AN OVERVIEW OF MONOCLONAL GAMMAPATHIES

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ABSTRACT

The neoplastic proliferation of single clones of plasma cells causes synthesis of very large amount of monoclonal immunoglobulins consisting of only one type of heavy either the gamma, alpha, mu, delta or epsilon chain or only kappa or lambda light chains. Each monoclonal immunoglobulin differs idiotypically from each other. These monoclonal immunoglobulins are also called paraproteins and are frequently associated with a broad heterogeneous group of plasma cell dyscrasias. Occasionally their presence is observed in a few benign conditions and in old age. In the present review a detailed account of different types of monoclonal gammopathies are described.

KEY WORDS : Monoclonal gammopathies, monoclonal immunoglobulins, paraproteins, myeloma proteins, cancer M proteins.

INTRODUCTION

Plasma cell dyscrasias associated with paraproteinemia or monoclonal gammopathies comprise a heterogeneous group of disorders characterized by the presence in serum or urine of a monoclonal immunoglobulins. Monoclonal immunoglobulins / paraproteins / Myeloma proteins / M proteins refer to a group of homogeneous immunoglobulins produced by plasma cells of lymphoreticular system (1-7). The neoplastic proliferation of one and rarely two specific clones of B cell series of immunocytes / plasma cells result in elaboration / amplification of large number of such clones which produce a single type of immunoglobulin molecule of homogeneous character, belonging to either of five classes of immunoglobulins. The neoplastic proliferation of single clone of plasma cell results in the over production of these proteins. Monoclonal immunoglobulins are identified by serum / urine paper or agar gel electrophoresis, immunoelectrophoresis, immunofixation and by their behavior on column chromatography and ultracentrifugation.

Hobbs has suggested that the term 'Immunocytoma' be used instead of 'plasmacytoma'

to describe various types of the tumors capable of producing immunoglobulins (8). Apitz for the first time used the term 'paraproteins' to denote foreign proteins produced by myeloma cells (9). The frequent association of paraproteinemia with myeloma and Waldenstrom's macroglobulinemia led Riva to coin the term 'M-protein' and the term 'monoclonal gammopathy' was suggested by Waldenstrom for disorders associated with 'M proteins' (10). However, the term has undergone considerable entymological evolution and 'M' now stands for 'monoclonal' rather than for myeloma, macroglobulinemia or malignant lymphoma and is coupled with 'globulin', 'peak', 'spike', 'component' etc.

The malignant paraproteinemias comprise approximately 1.5% of all malignancies. Whether the proteins produced in such a great amount in these disorders are truly abnormal or whether they represent normal components formed in great excess as a consequence of 'monoclonal dyscrasias' has not been resolved and consequently the designation 'Paraproteins' continues to be employed to avoid the unresolved normalcy issue. Each paraprotein is shown to contain antigenic determinant specific or unique to it (idiotype determinants) (11, 12).

HOMOGENEITY OF MONOCLONAL IMMUNOGLOBULINS

All the homogenous immunoglobulins produced by the proliferating plasma cells have been structurally unique to the patients in which they occur. Monoclonal gammopathies described to date include those due to overproduction of IgG, IgA, IgM, IgD or IgE and/or free light and heavy chains. Each 'abnormal' (monoclonal) immunoglobulin molecule consists of single class or subclass of γ , μ , α , δ or ξ - heavy chains and/or one type and subtype or K or λ light chains. Free light chains, either K- or λ - type in the urine or serum of patients with monoclonal gammopathies, are identical with Bence Jones proteins. Light chains from M-proteins on starch gel electrophoresis at acidic pH in 8M urea show only one or two bands, as opposed to light chain of normal immunoglobulin counterparts which show 6-10 bands.

