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Immunoglobulin G and Immunoglobulin M Antibody Responses of Patients with Malignancies to the O Antigens of Bacteria Causing Bacteremia

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Malignancy may be associated with impairment of the immune system. In children with acute leukemia, an impaired immunoglobulin M (IgM) antibody response to poliovirus was documented previously. It was of interest, therefore, to determine the immunoclass of antibodies produced against the O antigens of bacteria causing bacteremia in patients with leukemia and other malignancies. For control purposes, parallel studies were carried out in patients without malignancies but with infections caused by gram-negative bacteria. The patients with malignancies were adults, and those without malignancies were children. The serum specimens were selected from patients mounting an antibody response. IgG and IgM antibodies were identified by mercaptoethanol reduction and chromatography. Antibody titers against the O antigens of enteric bacteria were determined by the hemagglutination procedure. Antibodies of both IgM and IgG immunoclasses were produced by all but 1 of 16 patients with leukemia and by all but 1 of 12 subjects with other malignancies. Thus, a specific IgM immune deficiency in adult patients with leukemia or other malignancies complicated by bacteremia was not present; however, the magnitude of the antibody response of the patients with leukemia was less than that of the subjects with other malignancies, with the median antibody titers of the former being 320 and those of the latter being 2,560.

Malignancies and the associated cancer therapy may cause immunological abnormalities which, at least in part, may be responsible for the occurrence of serious complicating infections (2, 4, 5). Thus, cellular immunity may be impaired in Hodgkin's disease, and humoral immunity may be impaired in leukemia. So far as the latter is concerned, Bosu et al. (1) and Ogra et al. (11) observed the failure of children with acute lymphocytic leukemia to mount an immunoglobulin M (IgM) antibody response to inactivated poliovirus vaccine; this abnormality persisted even during remission. Shaw et al. (14) reported that patients with chronic leukemia, both individually and as a group, responded less effectively to immunization with typhoid, influenza, mumps, and diphtheria vaccines than did control subjects. Similarly, patients with leukemia and other malignancies of the reticuloendothelial system produced antibodies to the O antigens of bacteria causing bloodstream infection less frequently than did patients with solid tumors (9).

Treatment of leukemia is responsible, in part at least, for some of these immunological abnormalities. Thus, the serum of 33 children with acute lymphoblastic leukemia exhibited decreased opsonic activity against *Pseudomonas* after induction of remission but not before chemotherapy (17). In seeming contrast, the antibody response to influenza virus was normal in children with acute lymphoblastic leukemia during chemotherapy, but surprisingly, the antibody titers were abnormally high after discontinuation of treatment; a suppressor cell abnormality may account for these findings (6).

In view of the fact that an impairment of the IgM antibody response was documented in children with acute lymphocytic leukemia (1, 11), it was of interest to determine whether a similar abnormality exists in the immune response of adult patients with various forms of leukemia to the O antigens of bacteria causing bloodstream infection.

MATERIALS AND METHODS

For the study of the immunoclass of the antibodies produced by patients with leukemia and other malignancies to the O antigens of bacteria causing bacteremia, sera and antigens, kept frozen at −20°C, were available from previous studies (9, 15). For additional controls, sera available from previous investigations from subjects without malignant diseases but with

salmonellosis, shigellosis, pyelonephritis, bacterial peritonitis, or *Pseudomonas* infection complicating cystic fibrosis were employed (3, 7, 8, 10). The antibody response to the O antigens of the patients' own strains was measured by the passive hemagglutination test, as described previously (8, 10).

Determination of the presence of IgM was performed by mercaptoethanol reduction as follows (16). Serum in amounts of 0.1 ml was mixed with an equal volume of 0.2 M mercaptoethanol; the mixtures were incubated in a water bath at 37°C for 1 h. For control purposes, serum was prepared in the same manner with 0.1 ml of phosphate-buffered saline in place of mercaptoethanol. The reduced and unreduced sera were assayed in parallel immediately after incubation by the hemagglutination procedure.

In selected cases, 50 to 100 μl of serum was fractionated by chromatography on Bio-Gel A-5M (Bio-Rad Laboratories, Richmond, Calif.), as described by Pyndiah et al. (13). Analysis of the fractions was performed by the immunodiffusion method of Ouchterlony (12), using anti-human IgG- and IgM-specific antisera (Meloy Laboratories, Springfield, Va.). Fractions were assayed also for antibody activity by the hemagglutination method.

