Immune abnormalities in myelodysplastic syndromes

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SUMMARY The immune states of 52 patients with myelodysplastic syndromes classified according to the FAB criteria were studied. Serum electrophoresis and immunoelectrophoresis, direct Coombs test, and tests for organ and non-organ specific antibodies were performed. Twenty six patients had immunoglobulin abnormalities: six (11.5%) had monoclonal gammopathy; 17 (32.6%) had polyclonal increases in serum immunoglobulin; while in three (5.8%) immunoglobulin concentrations were decreased. The distribution of immunoglobulin abnormalities among the five myelodysplastic syndrome subtypes was fairly uniform. Results of direct Coombs test were negative in all cases. Organ specific antibodies were not detected in any of the patients tested, although two patients were found positive for antinuclear antibodies. The presence of immunoglobulin abnormalities indicates an involvement of the lymphoplasmatic system in myelodysplastic syndromes.

Immunological aberrations have been reported in various myelopathies.¹⁻⁵ Monoclonal gammopathy or polyclonal increases in serum immunoglobulin concentrations have recently been reported in chronic myelomonocytic leukaemia,^{6,7} but little is known about the immune state in the other types of myelodysplastic syndromes. We report the immunological findings on 52 patients with myelodysplastic syndromes classified according to the FAB proposed criteria.⁸

Material and methods

PATIENTS

Fifty two patients with myelodysplastic syndromes were studied prospectively from January 1982 to June 1984 before treatment with blood transfusions. They were 39 men with a median age of 70.5 years (range 50-85 years) and 13 women with a median age 71 years (range 53-82 years). Table 1 shows the ages and sex ratios of patients with the various types of myelodysplastic syndromes. In none of the patients studied were Auer rods found at presentation.

IMMUNOLOGICAL TESTS

Direct antiglobulin Coombs test, protein serum electrophoresis, and immunoelectrophoresis were carried out using standard techniques. Whenever necessary, immunofixation⁹ was used to identify light chain monoclonal immunoglobulins. All serum samples were also tested for cryoglobulins.

Serum immunoglobulin concentrations were measured using commercially available immunodiffusion plates (Meloy Laboratories Inc). Normal geometric mean values (in g/l) were as follows: IgG 11.4 (range 7.0-18.5); IgA 1.8 (range 0.78-4.4); and IgM 1.0 (range 0.29-3.5). Values that differed by more than two standard deviations from the normal mean values were considered abnormal.

An indirect immunofluorescence test on cryostat sections was used to detect antinuclear,¹⁰ anti-mitochondrial, anti-smooth muscle,¹¹ microsomal thyroid,¹² and parietal cell antibodies.¹³ Titres higher than 1/40 for antinuclear antibody, 1/20 for anti-mitochondrial antibody and anti-smooth muscle antibody, and 1/10 for thyroid microsomal antibody were considered positive. Serum samples for detecting parietal cell antibody were used undiluted. Antibodies to thyroglobulin were detected by means of passive haemagglutination.¹⁴ Antibodies to native DNA were detected by the radioimmunometric Farr (ammonium sulphate precipitation) method using the Amersham anti-DNA kit.

Table 1 *Myelodysplastic syndromes: subgroups and sexes and ages of patients*

Subtype	No of patients	% of total	Sex ratio M:F	Age (yr) Median (range)
Refractory anaemia	17	32.7	11:6	69 (54-82)
Refractory anaemia with ringed sideroblasts	10	19.2	4:6	72.5 (53-85)
Refractory anaemia with excess blasts	7	13.4	7:0	70 (65-77)
Chronic myelomonocytic leukaemia	7	13.4	6:1	72 (60-77)
Refractory anaemia with excess blasts in transformation	11	21.1	11:0	71 (50-84)

Table 2 *Type of monoclonal gammopathy and serum immunoglobulin concentrations in six patients with a monoclonal component*

Monoclonal component	Serum immunoglobulin concentration (g/l)		
	IgG	IgA	IgM
Refractory anaemia (n = 3)			
IgG/k + B-J	13.9	3.9	1.18
IgG/λ	8.3	3.15	0.65
IgM/κ	9.6	1.05	4.8
Refractory anaemia with excess blasts (n = 1)			
IgM/κ (cryoglob)	17.8	3.68	9.7
Refractory anaemia with excess blasts in transformation (n = 2)			
IgG/κ	21.12	1.58	1.35
IgG/κ	24.00	6.00	2.3

B-J = Bence-Jones proteinuria.

Cryoglob = cryoglobulinaemia.

Results

IMMUNOGLOBULINS

Abnormalities were found in half of the patients. Six patients (11.5%) had a monoclonal serum component: of these patients, three had refractory anaemia, one refractory anaemia with excess blasts, and two refractory anaemia with excess blasts in transformation. One of the six patients with a monoclonal component (IgG/κ) had Bence-Jones proteinuria (0.9 g/24h) and another patient (IgM/κ) had detectable cryoglobulinaemia. Table 2 shows the type of monoclonal component and the serum immunoglobulin concentrations of these patients. Only three of the six patients had concentrations of

the monoclonal immunoglobulin above the normal limits, while no suppression of the non-M-component immunoglobulins was found (Table 2).