OCCURRENCE OF MONOCLONAL IMMUNOGLOBULINS IN HUMAN SERUM

Varying incidence of association of M. component in plasma cell dyscrasias is reported in literature which is 75-90% (13-18). Zawadzki and Edward reviewed the incidence of the class of immunoglobulin identified in various lymphoreticular diseases (1). Out of their 200 cases showing positive myeloma peak, IgG myeloma protein was present in 53%, IgA myeloma protein in 28%, macroglobulin in 3.5%, IgD in 2% and Bence Jones proteins in 12.5% cases, Biclinal gammopathies were observed in 4.5% of cases. The ratio of Kappa to Lambda chains in various myeloma proteins varies from 62-63.4% : 30-36.4% which is closely similar to the normal sera. Structurally abnormal molecules of IgG in plasma cell dyscrasias have also been reported by various groups (19, 20). Monoclonal immunoglobulins are not specific to myeloma and macroglobulinemia which are the chief prototypes of monoclonal gammopathy. Monoclonal immunoglobulins occur, though rarely, in association with leukemias (21), lymphomas (22), lymphosarcomas (23, 24) and reticulum cells sarcoma (8).

Monoclonal immunoglobulinemia is not necessarily a manifestation of a malignant

immunocytopathic disease. Nonmyelomatous monoclonal immunoglobulinemia has been also reported (25). Clinical significance of nonmyelomatous monoclonal immunoglobulinemia is still poorly understood. It is characterized by protein aberrations which are associated with, or induced by a mosaic of possible pathological and genetic factors such as immunologic, infectious, metabolic and aging, exerting their influence separately or conjointly.

Presence of M-Component has been observed in such heterogeneous diseases as ataxia telangiectasia, bronchiogenic carcinoma, epithelial neoplasms, hypernephroma, chronic liver diseases, carcinomas, a few benign tumors, disorders of known or suspected autoimmune origin and in various pathological disorders. Transient M. components have been reported rarely in patients recovering from pneumonia, hepatitis and other infections. It is also observed in few instances after drug reactions and also in few cases after bone marrow transplantation. Transient paraproteinemia denotes the monoclonal protein which reaches a peak concentration, rapidly declines and finally disappears (26). It can be associated with immune deficiency states and in prosthetic heart valve insertion. In some instances monoclonal immunoglobulinemia has been described in sera of apparently healthy adults and occasionally it also occurs in old age. Axelsson et. al. in (27) have reported an overall incidence of paraproteinemia in Swedish adult population above 25 years to be 0.9% (men 1.1% and women 0.8%). The frequency increased progressively with age, from 0.16% in 25-49 years old to 1.6% in 50-79 age group, and 9.2% in 80-89 years of age. Simultaneous presence of more than one monoclonal immunoglobulin (biclonal gammopathy) in a single individual is uncommon and may reflect a tendency to multiple cell mutations (28-30). Triclonal gammopathy was also reported (31). Classification of disorders associated with monoclonal gammopathy is described in table 1.

MULTIPLE MYELOMA

Multiple myeloma is characterized by the presence of serum paraprotein in 80% of the cases,

Table 1. CLASSIFICATION OF PLASMA CELL DYSCRASIAS ASSOCIATED WITH MONOCLONAL GAMMAPATHY

Malignant Monoclonal Gammopathy

Multiple Myeloma
Waldenstrom's macroglobulinemia
Plasma cell leukemia
Solitary plasmacytoma of bone
Extramedullary plasmacytoma
Malignant B cell lymphoma
Chronic lymphocytic leukemia
Heavy chain diseases

Primary Amyloidosis

Benign Monoclonal Gammopathy

Monoclonal gammopathy of undetermined significance (MGUS) / Idiopathic M-proteins

Transient

Persistent

Secondary Monoclonal Gammopathy

Cancer (nonlymphoreticular)

Monocytic leukemia

Hepatobiliary disease

Rheumatoid disorders

Chronic inflammatory states

Cold agglutinin syndrome

Poplar mucinosis

Gauchers disease

Pseudoparaproteinemia

urinary paraprotein, Bence Jones and others in (50%) with reduction in serum levels of polyclonal immunoglobulins (14,17,18,32,33). In terms of incidence and severity, it is the most important plasma cell neoplasm. The average age adjusted annual incidence for myeloma in white population is 4.3 per 100,000 males and 3.0 per 100,000 females. In blacks the incidence is higher 9.6 per 100,000 males and 6.7 per 100,000 females. Multiple myeloma accounts for two thirds of monoclonal gammopathies in a hospital population. It is a diffuse neoplasm of plasma cell primarily occurring in bone marrow and is classified into IgG, IgA, IgM, Ig D, Ig E and Bence Jones type according to class of immunoglobulin increased as 'M' component in serum. IgM myeloma, a disorder clinically and pathologically distinct from Waldenstrom's macroglobulinemia with multiple bone lesions and without lymphadenopathy and hepatosplenomegaly was reported in 1986. IgG, and IgA myelomas are most common, IgM myeloma are