TABLE 1. *Immunoclass of antibodies produced against O antigens of bacteria causing bacteremia in patients with malignancies and other diseases*

Disease	Total no. of subjects	Immunoglobulin class of antibodies		
		IgM and IgG	IgM only	IgG only
Leukemia	16	15	0	1
Acute lymphocytic	3	3	0	0
Acute myelogenous	9	8	0	1
Chronic myelogenous	4	4	0	0
Other malignancies	12	11	1	0
Other diseases	23	23	0	0
Peritonitis	6	6	0	0
Pyelonephritis	6	6	0	0
Enteric disease	6	6	0	0
Cystic fibrosis with *Pseudomonas* infection	5	5	0	0

RESULTS AND DISCUSSION

In view of the fact that a deficiency in the production of poliovirus antibodies of the IgM class was documented in children with leukemia (1, 11), it was of interest to determine whether a similar immunological impairment exists in patients with leukemia or other malignancies regarding the immunoclass of antibodies produced against the O antigens of gram-negative bacteria causing bacteremia. For control purposes, the immunoclass of antibodies produced against the O antigens of gram-negative bacteria associated with nonbacteremic infections was studied in parallel. The patients with leukemia or other malignancies were adults, and those without malignancies were children. The majority of serum samples from the patients with malignancies were obtained within 3 weeks after the procurement of the positive blood cultures. The results of this study are shown in Table 1. Of 16 patients with leukemia, 15 produced antibodies of both the IgM and IgG classes. In one of the patients with acute myelogenous leukemia, a marked further increase in the titers of both IgG and IgM antibodies was demonstrated in a specimen taken 1 week later. In another patient with this disease who mounted IgM and IgG antibody responses, a further increase in the titer of IgG antibodies alone was documented in the second blood sample taken 3 weeks after the first specimen. In the only patient with an exclusive IgG antibody response, the single serum specimen available was obtained 6 weeks after the blood for culture was taken; therefore, it is conceivable that the early IgM immune response escaped detection. In one patient with acute lymphocytic leukemia, three sequential serum specimens were available; only IgM antibodies were detected in the first specimen, both IgM and IgG antibodies were detected in the second specimen, and only IgG antibodies were detected in the third specimen. Both IgM and IgG antibodies were produced by 11 of 12 patients with other malignancies (9 of 10 subjects with solid tumors and both patients with non-Hodgkin's lymphoma; only 1 subject produced IgM antibodies alone). So far as the quantitative aspects of the immune response are concerned, the antibody titers of the patients with leukemia ranged from 20 to 5,120 (median, 320), and those of the subjects with other malignancies ranged from 320 to 20,480 (median, 2,560), indicating a quantitative impairment of the humoral immunity response of the former group compared with the latter. This finding is in accord with the previously reported observation (9) that only 30% of patients with leukemia and related malignancies but 61% of subjects with solid tumors mounted a specific antibody response to the O antigens of gram-negative bacteria causing bacteremia. Table 1 also shows that all 23 patients without malignancies but with a variety of gram-negative infections produced antibodies of both immunoclasses. The results obtained with mercaptoethanol-reduced and unreduced sera were confirmed with samples obtained by chromatography from all three patients with acute lymphocytic leukemia and from two patients each with either acute or chronic myelogenous leukemia.

From these observations it is evident that a specific IgM antibody response was identified in almost all patients with leukemia complicated by bacteremia who did mount a humoral immune response. Previously, Bosu et al. (1) and Ogra et al. (11) documented the failure of children with acute lymphocytic leukemia to mount an IgM antibody response to inactivated poliovirus vaccine. It remains for future investigations to determine whether these differences are due to differences in the ages of the subjects, the type of disease, the nature of the antigen (protein versus polysaccharide), the amounts of the antigen, differences in the route of immunization (subcutaneous injection versus bacteremia), or the effects of chemotherapy alone or in combination with the above. It should be emphasized, however, that as reported previously (9), patients with leukemia and other reticuloendothelial system malignancies responded less well as a group to the O antigens of bacteria causing bloodstream infection than did patients with solid tumors, indicating a relative immunodeficiency in the former subjects.

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