No increase in the number of plasma cells (>5%) was seen in the bone marrow smears of any patients. The median age of the six patients with associated monoclonal components (median 70.5 years, range 59-85 years) did not differ from the ages of the rest of the patients (median 70.5 years, range 50-84 years).

Seventeen patients (32.6%) had polyclonal immunoglobulin increases (three IgG, six IgA, one IgM; six IgG and IgA; and one IgG, IgA, and IgM), while in three (5.8%) immunoglobulin concentrations were decreased (two IgG and one IgA). The

Table 3 *Number of patients with increased or decreased concentrations of polyclonal immunoglobulins increase or decreased levels according to myelodysplastic syndrome subgroup*

Immunoglobulins	Refractory anaemia (n = 17)	Refractory anaemia with ringed sideroblasts (n = 10)	Refractory anaemia with excess blasts (n = 7)	Chronic myelomonocytic leukaemia (n = 7)	Refractory anaemia with excess blasts in transformation (n = 11)
Increased concentrations					
IgG	2	2	2	4	0
IgA	4	3	1	3	2
IgM	0	1	1	0	0
Decreased concentrations					
IgG	1	0	0	1	0
IgA	0	0	0	0	1
IgM	0	0	0	0	0

distribution of the polyclonal immunoglobulin increase or decrease among the five subgroups of myelodysplastic syndrome was fairly uniform (Table 3).

COOMBS TEST AUTOANTIBODIES

Results of direct antiglobulin Coombs test were negative in all cases.

Organ specific autoantibodies were not found in any of the patients tested. In our group of normal controls older than 60 years the prevalence of these antibodies was 29%. The prevalence of non-organ specific autoantibodies was low in our group of patients. Only two were positive for antinuclear antibody, with relatively high titres, but results of tests for DNA antibodies were negative in these and in all other patients. The prevalence of non-organ specific antibodies in the normal controls was 22%.

Discussion

A considerable range of immune disorders have been reported in various myelopathies. Among them, myelofibrosis has a high frequency of immune abnormalities such as the presence of immune complexes,² polyclonal increases in serum immunoglobulin concentrations or monoclonal gammopathy, autoimmune antibodies, persistent rheumatoid factor, and positive Coombs test results.⁴ A number of immunological aberrations have also been described in erythroleukaemia,³ and monoclonal gammopathy has been reported in acute lymphoblastic leukaemia¹ and chronic myelocytic and acute myelocytic leukaemia.⁵

Barnard *et al*⁶ reported a case of chronic myelomonocytic leukaemia with monoclonal gammopathy, and Solal-Celigny *et al*⁷ found several immune abnormalities in a large series of patients with chronic myelomonocytic leukaemia.

In the present study, which aimed to determine the incidence of immunological aberrations in the various types of myelodysplastic syndrome, many abnormalities were found in all types. Monoclonal gammopathy was found in six of 52 patients (11.5%). As the incidence of monoclonal gammopathy in patients over the age of 70 is about 3%,¹⁵⁻¹⁷ the findings in our patients with myelodysplastic syndromes do not seem to be due to mere coincidence or to the patients' ages.

The exact significance of monoclonal gammopathy in myelodysplastic syndromes is not known, although there are several theories. The presence of an immunoglobulin monoclonal component indicates a B cell involvement in these patients. This association may represent the neoplastic transformation of a single progenitor capable of differen-

tiation into lymphoid or myeloid cells, as in chronic myelocytic leukaemia.¹⁸ This hypothesis is further supported by several reports describing a frequent coexistence of non-lymphoblastic leukaemia or myelodysplastic syndromes, even in untreated patients with multiple myeloma.¹⁹⁻²¹ Alternatively, monoclonal gammopathy in myelodysplastic syndromes may represent an antibody response against some antigen of the malignant proliferation, as in solid neoplasms.²²

The polyclonal increase in serum immunoglobulins is a frequent finding in all types of myelodysplastic syndrome, especially in chronic myelomonocytic leukaemia. It could result from non-specific stimulation of B lymphocytes. Monocytes, which are often increased in myelodysplastic syndromes,²³ secrete biologically active molecules which regulate the growth and differentiation of the lymphocytes.²⁴ Thus monocytic proliferation may be responsible, at least in some cases, for polyclonal B lymphocyte activation and an increase of immunoglobulin in myelodysplastic syndromes. Alternatively, hyperglobulinaemia in such patients may represent an immune reaction to antigens encountered during infections. Infections often occur in patients with myelodysplastic syndromes, and as Osserman and Takatsuki²⁵ suggested, protracted antigenic stimulation may give rise to a polyclonal reaction, which later assumes a monoclonal form.

Our results show that immunoglobulin abnormalities are common in myelodysplastic syndromes. The prognostic importance of this finding, however, remains uncertain and further studies are necessary.

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