(3) Serum Protein Abnormalities

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The plasma protein is composed of innumerable numbers of protein constituents, having different biological activities. Plasma protein abnormalities are encountered in many different pathophysiological conditions, and thus careful investigation of plasma protein abnormalities is extremely useful for the diagnosis of various disease conditions.

Serum protein abnormalities are first screened by testing the serum total protein concentration and its electrophoretic separation. With the cellulose acetate electrophoretic separation of the serum proteins, serum protein abnormalities may be classified into many characteristic patterns shown in Table 1. Using immunoelectrophoretic and various immunochemical quantitations, the serum concentration of various protein constituents has become able to be measured. Thus, pathophysiological analysis of serum protein abnormalities could now be possible.

Immunoglobulins are now known to be made up of two kinds of different polypeptide subunits, light chains and heavy chains, linked by disulfide bonds. Five different classes of immunoglobulins are identified on the basis of non-crossreacting antigenic differences of the heavy chains: IgG, IgA, IgM, IgD and IgE. At least, 4 subclasses of IgG are known: IgG1, IgG2, IgG3 and IgG4. One of the most character-

Table 1. Classification of Serum Protein Abnormalities Based on Cellulose Acetate Electrophoretic Patterns (by Kawai, 1969)

I. Hypoproteinemic pattern
I-1. Malnutritional pattern
I-2. Protein-losing pattern of non-selective type
II. Nephrotic pattern (protein-losing pattern of selective type)
III. Diffuse acute hepato-degenerative pattern
VI. Cirrhotic pattern
V. Acute inflammatory and stress pattern
VI. Chronic inflammatory pattern
VII. Broad hypergammaglobulinemic pattern (polyclonal hypergammaglobulinemia)
VIII. M-proteinemic pattern (monoclonal gammopathy)
IX. Hyperalpha-2-globulinemic pattern (hyperlipidemic pattern)
X. Pregnancy pattern
XI. Defect dysproteinemias
XI-1. An-albuminemic pattern
XI-2. An-alpha-1-globulinemic pattern
XI-3. A-beta-globulinemic pattern
XI-4. Agammaglobulinemic pattern

istic properties related to immunoglobulins, being quite different from other serum proteins, is heterogeneity or polyclonicity. Therefore, serum immunoglobulin abnormalities may be divided mainly into 3 groups: polyclonal hypergammaglobulinemia, monoclonal gammopathy (M-proteinemia) and immunoglobulin deficiency. In addition, abnormal immunoglobulin molecules such as pyroglobulin and cryoglobulin are encountered in some cases.

Polyclonal hypergammaglobulinemia: Polyclonal hypergammaglobulinemia is characterized electrophoretically by broad increase of the serum gamma globulin fraction. In most cases, a marked increase of IgG is accompanied with significant increase of IgM and IgA. However, in some cases, one or two classes of the serum immunoglobulins may increase predominantly. IgE must be evaluated separately from the major classes of immunoglobulins, and it will be discussed later.

Among a total of 371 cases with polyclonal hypergammaglobulinemia (the serum gamma globulin fraction being more than 2 g/100 ml), 51% of the cases were associated with liver diseases, 15% with collagen diseases, 9% with infections, 6% with malignancies, 18% with other various conditions. Among the infectious diseases mentioned above, pulmonary infections are most commonly encountered with hypergammaglobulinemia.

Monoclonal gammopathy (M-proteinemia): M-protein (monoclonal immunoglobulin, or pathological immunoglobulin) is an abnormally homogeneous population of immunoglobulin molecules, and is characterized by (1) the formation of electrophoretically discrete protein band and (2) idiotypic immunochemical specificity of both the heavy and light chains.

The M-proteins which have been identified up to date include 11 types, as shown in Table 2. The frequency of M-proteinemia encountered clinically has been increasing in recent years, mainly because of a significant progress of analytical techniques. Among 253 cases of M-proteinemias experienced in the author's laboratories, only 30% of the cases are of malignant M-proteinemia which include myeloma, primary macroglobulinemia and heavy chain diseases. The other 70% of the cases are of essential M-proteinemia, which is further divided into 3 groups, as shown in Table 3.

Table 2. Various Types of M-Proteins

I. M-proteins composed of both H chain and L chain
A. IgG type
B. IgA type
C. IgM type
D. IgD type
E. IgE type
F. 7S IgM type
G. Half-molecule IgG type
II. M-proteins composed of immunoglobulin fragments
A. γ type
B. α type
C. μ type
D. Bence Jones protein

Immunoglobulin deficiency: In primary immunodeficiency diseases, the serum immunoglobulins show not only quantitative changes but also qualitative abnormalities.

Quantitatively, agammaglobulinemia, hypogammaglobulinemia and dysgammaglobulinemia are frequently encountered in primary immunodeficiencies. A- and hypo-gammaglobulinemias denote almost complete deficiency and significant decrease of all major classes

Table 3. Frequency of Various M-Proteinemias Encountered in the Author's Laboratory

A. Neoplastic M-proteinemias (primary-malignant)	75(30%)
1. Multiple myeloma (65 cases)	
2. Solitary myeloma (4 cases)	
3. Primary macroglobulinemia (6 cases)	
4. Heavy chain disease (none)	
B. Essential M-proteinemias	177(70%)
1. The first group (secondary-malignant) (14 cases)	
2. The second group (secondary-benign) (108 cases)	
3. The third group (primary-benign) (55 cases)	

The first group : diseases with primary reticular abnormalities.

