BRIEF REPORT

Defective Synthesis of IgM Antibodies in Macroglobulinemia

By Neal C. Pitts and Frederic C. McDuffie

Since Waldenstrom's Macroglobulinemia was first described in 1944, it has become apparent that one of its frequent clinical manifestations is an increased susceptibility to infection. Several reports have also documented the fact that antibody response is impaired, but no attempt has been made to distinguish between impairment of IgG and of IgM antibody formation. The fact that the rate of infection is higher in multiple myeloma than in macroglobulinemia suggested to us the possibility that this finding might be due to an isolated deficiency of a perhaps physiologically less important immunoglobulin, IgM. The following report suggests that the IgM response to antigens is in fact impaired in macroglobulinemia.

MATERIALS AND METHODS

Antibody response to antigenic stimulation was measured in four patients with macroglobulinemia proved by bone marrow examination, electrophoresis, ultracentrifugation, and immunodiffusion; it was also measured in 27 controls. The antigens used were Brucellin (Merck Sharp & Dohme) and boiled sheep erythrocyte stroma. Antibody to Brucella was measured by the test-tube agglutination of whole killed organisms. Penicillamine, 0.1M, was added to one row of each series of serum dilutions to abolish the activity of IgM antibodies. Agglutination was completely abolished in nearly all sera by such treatment, and sucrose density gradient ultracentrifugation revealed all agglutinating activity to be present in the bottom fractions. The titers of eight sera were not completely abolished by penicillamine, and density gradient ultracentrifugation revealed the presence of agglutinating activity in both 19S and 7S fractions. Neither the whole sera, 7S fractions, nor IgG globulin prepared by chromatography on DEAE-cellulose showed any enhancement of agglutination by anti-IgG Coombs' serum so that it was not possible to distinguish between IgA and IgG antibodies in whole sera by the antiglobulin method.

IgM antibodies to sheep erythrocyte stroma also proved to be sensitive to 0.1M penicillamine but IgG antibodies could be specifically determined after penicillamine treatment by their ability to agglutinate sheep cells after addition of anti-IgG Coombs' reagent. All titers were recorded as the logarithms to the base 10 of the reciprocal of the highest dilution of serum showing 1+ or greater agglutination.

RESULTS

The IgM antibody response to an intensive schedule of immunization with sheep erythrocyte stroma is shown in Figure 1. All control subjects had

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This investigation was supported in part by Training Grant AM-5332 and Research Grant A-2074 from the National Institutes of Health, Public Health Service.

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Fig. 1.—Immune response, as IgM titer, to sheep cell stroma in 4 patients with macroglobulinemia (broken line) and 13 control subjects (solid line). Lines represent means; arrows show times of injection; horizontal bars indicate one SD from normal mean.

Fig. 2.—Immune response, as IgG titer, to sheep cell stroma in 4 patients with macroglobulinemia (1, 2, 3, and 4 indicate case number) and 13 control subjects (solid line).

responded by the third week (1 week after the second injection of antigen) with a log titer of at least 1.0, and the mean log response was 1.4. In striking contrast, none of the macroglobulinemic patients produced any measurable IgM antibody to sheep erythrocyte stroma at either the third or the eighth week.

The IgG antibody responses to sheep erythrocyte stroma are shown in Figure 2. All the control subjects had some IgG anti-sheep erythrocyte stroma in their
Fig. 3.—Immune response, as IgM titer, to Brucellin in 4 patients with macroglobulinemia and 13 control subjects (solid line).

sera prior to immunization. In spite of this, the mean increase in log titer at 3 weeks was only 0.5 but all subjects showed some increase. Similarly, the sera of all four patients contained IgG antibody prior to immunization and, although the responses were somewhat lower than those of the control group, the difference does not appear to be significant when one considers the lower preimmunization titers.

The IgM antibody response to an intensive course of immunization with Brucellin is shown in Figure 3. All the control subjects responded by the third week, with a log titer of at least 1 and a mean log response of 1.6. In contrast to their response to sheep erythrocyte stroma, three of the four macroglobulinemic patients responded to Brucellin by producing specific antibody identified as IgM in each case. In one patient (case 2) the antibody disappeared rapidly from the serum and could not be detected at 8 weeks.

The patients were reimmunized with the same antigen after they had been treated with chlorambucil for a period of 4 weeks. Two of the patients who had previously failed to respond produced measurable titers of IgM antibody to sheep cell stroma. The responses to Brucellin were essentially unchanged. One patient who failed to produce IgM antibody before or after receiving chlorambucil eventually died of peritonitis.

**DISCUSSION**

The results of the present study indicate that patients with macroglobulinemia have an impairment of IgM antibody synthesis that is more readily demonstrated with relatively weak antigens, such as sheep cell stroma, than with
a more potent antigen such as Brucellin. We do not know at present what the physiologic significance of this impairment may be. Fahey and associates found that in patients with macroglobulinemia, the total antibody response to four antigens was deficient and suggested that the defect might be related to the higher-than-normal incidence of infections in such patients (incidence about one third of that in patients with myeloma). Since the level of normal IgG in myeloma is probably depressed more than that of IgM, the lower infection rate in macroglobulinemia may reflect the less important role played by IgM in resistance to bacterial infection. The human body contains about 25 times more IgG than IgM and only about 25% of the IgM is extravascular as opposed to 60% of the IgG. There is, however, little data at the moment on the relative roles of these two immunoglobulins in bacterial resistance in vivo.

Why production of IgM antibodies should be specifically depressed in macroglobulinemia is not clear since synthesis of normal IgM does not depend on the serum concentration but on the level of antigenic stimulation. Furthermore, both normal and pathologic IgM are catabolized at a normal rate by patients with macroglobulinemia. The answer to this question must await the accumulation of more data concerning the production of IgM antibodies in normal and pathologic states.

**SUMMARY**

Four patients with macroglobulinemia demonstrated an impaired ability to produce IgM antibody when stimulated with a relatively weak antigen, sheep cell stroma, but not with a more potent antigen, Brucellin. The explanation of this defect is unknown. It may be in part the cause of the greater-than-normal infection rate seen in patients with macroglobulinemia.

**SUMMARIO IN INTERLINGUA**

Quatro patientes con macroglobulinemia manifestava un defective capacitate de producer anticorpore IgM quando stimulate con le relativemente debile antigeno, stroma de cellulas ovine, sed non quando stimulate con le plus forte antigeno, Brucellina. Le explication de iste defecto non es cognoscite. Il pare possibile que illo es le causa del cifras de infection plus alte que normal in patientes con macroglobulinemia.

**ACKNOWLEDGMENTS**

We thank Miss Sarah Dyre for her excellent technical assistance in some of this work.

**REFERENCES**

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