Primary immunoglobulin deficiency and haematological disorders

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Summary

Nine patients with immunoglobulin deficiency and various haematological disorders are presented. In all patients, recurrent infections had antedated the onset of the haematological disorder but, in most, the possibility of primary immunodeficiency had not been considered until after the haematological diagnosis had been established. The recognition of immunodeficiency is important since such patients may require steroids, immunosuppressive therapy or splenectomy. Gammaglobulin would appear to be the appropriate therapy in this situation. Infections were reduced in all 6 patients so treated.

KEY WORDS: immunodeficiency, haematological disease, auto-immunity.

Introduction

Low serum immunoglobulin concentrations may occur in a variety of haematological disorders, but the significance of this finding is not always recognised. In non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, immunodeficiency is believed to be secondary in most cases. In other disorders, however, immunodeficiency may be a pathogenetic factor. Patients with late onset hypogammaglobulinaemia or IgA deficiency have an increased frequency of auto-immune disease, including haematological disorders such as auto-immune haemolytic anaemia (AIHA), idiopathic thrombocytopenic purpura (ITP) and pernicious anaemia (PA) (Asherson and Webster, 1980). Conversely, patients with AIHA have a high prevalence of low serum immunoglobulin concentrations (Blajchman *et al.*,

1969). We have been impressed by the benefit which can be obtained by careful assessment and management of the immune defect in some patients, particularly those in whom there is a history of abnormal susceptibility to infection.

We describe a group of patients with haematological disease and immunoglobulin deficiency, all of whom had recurrent infections before the onset of the haematological disease. Gammaglobulin therapy was effective in all 6 patients treated.

The recognition and treatment of immunoglobulin deficiency is particularly important in such patients since steroids, immunosuppressive therapy and splenectomy may exacerbate the predisposition to infection.

Materials and methods

Patients

All 9 patients were seen by the Department of Haematology and selected by virtue of either: (1) the development of haematological disorders complicating recognised immunodeficiency or; (2) the presence of immunoglobulin deficiency and symptomatic immunodeficiency in patients with haematological disorders.

At the time of investigation none of the patients was receiving steroid, immunosuppressive or gammaglobulin therapy.

Methods

Serum immunoglobulins were measured by radial immunodiffusion (Oxford). Antinuclear antibodies (ANA), smooth muscle antibodies (ASM), mitochondrial antibodies (AMC), parietal cell antibodies (APC) and thyroid microsomal antibodies (ATM) were measured by indirect immunofluorescence (Hawkins *et al.*, 1979) and thyroglobulin antibodies (ATG) by passive haemagglutination (Thymune,

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Burroughs-Wellcome). Cold reactive lymphocytotoxic antibodies (LCA) were measured by a complement-dependent cytotoxicity method (Zilko *et al.*, 1979). In one patient, anti-IgA antibodies were demonstrated by Dr J. V. Wells of the Kolling Institute, Royal North Shore Hospital, New South Wales. Routine haematological methods described by Dacie and Lewis (1975) were used.

Six of the 9 patients underwent additional immunological assessment. The methods used for immune function testing and criteria for symptomatic immunodeficiency will be given elsewhere (French *et al.*).

Results

The clinical and laboratory findings in the 9 patients are summarised in Tables 1 and 2. The cases

were composed of 4 cases of AIHA, one of chronic idiopathic neutropaenia, one of ITP, 2 of PA and one of non-Hodgkin's lymphoma.

Autoimmune haemolytic anaemia

Warm reactive IgG erythrocyte autoantibodies were present in 3 of the 4 patients with AIHA. Cold reactive IgM erythrocyte autoantibodies were demonstrated repeatedly over a 15-year period in patient no. 4. Although the highest titre of serum cold agglutinins only reached a maximum of 1/256, it was shown on several occasions that the direct Coombs' test was only positive at 4°C and that the indirect Coombs' test became negative following absorption

TABLE 1. Clinical details

Patient	Sex	Age	Haematological disorder	History of antecedent infections	Other features of primary immunoglobulin deficiency	Splenectomy	Gammaglobulin therapy
1	F	23	AIHA	Recurrent bronchitis, sinusitis and otitis media	—	+	+
2	F	66	AIHA	Recurrent respiratory infections	Asthma, allergic rhinitis		+
3	F	37	AIHA	Recurrent respiratory infections. Bronchiectasis	Systemic lupus erythematosus. Hypothyroidism		
4	F	73	AIHA	Recurrent bronchitis	Epilepsy		
5	F	56	Chronic idiopathic neutropaenia	Recurrent respiratory infections. Bronchiectasis	—	+	+
6	M	33	ITP	Recurrent skin furunculosis	—	+	
7	M	70	PA	Recurrent bronchitis and sinusitis	Coeliac disease, giardiasis		+
8	F	38	PA	Chronic sinusitis	Coeliac disease, bronchial carcinoma		+
9	F	34	Lymphocytic lymphoma	Recurrent bronchitis and sinusitis	—	+	+

AIHA = autoimmune haemolytic anaemia; ITP = idiopathic thrombocytopenic purpura; PA = pernicious anaemia.

