Chlorambucil Treatment of Patients With Cold Agglutinin Syndrome

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THE COLD AGGLUTININ SYNDROME (C.A.S.) is characterized by high-titre cold agglutinins, a hemolytic anemia, Raynaud phenomena in the cold, various degrees of hemoglobinuria, and sometimes gangrene. Because of the hemolysis, the syndrome is most often classified as an autoimmune hemolytic anemia. However, treatment with ACTH, corticosteroids or splenectomy, most often used in this condition, has been without effect.[1]

It is now generally agreed that the primary pathogenic factor in the desease is the presence of monoclonal IgMK globulins[2] causing agglutination of red cells at temperatures below the normal human body temperature. In many respects the C.A.S. is related to Waldenström's macroglobulinaemia although the concentration of the IgM M-component in this disease is usually higher, and the IgM molecules do not agglutinate red cells in the cold.

Patients with C.A.S. living in a temperate climate are often prevented from working or moving outdoors in the winter time, and death caused by serious attacks of hemoglobinemia has been reported. For this reason, four patients have been treated with chlorambucil (Leukeran®, NN-Di-2-chlorethyl-p-aminophenyl-butyric acid). This cytostatic agent reduces the concentration of IgM in macroglobulinemia Waldenström[3] and, as will be seen, has a similar effect in C.A.S.

Patients

Case IV—A.J., a 78 year old woman with Raynaud phenomena and hemoglobinuria from the age of 70 (1961). Before treatment the Cold Agglutinin Titre (C.A.T.) was 150,000 at 4°C.

The patient was treated with chlorambucil 10 mg. orally per day for 50 days each winter from 1962 to 1967. The effect obtained from 1962 to 1964 has been reported.[4]

Case IX—L.C., a 65 year old widow with Raynaud phenomena, icterus, and hemoglobinuria from the age of 62 (1966). At that time C.A.T. was 80,000 at 4°C. Over the period April to July 1966 the patient was treated with cyclophosphamide (Endoxan®), 50 mg. three times daily, but treatment had to be discontinued because of dyspepsia and loss of hair. Since February 1967, chlorambucil, 20 mg. per day, has been given for 50 days every third to fourth month.

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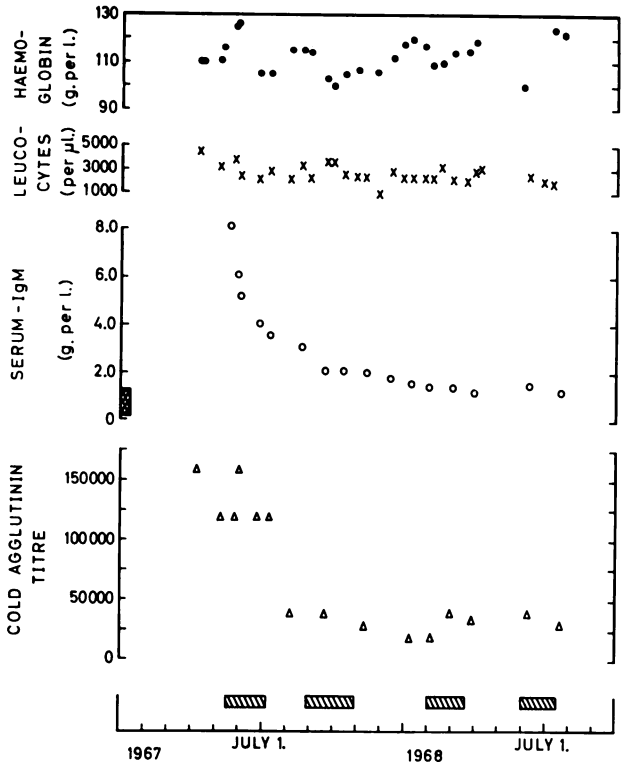

Fig. 1.—Hemoglobin, leukocytes, serum-IgM, and cold agglutinin titres before and during treatment period indicated by slanted lines within box with chlorambucil (Patient X—G.H.). Cross-hatched box indicates normal range of IgM-concentration in serum (0.11–1.23 Gm./L).

Case X—G.H., a 62 year old farmer with Raynaud phenomena and hemoglobinuria from the age of 57 (1964). C.A.T. was 138,000 at 4°C. For periods of treatment, see Fig. 1.

Case XII—E.J., a 63 year old man with Raynaud phenomena, hemoglobinuria, and gangrene of the fingertips at the age of 61 (1967) when the C.A.T. was 29,000 at 4°C. Chlorambucil has been given continuously from May 1, 1968. The dose of 8 mg. per day was reduced to two mg. per day from August 28, 1968.

Methods

Agargel electrophoresis was performed according to Laurell and Niléhn.[5] Immunoelectrophoresis was performed according to Scheidegger[6] with specific antisera to IgM, IgG, IgA, kappa, and lambda light chains. Quantitative IgM determinations were made by immunodiffusion.[7]

The titration for cold agglutinins has been described by Lind et al.[8] Each patient's sera from various times during the investigation were titrated in parallel rows in one experiment and incubated at different temperatures for 18 hours before reading.

The titres obtained at 20, 22, and 24°C., or at 22, 24, and 26°C were plotted on the ordinate in a semilogarithmic system, with the temperature as abscissa. For an example, see Fig. 2. It has been shown[4] that there is a logarithmic relationship between the decrease in temperature and the increase in titre, because of the highly negative entropy change for the reaction. Hence, a straight line could be drawn through the points. The extrapolation to the abscissa at titre one, represents the thermal amplitude for the serum. This is the highest temperature at which the undiluted serum still agglutinates red cells.

