemoglobin was 5.1 g/dl 1 hr after birth. Peripheral blood smear showed slight polychromasia, anisocytosis, and obvious microspherocytosis. Babies blood group was A Rh-positive, and direct antiglobulin test was initially reported to be negative. The case was consulted with blood center, and the mother's serum was tested immediately for an irregular antibody. The antibody in the maternal serum was identified as anti-M. The mother was ANN. The same antibody failed to agglutinate MM cells modified by bromelin. In order to demonstrate the IgG fraction, maternal serum was absorbed with OMM cells, for 2 hr at 37°C. After absorption, washed cells agglutinated with anti-Ig G serum, but did not react with anti-IgM and anti-IgA sera. Eluate from those cells again showed anti-M specificity at the antiglobulin phase. Additional tests with anti-IgG, anti-IgM, and anti-IgA sera were also negative. Repeated tests using varying dilutions of the antihuman globulin serum gave weak positive results at $^1/_2$, (+) at $^1/_4$, and weak positive results at $^1/_8$ dilutions after 10 min [2]. The infant's unwashed cells were mixed with an equal volume of 30% albumin and incubated at 37°C. Within 30 min, (++) spontaneous agglutination developed. The same test, using O MN normal newborn infant red cells, gave negative results, showing that in vivo sensitization of the red cells had occurred in our patient [2,3]. In addition, while the initial antiglobulin tests were negative, when the infant's red cells were incubated 1 hr at 37°C, the eluate with anti-M specificity gave a weak positive reaction with two different antiglobulin sera. The father's group was O Rh-negative (MN). After two A Rh-positive (NN) red-cell transfusions, the infant's hemoglobulin rose to 12.8 g/dl and showed permanent improvement.

Anti-M, which develops during pregnancy, apparently as an immune antibody, may fail to affect the fetus, as in the case described by Bowley and Dunsford [4].

However, in rare cases in which the mother's serum has very potent IgG anti-M, hemolytic disease develops and is occasionally responsible for hydrops fetalis and intrauterine deaths [2,3,5].

In cases described by Stone and Marsh [2] and Freiesleben and Jensen [3], infants had hemolytic disease due to anti-M. There were two features which resemble ABO hemolytic disease rather than Rh and in reason other subgroup incompatibilities. First, the direct antiglobulin tests were negative or weakly positive, but unwashed red cells agglutinated spontaneously in a colloid medium. Second, the osmotic fragility of the red cells was definitely increased. The authors suggested that, in all cases of hemolytic disease of the newborn of unusual or unknown etiology, if the direct antiglobulin test is negative, a marked increase of red cell osmotic fragility may be accepted as evidence of red-cell sensitization [2,3]. Microspherocytosis, which was