TABLE 2. Laboratory findings

Patient	Serum immunoglobulins (g/l)			Autoantibodies						
	IgG	IgM	IgA	ANA	ASM	AMC	APC	ATM	ATG	LCA
1	4.7	1.7	0.04	—	—	—	—	—	—	—
2	7.4	5.6	0.24	+	+	—	—	+	—	+
3	13.6	0.1	0.3	+	—	—	—	+	+	+
4	6.8	1.0	0.2	—	—	—	—	—	—	—
5	1.9	0.32	0.04	—	—	—	—	—	—	—
6	15.0	3.0	0.3	—	—	—	—	ND	ND	ND
7	3.1	0.1	0.04	—	—	—	—	—	—	—
8	1.7	<0.1	0.04	—	—	—	—	—	—	—
9	2.2	1.4	0.04	—	—	—	—	—	—	ND

ND = not done; + = present; — = absent.

of serum cold agglutinins. The antibody showed i-antigen specificity.

Haemolysis was controlled by steroids in all patients except no. 1 and this treatment continues in patients 2 and 3. The latter patient also had systemic lupus erythematosus (SLE). Patient 4 died from unknown causes shortly after discontinuing steroid therapy. Splenectomy was eventually necessary in patient 1, and no further therapy for AIHA has since been required.

In all 4 patients, there was an antecedent history of recurrent sino-pulmonary infections. Serum immunoglobulins were not measured until 12 years after the onset of AIHA in patient 2. In patients 3 and 4, immunoglobulin deficiency was detected at the onset of disease. Gammaglobulin therapy was beneficial in patients 1 and 2, but was discontinued in the latter because of febrile myalgia following one of the injections. Serum antibodies to IgA were demonstrated at a titre of 1/8.

Chronic idiopathic neutropaenia

Chronic idiopathic neutropaenia occurred in a female (no. 5) with a 26-year history of recurrent sino-pulmonary infections and bronchiectasis. A neutrophil count of $0.9 \times 10^9/\text{litre}$ was found following a respiratory infection. One year earlier, the count had been normal. Splenomegaly had been noted for the past 10 years. Although splenectomy resulted in a return to normal of the neutrophil count, sino-pulmonary infections became more severe. There was marked improvement following the introduction of gammaglobulin therapy.

Idiopathic thrombocytopaenia

Poor haemostasis following surgical drainage of a skin abscess was due to ITP in patient 6. A history of recurrent skin furunculosis dating from childhood, prompted investigation for impaired humoral immunity and partial IgA deficiency was discovered. Thrombocytopaenia resolved after splenectomy. On review 6 years later, ITP was in continued remission, serum IgA was 0.3 g/litre, and so far he has been free of sino-pulmonary infection.

Pernicious anaemia

Pernicious anaemia in 2 patients was associated with coeliac disease and giardiasis in both. There was an antecedent history of sino-pulmonary infections in both, but in one patient, (no. 7), immunoglobulin deficiency was not considered and not found until 18 years after the diagnosis of PA. In both patients, sino-pulmonary infections improved after gammaglobulin therapy, which also appeared to benefit the diarrhoea. Shortly after the commencement of gamma-

globulin, a bronchial carcinoma was found in patient 8. Interestingly, delayed hypersensitivity to recall antigens and dinitrochlorobenzene was absent, and phytohaemagglutinin lymphocyte transformation decreased whereas they were previously normal. Death occurred despite chemotherapy and radiotherapy.

Lymphocytic lymphoma

In the single patient with lymphocytic lymphoma IgG and IgA deficiency were found on routine investigation. Recurrent sino-pulmonary infections over many years had preceded the onset of lymphoma. Regular gammaglobulin therapy was effective in reducing the frequency and severity of infections during her 4 years remission which continues to date. In view of the fact that the patient was splenectomised at diagnosis and had received intensive chemotherapy over a period of 15 months, the reduction in episodes of infection is notable.

Immunological findings

Various patterns of combined and isolated immunoglobulin deficiency were present (Table 2). Absolute or partial IgA deficiency was present in all. Serum IgG ranged from 1.9 g/litre to 14 g/litre and IgM from 0.1 g/litre to 5.6 g/litre. In the single patient with haemolytic anaemia and cold agglutinins (no. 2), the serum IgM concentration varied from 5.6 g/litre to 15.6 g/litre over a 4-year period. Peripheral blood T and B cells were present in all patients. In two, (nos. 2 and 3) there was lymphopenia associated with serum lymphocytotoxic antibodies.

