

TRH stimulation test was performed in 11 patients (5 HD) at weeks 0 and 9. Plasma levels of thyroid hormones were determined within a single assay using commercially available kits, and differences between mean values were tested by the Student's t-test for matched data.

None of the patients developed hypothyroidism. Although thyroid hormone values remained within the reference range, all patients at week 1, after only one week of steroid therapy, showed a reduction in T3 and free-T3 (FT3) levels compared to basal values, with a contemporary transient increase of reverse T3 values. This difference was consistent in both the SD and HD groups, but was significant ( $p < .005$ ) in the SD group only, due to the higher number of patients. Complete reversal of this pattern was evident at week 4 (Figure 1). FT3 remained low normal in all patients. TSH was not increased even at week 1 during the transient reduction of T3 and FT3. TBG, T4 and FT4 remained normal. TG was steadily low normal. The transient reduction of TBG was concomitant with that of thyroxine levels.

TRH stimulation test in 11 patients (5 HD) showed normal TSH peak time and height, and AUC at both evaluations. Thyroid function was not markedly impaired by second exposure to Erwinia ASP, either by short treatment at SD or by protracted treatment at HD (cumulative dose 500,000 IU/m<sup>2</sup>). Both groups experienced a transient reduction of T3 and FT3, with an increase in rT3 but not TSH, that was evident after one week of steroid therapy before ASP was started. Thus a pathogenic role for ASP seems to be ruled out.

Ferster *et al.*<sup>3</sup> reported a significant reduction of T3, T4, and TBG during induction, with a modest T3 and TBG decrease during reinduction, attributed to the higher dose of *E. coli* ASP

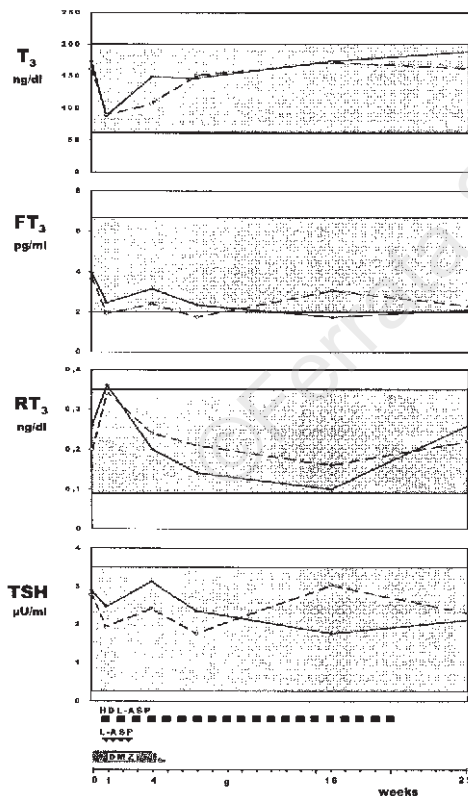


Figure 1. Mean values of T3, FT3, rT3, T4, FT4 and TSH in 23 children affected by ALL, measures at week 0, 1, 4, 9, 16 and 21 to 25 of reinduction. Continuous line: patients treated with standard doses of ASP (n=16). Dashed line: patients treated with high doses of ASP (n=7). Shaded area: range of normal values.

(105,000 vs 40,000 IU/m<sup>2</sup>) and the more frequent administration (daily vs every 4 days) during induction. Despite a much higher dose of ASP in one arm, none of our patients showed marked thyroid dysfunction.

Failure to observe expected ASP-dependent biological effects might depend on ineffective asparagine depletion. Recently, greater clinical efficacy for the *E. coli*-ASP- vs the Erwinia-ASP-containing chemotherapy regimen,<sup>4</sup> as well as lower asparagine depletion with Erwinia vs *E. coli* ASP have been reported.<sup>5</sup> This is in keeping with the association of thyroid dysfunction and use of *E. coli* ASP in Ferster's study.<sup>3</sup> In addition, failure to obtain asparagine depletion by second exposure to ASP may be due to antibody-mediated *silent inactivation*. Taken together, both of the above mechanisms might explain the failure to observe thyroid dysfunction as a consequence of second exposure to Erwinia ASP in our patients.

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#### Autoimmune hemolytic anemia with anti-DC specificity following a primary infection by Varicella virus

Sir,

The association of hemolytic anemia and Varicella virus infection has been reported on three occasions.<sup>1-3</sup> Cold antibodies of the IgM type were involved in two of them. Both of these showed anti-Pr specificity. We describe here an association of autoimmune hemolytic anemia, due to warm antibodies with anti-DC specificity linked to a primary infection by the varicella virus.<sup>4</sup> In August 1993, a patient was admitted to the emergency room complaining of fever, myalgia and general malaise. The presence of a macula-vesiculate eruption lead us to formulate a diagnosis of varicella. Physical examination revealed mild icterus and splenomegaly without adenopathies.

Routine laboratory analysis upon admission was as follows: hemoglobin 5.8 g/dL, HCT 16.4%, MCV 112 fL, leukocytes  $5.7 \times 10^9/L$  (differential: 45% lymphocytes, 42% neutrophils), platelets  $116 \times 10^9/L$ , ferritin 351 mg/dL, bilirubin 5.1 mg/dL (indirect 4.4), LDH 2047 U/L, haptoglobin was not detectable.

Morphological study determined the presence of 2% erythroblasts in the peripheral blood with no myeloma. The corrected amount of reticulocytes was 60%. The direct Coombs' test was positive, with the presence of autoantibodies of the

IgG<sub>3</sub> type. The hematic and serous blood group was identified as 0 Rh positive; anti-DNA and ANA antibodies were negative.