not very common, whereas relatively few reports are available on IgD myeloma and IgE myeloma (34-38). However, not all cases of myeloma exhibit these characteristic changes i.e. the presence of M.component in serum and urine. Non secretory myeloma is well recognized as an entity where monoclonal immunoglobulins were identified in cytoplasm or on membrane by immunofluorescent methods (39).

Cryoglobulinemia in Multiple Myeloma

The cryoglobulins are mostly gammaglobulins that are insoluble at near zero temperature but solubilize at body temperature and therefore present with symptoms of cold intolerance. The phenomenon of cryoprecipitation was well documented in sera of patients with multiple myeloma having 7S monoclonal IgG paraprotein (40). Monoclonal single type of cryoglobulins are most frequently observed in lymphoproliferative disorders. Virella (40a) noted that cryoprecipitation was more common in IgG 3 subclass and that it may be due to some structural peculiarity of this molecule, resulting in a tendency to form concentration dependent aggregates. The mechanism of temperature dependent precipitation of gammaglobulins is not known. No chemical or structural characteristics unique for cryoglobulins have been described although they retain the specificity of paraproteins when present as monoclonal bands (41, 42).

Clinical features

Anemia, bone pain, vertebral body compression, elevated erythrocyte sedimentation rate (ESR), hypercalcemia due to wide spread osteolytic bone destruction, renal dysfunction due to renal tubular obstruction and damage by abnormal circulating proteins and decreased resistance to infection due to deficiency of normal antibody production. Less common clinical features comprise coagulation abnormalities presenting as bleeding tendency, cryoglobulinemia with or without Raynaud's phenomenon and hyperviscosity of serum presenting with bleeding, retinopathy and peripheral neuropathy. POEMS' syndrome constitutes characteristics of peripheral neuropathy, osteosclerosis, endocrinopathy,

myeloma spike and skin changes.

Radiological Features in Multiple Myeloma:

No bone is exempted from involvement in myeloma but the most common sites are the vertebral, ribs, sternum, pelvic bones, skull, proximal humeri and femurs and the facial bones. A variety of radiological findings ranging from osteoporosis to large areas of osteolysis are observed. Multiple predominantly osteolytic "punched-out" areas of bone destruction of varying sizes are concentrated only in advanced cases. They are sharply demarcated from the surrounding bone except when the surrounding bone is markedly osteoporotic. In the long bones and ribs, the lytic lesions are circular or oval and may be quite extensive, producing a "soap-bubble" appearance to the bone. Slight sclerosis may occur about the periphery of these lesions except when they involve the pelvis. Thinning of the cortex and endosteal destruction with a wavy appearance are the result of medullary bone destruction by the malignant myeloma cells. A diffuse pattern of osteoporosis is frequently evident in the vertebrae and is often associated with vertebral compression fractures. In case of multiple myeloma with diffuse osteoporosis, the myeloma cells diffusely replace the marrow and destroy both bony trabeculae and cortex, rendering the bone very soft. Classically, the lytic lesions of the calvarium are sharply circumscribed "punched-out" lesions. At times, the lytic calvarial lesions become extremely large. The absence of skull lesions does not exclude the diagnosis of multiple myeloma. In some individuals with severe osteoporosis and lytic lesions, multiple pathologic fractures may cause a grotesquely distorted thoracic cage and spine. Occasionally, multiple myeloma will present with a diffuse osteopenia resulting from osteomalacia as a consequence of renal insufficiency and renal tubular acidosis. The exact mechanism of osteolysis in multiple myeloma is uncertain, but perhaps the myeloma cells secrete an osteoclastic stimulating factor that activates osteoclasts in the areas of bone resorption. This mechanism does not explain the rare cases in which osteosclerosis is found. The osteosclerosis is usually limited to a single focus, while the remainder of the bony lesions are lytic. Occasionally, lytic lesions will

become sclerotic after chemotherapy or radiation therapy.