Serum autoantibodies, other than anti-erythrocyte antibodies, were detected in only 2 patients, both of whom had more than one autoantibody (Table 2). Definite SLE was associated with increased serum DNA binding in one of these patients (no. 3). Parietal cell antibodies were not detected on repeated examinations of sera from both patients with PA.

Immune function tests

Titres of serum *E.coli* antibody (normal $> \frac{1}{8}$) and isohaemagglutinins (normal $> \frac{1}{8}$) were low in 5 of the 6 patients studied. Peak tetanus toxoid antibody titres (normal $> \frac{1}{160}$) were low in 3 patients. Two of these and one other has low peak *Salmonella typhi* H antibodies (normal $> \frac{1}{80}$).

Discussion

Nine patients presenting with various haematological diseases are described, all of whom had antecedent recurrent infections attributable to primary immunoglobulin deficiency. In only one patient was immunoglobulin deficiency identified before the

diagnosis of the haematological disease. The history of abnormal susceptibility to infection in all patients is interpreted as evidence for a primary immunoglobulin deficiency syndrome although most patients did not have hypogammaglobulinaemia. Some supporting evidence for an antibody deficiency syndrome is provided by the demonstration of low titres of *E. coli* antibodies and isohaemagglutinins and low antibody responses following immunisation in some patients. However, haematological disorders, particularly auto-immune cytopaenias are a complication of IgA deficiency (Sandler and Zlotnik, 1976) and other dysgammaglobulinaemias (Stoelinga, Van Muster and Sloof, 1969).

The interpretation of low serum immunoglobulins in patients receiving steroid or immunosuppressant therapy may be difficult and the effects of therapy may have been a factor in some of the patients described by Blajchman *et al.* (1969). This was not a factor in the patients described here. It is important to look for immunoglobulin deficiency before starting immunosuppressive or steroid therapy, particularly in patients with an increased susceptibility to infections.

The presence of primary immunoglobulin deficiency in patients with a variety of haematological diseases is of interest from 2 points of view. Firstly, it is possible that the underlying immunoglobulin deficiency may predispose to the haematological disorder. Secondly, the recognition of an associated immunodeficiency syndrome is important in further clinical management.

Several mechanisms whereby immunoglobulin deficiency may be implicated in the pathogenesis of autoimmune haemolytic disease have been suggested (Blajchman *et al.*, 1969; Zueler *et al.*, 1970; Amman and Hong, 1970). Pernicious anaemia, with or without giardiasis and coeliac disease, occurs in approximately 20% of patients with late onset hypogammaglobulinaemia (Hermans, Diaz-Buxo and Stobo, 1976). A search for immunoglobulin deficiency is, therefore, justified in PA, especially if there is a background of recurrent diarrhoea and infections. The absence of serum parietal cell antibodies is a feature of this variety of PA. Presumably, therefore, the autoantibody is not responsible for the atrophic gastritis in this and other forms of PA (Editorial, 1970).

Unlike AIHA, ITP and PA, chronic idiopathic neutropaenia is infrequently associated with primary immunoglobulin deficiency (Ng & Pranker, 1976; Webster *et al.*, 1981). It has been suggested that chronic idiopathic neutropaenia may be an autoimmune disease (Boxer *et al.*, 1975) and the cases of neutropaenia associated with late onset hypogammaglobulinaemia described by Webster *et al.* (1981) had autoantibodies to neutrophils. It is probable, there-

fore, that this is a further example of an autoimmune disease occurring with primary immunoglobulin deficiency.

Immunoglobulin deficiency in most patients with non-Hodgkin's lymphoma is secondary to the lymphoproliferative process. However, an increased incidence of lymphoproliferative disease has been reported in individuals with primary immunoglobulin deficiencies (WHO, 1979). A history of recurrent sinopulmonary infections before the onset of lymphoma in our patient suggests that the immunoglobulin deficiency was primary.

It is important to search for primary immunoglobulin deficiency in patients such as those described here. Patients with recurrent infections may be given the benefit of gammaglobulin. In the absence of symptomatic deficiency, careful follow-up is desirable. The increased susceptibility to infection due to primary immunoglobulin deficiency may be exacerbated by the use of immunosuppressants or by splenectomy (Eicher, 1979).

Finally, blood transfusion may be complicated by reactions possibly due to anti-IgA antibody (Vyas, Perkins and Fudenberg, 1968).

As illustrated by these cases, gammaglobulin therapy can be effective in partial and selective immunoglobulin deficiency as well as hypogammaglobulinaemia (Buckley, 1976; Koistinen, Heinkila and Leikola, 1978). The risk of reactions to therapy is probably not as great as once thought (Koistinen *et al.*, 1978), and only prevented one of our 6 patients from continuing treatment.

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