The distance on the abscissa between the thermal amplitude for serum before and after treatment expresses the enhanced tolerance of the patient to the cold. In order to compare the effect of the treatment on the C.A.T. in the four patients, the titre after the treatment period has been expressed as a per cent of the initial value.

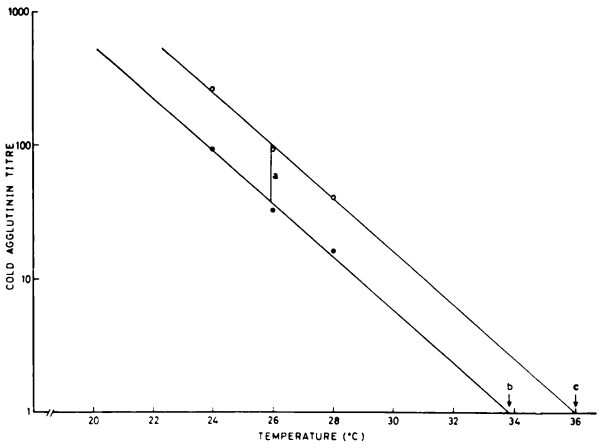

Fig. 2.—Cold agglutinin titres in semilogarithmic plot at 24, 26, and 28°C before (○–○) and after (●–●) treatment. Vertical line (a) indicates decrease in titre to 37 per cent of the pretreatment value. Arrows c and b indicate temperature at titre one, i.e., undiluted plasma. Difference between c and b is decrease in thermal amplitude, i.e., 2.2°C (Patient IX—L.C.).

Results

At present, after the treatment period, none of the patients suffer from Raynaud phenomena or hemoglobinuria, and the two male patients have been able to work outdoors during the winter.

Patient IV—A.J. has been unwilling to take the chlorambucil tablets from 1967, because of dyspepsia. Up until now this has not resulted in any increase in her IgM concentration or C.A.T.

Patient IX—L.C. was initially treated with cyclophosphamide for a period of four months in 1966, resulting in a decrease in the number of leucocytes and the C.A.T. This treatment had to be discontinued because of loss of hair and dyspepsia.

None of the patients developed leucopenia or thrombocytopenia. The effect of the treatment as measured by the laboratory data is shown in the Table.

In two patients (IV—A.J., and XII—E.J.) the hemoglobin concentration increased to within the normal range, and some increase was recorded in the

Table 1.—Laboratory Data Before and After Treatment with Chlorambucil

Patient			Serum–IgM Concentration* (Gm./L.)	Cold Agglutinin Titre in Per Cent of Initial Titre†	Thermal Amplitude Decrease (°C)	Extrapolated Values (°C)	Hemoglobin (Gm./L.)
IV—A.J.	January	1962	7.2	100	3.3	35.6	115
	June	1968	1.0	17		32.3	135
IX—L.C.	March	1966	6.6	100	2.2	36.0	90
	March	1968	1.8	37		33.8	100
X—G.H.	April	1967	8.2	100	2.6	29.9	110
	March	1968	1.3	14		27.3	125
XII—E.J.	March	1968	13.2	100	7.2	34.8	105
	January	1969	4.7	3		27.6	137

* Normal range 0.11–1.23 Gm./L.[13]

† Calculated (see text) from titres obtained at different temperatures.

two others. A considerable decrease in the IgM concentration occurred, and in two cases (IV—A.J., and X—G.H.) normal values were obtained after treatment during three years and one year, respectively. The reduction was most prenounced during the first six months. The C.A.T. decreased concomitantly, resulting in a reduction in the thermal amplitude of between two and seven degrees centigrade.

The decrease in the amount of IgM globulin and cold agglutinin in the sera was also reflected in loss of intensity of the M components seen by agargel electrophoresis and immunoelectrophoresis, although these methods did not allow quantifying.

Discussion

The C.A.S. is a rare condition. At present, thirteen patients out of 4.5 million inhabitants in Denmark are known to suffer from the disease.[9] Most often it runs a benign course. However, the symptoms induced on exposure to the cold are unpleasant and invalidating,[10] and death caused by renal[11] or hepatic[8,11] insufficiency has been reported.

The treatment with chlorambucil is gratifying, since good results were obtained both from the point of view of the patients and the laboratory records. The only side effect of the treatment has been the moderate dyspepsia in patient IV, A.J.

The extrapolated values for the thermal amplitude given in the Table refer to in vitro conditions, where 250× less red cells are used than are normally present in whole blood. However, it seems fair to assume that the decrease in the thermal amplitude of cold agglutinins in the patient as reflected in a decreased susceptibility to the cold, is of a similar size as the one calculated from the titres.

The reason for the delayed effect of the treatment is the rather slow or mild action of chlorambucil on the cold agglutinin-producing lymphocytes combined with the half-life of 5–10 days for cold agglutinins.[12]

Chlorambucil reduced the amount of cold agglutinins in the patients, whether given continously or in periods. From the present limited study one cannot judge which schedule is preferable. In one patient, cyclophosphamide had the same effect, but the treatment had to be discontinued because of side effects.

It is essential to treat and to control the patients for long periods or even for a lifetime.

Summary

Four patients aged 62 to 78 years with the cold agglutinin syndrome have been treated intermittently or continuously with chlorambucil for one to seven years. This resulted in a decreased susceptibility to the cold so that Raynaud phenomena and hemoglobinuria were avoided in the winter. The hemoglobin value increased, the concentration of IgM-globulin in serum was nearly normalized, and the cold agglutinin titre decreased by a factor 3–30. The thermal amplitude was lowered by 2.2–7.2°C.

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