The second group : diseases usually associated with polyclonal hypergammaglobulinemias.

The third group : diseases usually not related to reticular abnormalities

of the serum immunoglobulins. Agammaglobulinemia is found in the cases with infantile X-linked agammaglobulinemia ("Bruton's disease") and severe combined immunodeficiencies such as Swiss type agammaglobulinemia. In dysgammaglobulinemias, deficiency is limited to one or two major classes of immunoglobulins, and many different types of dysgammaglobulinemias have been reported. Among those types (Table 4), selective IgA deficiency has been most frequently encountered and has been best characterized. Ataxia telangiectasia is frequently associated with selective IgA deficiency, but IgA deficiency has been recognized even in some normal individuals. Hyper-IgE associated with primary cell-mediated immune deficiency occurs frequently in the cases with thymic hypoplasia (Di George syndrome), immunodeficiency with thrombocytopenia and eczema (Wiskott-Aldrich syndrome) and severe combined immunodeficiency, and it is important in understanding the regulatory mechanism of the thymus against IgE synthesis.

Qualitatively, many different abnormalities of the serum immunoglobulins are encountered almost constantly in primary immunoglobulin deficiencies. In normal individuals, the K/L ratio of the serum immunoglobulins show almost constant values. However, in general, the K/L ratio of whole serum in infants tend to be slightly smaller than those in neonates and adults. In hypogammaglobulinemic individuals,

Table 4. Classification and Frequency of Dysgammaglobulinemias

Classification		IgG	IgA	IgM	Frequency	
by Janeway	by Hobbs				by Hobbs*	by Kawai, et al.**
Type II	I	N	↓	↓	6	8
Type I	II	↓	↓	↑, N	0	2
	III	↓	N	N	1	3
Type III	IV	N	↓	N	24	16
	V	N	N	↓	23	11
	VI	N	N	N	3	5
	VII	↓	↑	↓	1	1

* Frequency found among 11,000 in-patients.

** Frequency found among 200 infants with repeated upper respiratory infections and other infectious diseases.

variation in K/L ratio has been noted, and even kappa-chain deficiency with recurrent respiratory infections has been reported.

Normal serum IgG shows a characteristic long precipitin line on immunoelectrophoresis, indicating its polyclonal nature. However, in many cases of primary hypogammaglobulinemia, the electrophoretic distribution of IgG showed less heterogeneity, suggesting that only a part of the total potential of the IgG-producing apparatus is functioning normally in primary immunoglobulin deficiency.

In some cases with primary immunodeficiencies, imbalances of IgG subclasses in serum have been noted. Furthermore, M-proteinemias have been noted rarely in primary immunodeficiencies such as thymic aplasia and Wiskott-Aldrich syndrome. M-proteinemia was recognized also in Swiss type agammaglobulinemia after lymphoid cell transplantation. We have experienced one of the most interesting cases having severe combined immunodeficiency associated with multiple M-proteins, as shown in Fig. 1. The patient's serum contained only IgG1-K and IgA2-K molecules, in association with possible IgM type M-protein and a decreased amount of IgE. The immunoglobulin abnormalities recognized in this patient are extreme varieties similar to a disproportionate K/L ratio, limited heterogeneity and imbalances of immunoglobulin subclasses. In addition, our cases demonstrated a marked defect of Gm and InV factors which are the genetic markers for IgG molecules. Therefore, genetically determined immunodeficiencies in man may arise from mutations of structural or regulator genes controlling the structure and synthesis of immunoglobulins.

Cryoglobulinemia: Cryoglobulins are the globulins which show reversible cryo-

Fig. 1. Immunoelectrophoretic pattern of the serum proteins in a 7 month-old female infant with severe combined immunodeficiency. The immunoelectrophoretic patterns are most unusual, showing IgG1-K type M-protein (146 mg/100 ml) and IgA2-K type M-protein (250 mg/100 ml). IgM precipitin line shows a characteristic M-bow formation, suggesting to be of monoclonal nature.

precipitation or cryogelation when cooled to 0-4°C. Cryoglobulinemia is the state where cryoglobulin appears in the blood. All the serum cryoglobulins are of abnormal immunoglobulins, and they are divided into two groups: single component type and mixed type. The former consists exclusively of M-protein. In mixed type, however, the one immunoglobulin component carries a M-protein character, while the other is not usually of monoclonal. Recently, some of the cryoglobulin complexes have been found to have specific antibody activities such as rheumatoid factor, antinuclear antibody, anti-cytomegalovirus, cold hemagglutinin and anti-complement activity. Therefore, the cryoglobulin, particularly the mixed type cryoglobulin, is suggested to be immune complex. In fact, the mixed type cryoglobulin has been not infrequently encountered with autoimmune diseases, collagen diseases, and other similar diseases.

Cryoglobulinemia may cause clinically Raynaud's symptom or cryopathy, resulting in purpura, arthralgia and anemia. However, not all the cases with cryoglobulinemia are associated with Raynaud's symptom, and some patients may be entirely asymptomatic.