Viral serology demonstrated IgM<sup>+</sup> anti-varicella antibodies, anti-HIV, CMV, infectious mononucleosis and hepatitis serology was negative. An immunohematological study carried out at the regional transfusion center showed the 3+/4+ positivity for the direct Coombs' test with the antibody type corresponding to an IgG<sub>3</sub>. A search for allo-antibodies was negative. Elution of the autoantibody showed anti-DC specificity (concentration <1/128). The patient's genotype, determined by saline monoclonal sera, was CDe/CDe. Variants of the D antigen were ruled out using a panel of anti-D monoclonal sera.

The patient required a transfusion of two concentrates of O group Rh negative erythrocytes. Cross tests were negative in the saline and Coombs' phase. The transfusion was carried out under intensive care, without provoking an acute hemolytic reaction. Corticoid treatment at a dose of 2 mg/kg/day was begun and produced a progressive rise in the hemoglobin (14 gr/dL). At that time, the patient still showed slight hemolysis making it necessary to continue corticoid treatment. Abdominal CT documented the persistence of moderate splenomegaly and erythrokinetics evidenced shortened average erythrocyte survival (12 days) with a pattern of splenic sequestration.

Splenectomy was performed and the patient's clinical course has been satisfactory. He currently maintains a normal hemoglobin level with no treatment at all.

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#### Unusual evolution to immunoblastic lymphoma of a case of Waldenström macroglobulinemia presenting with thrombocytopenia

Sir,

Waldenström macroglobulinemia (WM) is a lymphoproliferative disease characterized by the secretion of elevated quantities of monoclonal IgM; approximately 6% of cases evolve to immunoblastic lymphoma (IL).<sup>1,2</sup> On the other hand, the association of lymphoproliferative processes with thrombocytopenia is well known.<sup>3</sup> We report a 65-year-old woman who came to our service with mucocutaneous bleeding and thrombocytopenia as the initial manifestations of WM which rapidly evolved to IL. At presentation the patient showed hepatosplenomegaly, platelets  $14 \times 10^9/L$ , leukocytes  $6.9 \times 10^9/L$  with normal differential count, and hemoglobin 10 g/dL. Immunoglobulin quantification was: IgG 1141 mg/dL, IgA 151 mg/dL, and IgM 333 mg/dL, with a normal immunoelectrophoretic pattern. Anti-platelets antibodies (IgG and IgM) were strongly positive. Marrow aspiration revealed abundant megakaryocytes and peripheral blood immunophenotype showed 30% CD19<sup>+</sup>, CD22<sup>+</sup>, Dr<sup>+</sup>, FMC7<sup>-</sup> lymphocytes, positive surface immunoglobulins with  $\lambda$  monoclonality (++) , CD5<sup>+</sup>, CD25<sup>+</sup>, and CD10<sup>-</sup>. Steroid treatment was begun with only a partial response, platelets remained at  $100 \times 10^9/L$  for four months, after which they fell to  $10 \times 10^9/L$ . Abdominal CT was normal, as were new

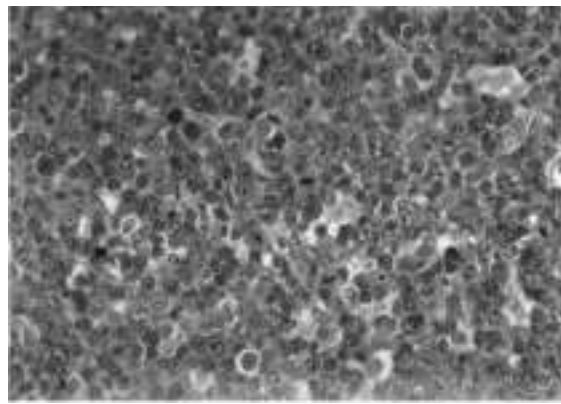


Figure 1. Microscope examination of a cervical peripheral lymph node (H.E. 400x): immunoblastic lymphoma (polymorphic immunocytoma). Diffuse proliferation of lymphoplasmacytoid cells and large cells with numerous mitoses are shown.

marrow aspiration and repeated immunophenotyping. This is difficult to explain except for the possibility that it was caused by the lympholytic action of the steroids or by focal bone marrow involvement. Splenectomy was performed and histological examination revealed a lymphoplasmacytoid/immunocytoma lymphoma with  $\lambda$  monoclonality. Following splenectomy there was a partial response and for a few months the platelet level was maintained, after which another abdominal CT scan revealed low density hepatic lesions with internal adenopathies. Immunoelectrophoresis demonstrated a monoclonal IgM peak of 2 g/dL and Bence Jones proteinuria with monoclonality.

Six months later the IgM had risen to 10 g/dL and marrow aspiration showed 10% plasma cells, some of which were binucleated, and a minimum of lymphoid infiltration in some zones. At this time the platelet count normalized. Treatment with cycles of chlorambucil and prednisone was begun along with plasmapheresis. There was no change in the amount of the IgM and a monoclonal IgG peak (2 g/dL) also appeared. A few weeks later numerous peripheral adenopathies developed and a biopsy of one of these revealed an immunoblastic lymphoma with  $\lambda$  monoclonality (Figure 1). The patient died of pulmonary hemorrhage twenty months after diagnosis. Several aspects stand out in this case: the appearance of thrombocytopenia before WM; its disappearance when the monoclonal peak rose (for which we have no explanation); the rapid evolution to IL with identical monoclonality, as reported by others,<sup>4</sup> and the appearance of monoclonal IgG along with the monoclonal IgM at the end of the disease evolution. To our knowledge, only one other such case has been reported previously.<sup>5</sup>

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