PRIMARY (WALDENSTROM) MACROGLOBULINEMIA

Primary macroglobulinemia is a plasma cell dyscrasia, first described by Waldenstrom in 1944, characterized by presence of neoplastic plasmacytoid lymphocyte in blood, elevation of monoclonal 19 S macroglobulin (IgM) in serum. Lymphadenopathy and hepatosplenomegaly are common clinical features. These patients often present with visual disturbances secondary to retinal hemorrhages due to hyperviscosity caused by increased concentration of the large macroglobulin. Radiologically, bone lesions are found in only 25% of patients. The bone lesions appear similar to those found in the multiple myeloma except that lytic lesions are uncommon. Diffuse osteopenia particularly involving the spine is common (43-45).

PLASMA CELL LEUKEMIA

Rarely monoclonal gammopathy is associated with plasma cell leukemia in 2 to 6% of plasma cell neoplasms (46, 47). Peripheral blood in these patients shows increased plasma cells. Lymphadenopathy and hepatosplenomegaly may be present.

PLASMACYTOMA

Monoclonal gammopathy occurs though very rarely, in association with solitary plasmacytoma of bone and in extramedullary plasmacytoma (48-50).

HEAVY CHAIN DISEASE

Heavy chain diseases in lymphoproliferative malignancies are relatively rare diseases characterized by serum paraprotein comprised of incomplete heavy chains or Fc fragment of homogeneous immunoglobulins without light chains in the serum or urine or both and are usually associated with malignant lymphomas. Four distinctive clinical syndromes of heavy chain disorders exist. These are gamma heavy chain, mu-heavy chain, alpha

heavy chain and delta heavy chain (very rare) diseases (51-54). Delta heavy chain disease is extremely rare. No case of epsilon heavy chains is reported. The paraprotein is generally present in relatively low concentration in blood and biological fluids and shows broad zone gamma band on serum electrophoretic pattern, but it is frequently excreted in urine in measurable amounts.

BENCE JONES PROTEINS (LIGHT CHAIN DISEASE)

Bence Jones proteinemia or light chain myeloma with or without kappa and lambda Bence Jones proteinuria occurs in 20-30% of myeloma patients and in 11% of Wadenstrom's macroglobulinemia. Bence Jones proteins have unique thermal properties i.e. the protein precipitates at low temperature and solubilizes at boiling temperature in urine (55, 56). Bence Jones proteins are made up of monomeric or dimeric forms of monoclonal kappa or lambda type light chains. Lower incidence of free light chains are observed in nonmyelomatous paraproteinemia than in myelomatoses and macroglobulinemia. Urinary light chains were also detected in 25% patients of leukemia and lymphoma associated with monoclonal gammopathy.

AMYLOIDOSIS

Amyloidosis may be defined as a group of diseases characterized by the extracellular deposition of fibrous protein in osteolytic areas of bone, perivascular areas, joints, kidney and marrow etc (57-59). Tracheobronchial amyloidosis had been

reported by Anthony et. al. (59). Amyloidosis is most frequent in Bence Jones myeloma and may dominate the clinical course. Amyloid deposits in various tissues are due to 8.5 nm wide non-branching fibrils of varying length. The primary structure of fibril indicates heterogeneity among the amyloid. Primary immunocyte derived or amyloid of immune origin (AIO) consists of light chain or variable fragment of light chains of immunoglobulins. In immunoproliferative disorders, mostly light chains or its fragments are deposited, with a predominance of the lambda light chains.

The radiologic manifestations of bone amyloidosis depends on the type and extent of involvement of bone and joints.

PARAPROTEINEMIA IN BENIGN CONDITIONS AND IN OLD AGE

Occasionally their presence is observed in a few benign conditions and in old age (60-63).

PSEUDOPARAPROTEINEMIA

If the concentration of any homogeneous protein exceeds 300 mg/dl it may present as a homogeneous band on electrophoresis. Such pseudoparaproteins may occur in sera with high titres of Rheumatoid factor, hyperlipidemia, heavy hemolysis and contaminated serum. Hypertransferrinemia seen in severe iron deficiency anemia and hyperhaptoglobulinemia, gives peaks in the beta and alpha-2 globulin regions respectively (64).

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